Received: 7 March 2023 | Revised: 9 May 2023 | Accepted: 14 June 2023

DOI: 10.1002/ijc.34652

SHORT REPORT

Cancer Therapy and Prevention

IJC INTERNATIONAL JOURNAL of CANCER

# Ramucirumab beyond progression plus TAS-102 in patients with advanced or metastatic esophagogastric adenocarcinoma, after treatment failure on a ramucirumab-based therapy

Thorsten Oliver Goetze[1,2,3] | Alexander Stein[4] | Sylvie Lorenzen[5] | Timorshah Habibzada[2] | Eray Goekkurt[4] | Peter Herhaus[5] | Maria Loose[1] | Disorn Sookthai[1] | Tanita Brulin[1] | Kristina Ihrig[1] | Claudia Pauligk[1] | Salah-Eddin Al-Batran[1,2]

[1]Institute for Clinical Cancer Research IKF, Frankfurt, Germany

[2]University Cancer Center Frankfurt, Krankenhaus Nordwest, Frankfurt, Germany

[3]University Cancer Center Frankfurt, Goethe University, Frankfurt, Germany

[4]Hämatologisch-Onkologische Praxis Eppendorf (HOPE) und Universitäres Cancer Center Hamburg (UCCH), Hamburg, Germany

[5]München Klinikum rechts der Isar der TU München III. Medizinische Klinik und Poliklinik, Munich, Germany

**Correspondence**
Thorsten Oliver Goetze, Institute of Clinical Cancer Research IKF and Krankenhaus Nordwest, UCT-University Cancer Center, Steinbacher Hohl 2-26, University Cancer Center Frankfurt, Goethe University, Frankfurt 60488, Germany.
Email: goetze.thorsten@ikf-khnw.de

**Funding information**
Lilly Deutschland

## Abstract

Based on results of prior trials (TAGS, REGARD, RAINBOW), the combination of ramucirumab beyond progression with TAS-102 (trifluridine/tipiracil) seems to be promising in advanced esophagogastric adenocarcinoma (EGA). In this multicenter, non-randomized, open-label, investigator-initiated pilot trial, ramucirumab-pretreated patients with metastatic EGA received a maximum of 4 cycles of ramucirumab (8 mg/kg i.v. on day 1 and 15, Q2W) plus TAS-102 (35 mg/m$^2$ p.o. bid on day 1-5 and day 8-12; Q2W). Primary endpoint was tolerability and toxicity, defining a positive trial if the SAE rate according to CTCAE 5.0 will increase <30% (up to 55%) compared to historical results from TAGS trial (SAE rate 43%). Secondary endpoints were further evaluation of safety and assessment of efficacy according to tumor response and overall and progression-free survival (OS/PFS). Twenty patients, 20% gastric and 80% GEJ cancers and 55% with ECOG 0 were enrolled. In total, nine SAEs were reported in 25% [95% CI: 8.7-49.1] of the patients, all without relationship to the systemic therapy. The median OS and PFS were 9.1 months [5.4-10.1] and 2.9 months [1.7-4.8], respectively. In addition, a disease control rate of 45% was obtained. The trial showed a favorable safety profile with a numerically lower incidence of SAEs for the combination of ramucirumab with TAS-102 compared to historical TAGS trial. Furthermore, the combination demonstrated efficacy in the beyond progression setting and therefore warrants further evaluation in a randomized trial compared to TAS-102 alone.

**Abbreviations:** (S)AE, (serious) adverse event; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; EGA, esophagogastric adenocarcinoma; GEJ, gastroesophageal junction; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; Ram, ramucirumab; SOC, standard of care; TAS-102, trifluridine/tipiracil; VEGF(R), vascular endothelial growth factor (receptor).

KEYWORDS
metastatic esophagogastric adenocarcinoma, ramucirumab, TAS-102, treatment beyond progression

**What's new?**

This multicenter, non-randomized, open-label, investigator-initiated pilot trial evaluated the efficacy of the combination of VEGFR-targeting antibody ramucirumab beyond progression with TAS-102 (trifluridine/tipiracil) in advanced esophagogastric adenocarcinoma. The findings of the RE-ExPEL pilot trial suggested that the combination was safe and well tolerated with promising efficacy compared to historical TAS-102 monotherapy trial data. Beyond-progression treatment may thus be feasible and could be a good option not only for patients with colorectal cancer but also gastric cancer. The combination warrants further evaluation in a randomized trial.

## 1 | INTRODUCTION

Esophagogastric adenocarcinoma (EGA, comprising gastric cancer and adenocarcinoma of the gastroesophageal junction [GEJ]) belong to the most common malignancies worldwide, with an incidence of 2.75 cases per 100 000 adults per year. Furthermore, EGA is associated with a high disease-related mortality resulting in a median 3-year survival of 26%.[1] Patients with advanced and metastatic gastric cancer are treated with chemotherapy regimens containing 5-fluorouracil (5-FU) and related compounds, taxanes, platinum derivatives or irinotecan. A meta-analysis showed that combination chemotherapy in addition to best supportive care improved overall survival, as well as quality of life when compared to best supportive care alone and that combination regimens were superior to single-agent chemotherapy.[2]

The vascular endothelial growth factor (VEGF) family is a key mediator of angiogenesis and comprises five members (VEGF-A,B,C,D and placenta growth factor [PGF]), which bind with different affinities to three receptors (VEGFR1-3) expressed on vascular endothelial cells. Up-regulation of VEGF by oncogene expression results in an "angiogenic switch," that is, formation of new vasculature in and around the tumor allowing it to grow exponentially.[3] Thus, using antiangiogenic therapy is now a common form of treatment for various malignancies. The human monoclonal antibody ramucirumab specifically binds to VEGFR2 preventing its interaction with the VEGFR ligands VEGF-A, VEGF-C and VEGF-D.[4] Based on the results of the REGARD and the RAINBOW trial ramucirumab was approved for the treatment of patients with advanced or metastatic EGA after prior chemotherapy.[5,6] In other tumor entities the concept of maintenance therapy with VEGF inhibition plus standard second-line chemotherapy beyond disease progression had shown to be efficacious. Bevacizumab plus standard second-line chemotherapy has shown clinical benefits in patients with metastatic colorectal cancer in the TML study.[7] Also, in the RAISE study, survival in the same population for FOLFIRI in combination with ramucirumab was demonstrated by continuation of VEGF blockade beyond progression and was also well tolerated.[8]

Recently, the randomized, phase III TAGS trial showed that TAS-102 plus best supportive care significantly increased overall and progression-free survival (OS/PFS) compared to placebo plus best supportive care in heavily pretreated (63% with ≥3 previous lines of systemic therapy) EGA patients.[9] These results led to the approval for TAS-102 in metastatic gastric and GEJ adenocarcinoma previously treated with at least two prior lines of chemotherapy in 2019.

The combination of VEGF-targeting drugs in combination with chemotherapy demonstrated promising beyond progression-results in metastatic colorectal cancer according to for example, RAISE-, TML- or VELOUR- phase III trials.[7,8,10] This provided a strong rationale to conduct a study evaluating if VEGF-targeting in combination with TAS-102 chemotherapy in patients with refractory metastasized gastric or gastroesophageal junction cancer can improve efficacy and prevent resistance. It was believed that a combination of TAS-102 and ramucirumab can be safely administered in patients with gastric carcinoma, and ramucirumab is efficacious beyond progression, since VEGF-signaling blockade appears to be effective and very well tolerated in the refractory patients, in monotherapy as well in the combination therapies.

The purpose of the RE-ExPEL pilot trial was to investigate the tolerability, safety and benefit of ramucirumab beyond progression in combination with a change of backbone from, for example, paclitaxel/FOLFIRI + ramucirumab or ramucirumab mono to TAS-102 + ramucirumab (Ram + TAS) in EGA.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and participants

The RE-ExPEL/IKF-t028 trial was an investigator-initiated, interventional, prospective, nonrandomized, open-label, multicenter single-arm pilot study.

Eligible patients had histologically confirmed locally advanced or metastatic adenocarcinoma of the gastroesophageal junction or the stomach and showed disease progression during or within 4 to 6 weeks after the last dose of a ramucirumab-based second-line therapy. Main eligibility criteria comprised: Patients aged ≥18 years; Eastern Cooperative Oncology Group (ECOG) performance status ≤2; adequate hematological, hepatic and renal function parameters. Main exclusion criteria were: history of other malignancies not curatively treated and without evidence of disease for more than 5 years, except

for curatively treated basal cell carcinoma of the skin and in situ carcinoma of the cervix; known brain metastases and chronic antiplatelet therapy.

## 2.2 | Procedure

All enrolled patients received ramucirumab (8 mg/kg, i.v. on day 1 and day 15 of a 28-day cycle) plus TAS-102 for a maximum of 4 cycles (~4 months), whereat TAS-102 was prescribed and administered within its label and according to clinical routine and thus represents Standard of Care (SOC) treatment (35 mg/m$^2$ p.o., twice daily on day 1-5 and day 8-12 of a 28-day cycle). Therapy was terminated prematurely for unacceptable toxicity, disease progression, death or at patient's request.

Tumor assessment was performed according to clinical routine at screening and every 8 weeks (±7 days) during the treatment phase as well as every 12 weeks during follow-up until disease progression, death or end of follow-up.

## 2.3 | Study objective and endpoints

The objective was to determine whether a combination of ramucirumab plus TAS-102 shows good tolerability without safety issues regarding the serious adverse event rate of any cause, and whether the combination shows positive initial signals for efficacy. The primary endpoint was tolerability defined by the rate of SAEs of any cause according to CTCAE v5.0. Secondary endpoints were rate of treatment-related AEs and SAEs as well as rate of grade ≥3 neutropenia, anemia, leucopenia and/or thrombocytopenia. Efficacy secondary endpoints were objective response rate defined as proportion of patients showing complete or partial response, progression-free survival defined as time from enrollment to disease progression or death of any cause, and overall survival defined as time from enrollment to death of any cause.

## 2.4 | Statistical analysis

The statistical concept was mainly exploratory without formal sample size calculation, focusing on calculating the expected 95% CI intervals for the primary endpoint.

SAEs of any cause in the TAGS trial were reported in 43% in the TAS-102 treated group.[9] An increase of 30% compared to the SAE rate of the TAS-102 treated group of the TAGS trial was considered to be clinically meaningful and would result in a SAE rate of 55%. With a sample size of 20 patients this yields an exact two-sided 95% CI of 0.332 to 0.768 which was considered acceptable for an early phase exploratory trial. Therefore 20 patients were enrolled.

The statistical evaluation was purely descriptive, and the primary endpoint was not statistically evaluated. All parameters were evaluated in descriptive manner, providing means, medians, interquartile and total ranges, standard deviations and/or confidence intervals, absolute and relative frequencies or Kaplan-Meier curves, as appropriate for the respective data types. Event-related data like PFS and OS were estimated by the product limit method, providing the numbers of events and censored cases, median survival time along with its 95% CI (if applicable). Incomplete time-to-event observations were handled as censored measurements. Adverse events were graded according to NCI CTCAE v5.0. The analyses were carried out using SAS software program version 9.4.

# 3 | RESULTS

Between 28 October 2020 and 11 August 2021, 20 patients were enrolled. Since all patients received at least one dose of ramucirumab plus TAS-102, all were included in the intention-to-treat (ITT) as well as the safety population. The median age was 56.5 years and 80% of the patients were male. More than half of the patients had an ECOG of 0 and the majority of patients had GEJ adenocarcinomas. All patients showed metastatic disease, with lung and lymph node as most prominent sites for metastases localization, and all received at least two prior systemic treatment lines. Half of the patients had received ramucirumab plus paclitaxel as last previous therapy (Table 1).

Six (30%) patients completed the maximum study treatment of 4 cycles. Four of these patients received all planned 8 ramucirumab and 80 corresponding TAS-102 administrations, one patient received all planned 8 ramucirumab and 79 corresponding TAS-102 administrations and one patient had only 6 ramucirumab applications within the 4 cycles (2 applications not performed). The major reason for premature discontinuation was disease progression (n = 12) followed by patient decision (n = 2) (Figure 1A). Three patients missed at least one dose of ramucirumab, two patients due to toxicity and one patient due to an upcoming elective surgery. One patient received only ramucirumab but no TAS-102 in cycle 2 due to a SAE.

A total amount of 103 AEs were recorded in this trial, most of which were classified as grade 1 or 2 and only 12 had a grade ≥3. Out of the 20 patients, 19 (95%) had at least one AE. The most frequent AEs (incidence ≥20%) were anemia, increase of C-reactive protein, fatigue, leukopenia, nausea, neutropenia, pain and thrombocytopenia. Five out of 20 patients (25% [95% CI: 8.7-49.1]) experienced at least one SAE. Overall, a total amount of nine SAEs were recorded, five of them were grade ≥3. One fatal SAE occurred without relation to study treatment (respiratory failure). Fifteen out of 20 patients (75%) had at least one treatment-related AE, whereas treatment-related SAEs were not reported during the trial. The majority of the adverse reactions was related to TAS-102 only. Overall, eight patients (40%) experienced at least one treatment-related AE with grade 3, almost all of these were related to TAS-102 only, and none of the treatment-related AEs was grade 4 or 5. Overall, three events were classified as adverse event of special interest in relation to ramucirumab—hypertension grade 2, proteinuria grade 1 and thrombosis V. subclavia grade 2 (Table 2).

**TABLE 1** Patient listing of major study parameters.

| Patient no | Age | Gender | Localization of primary tumor | Localization of metastases at study entry | No previous systemic treatment lines | Last systemic treatment | Number of treatment doses (ram/TAS-102) | Reason for treatment discontinuation | BOR | PFS[a] (months) | OS[b] (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 001 | 58 | M | AEG I | Liver, lung, lymph node | 2 | Ramucirumab/paclitaxel/ avelumab | 3/20 | PD during treatment | PD | 1.22 | 8.44 |
| 002 | 43 | F | Stomach | Krukenberg metastasis, peritoneum | 2 | Ramucirumab | 7/60 | PD during treatment | SD | 2.99 | 5.42 |
| 003 | 62 | M | AEG II | Liver, ling | 3 | Ramucirumab/paclitaxel | 8/80 | Completed treatment per protocol | SD | 9.59 | 9.59 |
| 004 | 57 | M | AEG I | Lung | 2 | Ramucirumab/FOLFIRI | 5/38 | PD during treatment | PD | 2.00 | 9.63++ |
| 005 | 60 | F | AEG II | Liver, lymph node | 3 | Ramucirumab/paclitaxel | 8/80 | Completed treatment per protocol | SD | 3.68 | 10.09 |
| 006 | 56 | F | Stomach | Lymph node, ovarial, peritoneum | 2 | Ramucirumab/paclitaxel | 4/40 | PD during treatment | PD | 1.97 | 4.99 |
| 007 | 44 | M | AEG I | Lung, lymph node | 2 | Ramucirumab/paclitaxel | 7/60 | PD during treatment | SD | 3.25 | 4.14 |
| 008 | 55 | M | AEG I | Lymph node | 2 | Ramucirumab/paclitaxel | 8/80 | Completed treatment per protocol | SD | 4.07+ | 5.72++ |
| 009 | 63 | M | AEG III | Bone, lymph node, mediastinum | 2 | Ramucirumab/paclitaxel/ avelumab | 6/59 | Completed treatment per protocol | SD | 10.45 | 10.45 |
| 010 | 36 | F | Stomach | Ovar left and right | 2 | Ramucirumab/paclitaxel | 2/17 | PD during treatment | PD | 0.62 | 9.07 |
| 011 | 36 | M | AEG I | Esophagus, liver, lymph node | 2 | Ramucirumab/paclitaxel | 4/40 | PD during treatment | PD | 1.74 | 4.96 |
| 012 | 57 | M | AEG II | Lymph node, skin | 2 | Ramucirumab/paclitaxel/ avelumab | 4/60 | PD during treatment | SD | 2.89 | 9.20++ |
| 013 | 55 | M | AEG I | Liver, lymph node | 2 | Ramucirumab/paclitaxel/ avelumab | 1/20 | Patient's wish | NE | 4.80 | 4.80 |
| 014 | 53 | M | AEG III | Liver, lymph node peritoneum | 2 | Ramucirumab/FOLFIRI | 1/10 | Patient's wish | NE | 0.36+ | 0.36++ |
| 015 | 37 | M | AEG I | Liver, lung, lymph node | 2 | Ramucirumab/paclitaxel/ avelumab | 5/40 | PD during treatment | PD | 2.04 | 6.67++ |
| 016 | 55 | M | AEG II | Liver, lymph node | 2 | Ramucirumab/paclitaxel | 8/80 | Completed treatment per protocol | SD | 3.71+ | 5.09++ |
| 017 | 58 | M | Stomach | Liver, lymph node | 2 | Ramucirumab/paclitaxel | 8/80 | Completed treatment per protocol | SD | 9.53 | 9.53 |
| 018 | 62 | M | AEG II | Bone, liver | 2 | Ramucirumab/irinotecan | 4/40 | PD during treatment | PD | 1.91 | 7.66 |
| 019 | 55 | M | AEG II | Lymph node, soft tissue | 2 | Ramucirumab/paclitaxel | 4/40 | PD during treatment | PD | 1.71 | 6.64 |
| 020 | 57 | M | AEG II | Lymph node | 2 | Ramucirumab/paclitaxel | 2/20 | PD during treatment | NE | 1.08 | 5.52++ |

[a]"+" behind the number of months indicates that the patient showed no progression at the end of the study.
[b]"++" behind the number of months indicates that the patient was still alive at end of the study.
Abbreviations: AEG, adenocarcinoma of esophagogastric junction; BOR, best overall response; F, female; M, male; NE, not evaluable; OS, overall survival; PD, progression disease; PFS, progression free survival; ram, ramucirumab; SD, stable disease.

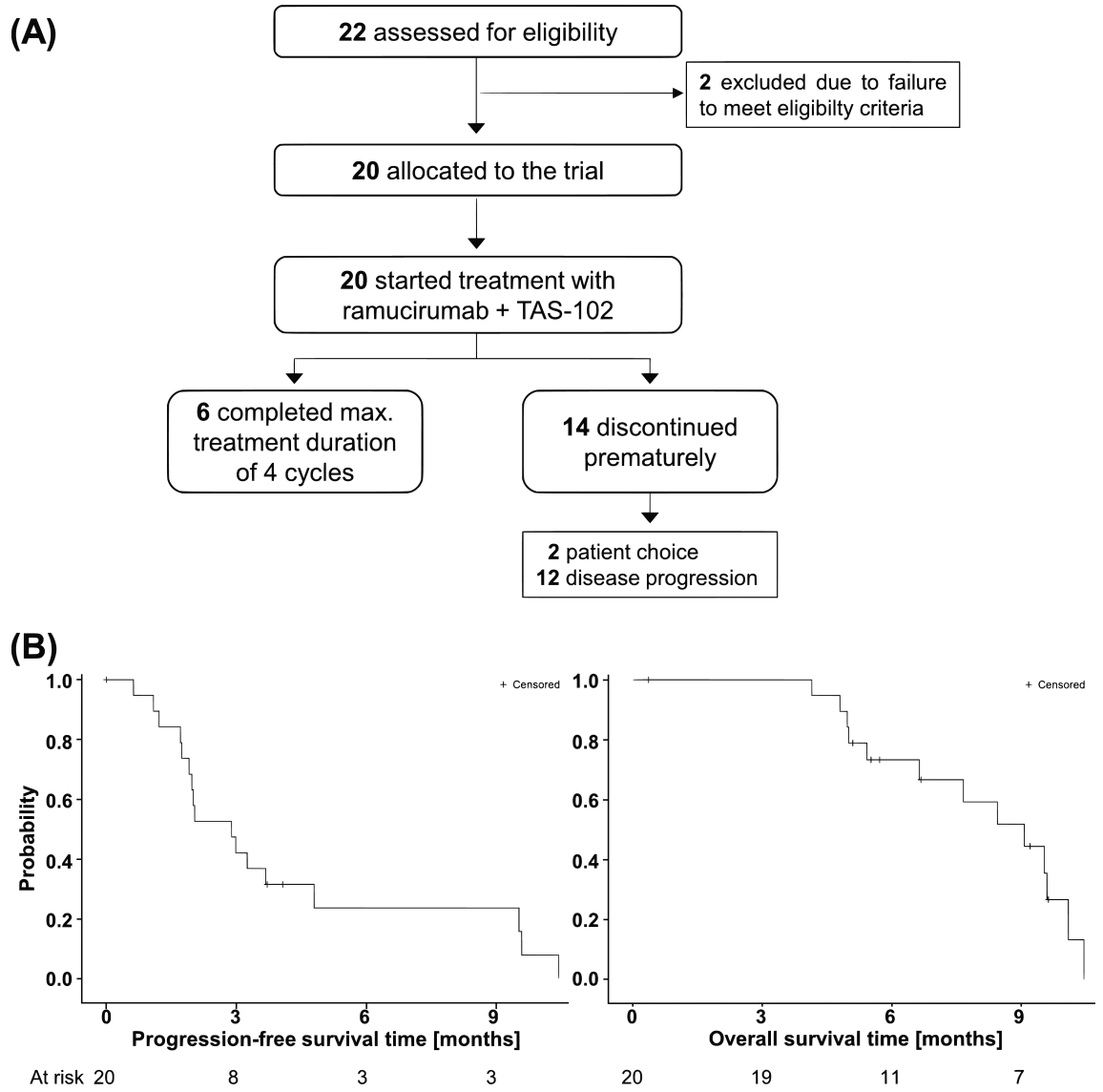


**FIGURE 1** CONSORT diagram and Kaplan-Meier estimates. (A) All allocated patients included in the ITT population analysis set. The safety population comprised all patients who received at least one dose of study treatment. (B) Progression-free and overall survival of the ITT population.

For three patients no tumor response was assessed. Two patients refused further tumor assessments after they had discontinued the treatment at their own request before the first on-treatment imaging and for one patient the investigator decided to skip the imaging due to clinical signs of progression. Out of the analyzed 17 patients in the ITT population, nine had stable disease as best overall response. The remaining patients showed disease progression according to RECIST v1.1. (Table 1). Four out of the 9 patients with stable disease showed disease progression until the end of the study, whereas the median duration of disease stabilization was 2.04 months (95% CI: 0.95-NE). The overall median follow-up time was 6.7 months (0.4-10.4 months), and the median follow-up for patients who were alive at the end of the study was 5.7 months (0.4-9.6 months). The Kaplan-Meier estimation of the PFS and OS was calculated from the date of subject enrolment based on 17 (85%) and 13 (65%) observed events, respectively, in the ITT population. The median PFS time was 2.9 months (95% CI: [1.7-4.8]). The median OS time was 9.1 months (95% CI: [5.4-10.1]) and the 3-, 6- and 9-months survival rate was 100%, 73% and 52%, respectively (Table 1, Figure 1B).

## 4 | DISCUSSION

The RE-ExPEL pilot trial was conducted to evaluate the safety and tolerability of a combination of ramucirumab with TAS-102 as treatment beyond progression after second line ramucirumab-based SOC treatment. In addition, the study should determine whether the combination shows positive signals regarding efficacy compared to historical data of TAS-102 monotherapy according to the TAGS trial.

Overall, the majority of adverse events observed within the RE-ExPEL pilot trial were grade 1 or 2. Grade 3 or worse

**TABLE 2** Adverse events (whether related or not) assessed in the safety population (max. grade by patient and category).

| Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Anemia | 1 (5%) | 4 (20%)[a1,c3] | 1 (5%) | | |
| Anorexia | 1 (5%)[a] | 2 (10%)[a1;c1] | | | |
| Ascites | | 1 (5%) | 1 (5%) | | |
| Bronchitis | | **1 (5%)** | | | |
| Chills | 1 (5%) | | | | |
| Cholangitis | | | **1 (5%)** | | |
| Cholestasis | | | 1 (5%) | | |
| Constipation | 1 (5%)[c] | 1 (5%)[c] | | | |
| Cough | 1 (5%) | | | | |
| C-reactive protein increased | | 4 (20%) | | | |
| Diarrhea | 2 (10%)[a1;c1] | | 1 (5%) | | |
| Dysphagia | 1 (5%) | 1 (5%) | | | |
| Dyspnea | 1 (5%) | | | | |
| Edema limbs | | 1 (5%)[b] | | | |
| Epistaxis | 1 (5%) | | | | |
| Fatigue | 4 (20%)[a2;c1] | 2 (10%)[c] | | | |
| Fever | **2 (10%)[#]** | | | | |
| Flu-like symptoms | | 1 (5%) | | | |
| Hematuria | | 1 (5%) | | | |
| Hypertension | | *1 (5%)[b]* | | | |
| Hypokalemia | | | 1 (5%) | | |
| (sub)Ileus | | **1 (5%)** | | | |
| Infections | | | | | |
| Bronchial | | 1 (5%) | | | |
| Lung | | 1 (5%) | | | |
| Mucosal | 1 (5%)[c] | | | | |
| Salivary gland | | | **1 (5%)** | | |
| Unknown focus | 1 (5%) | | | | |
| Urinary tract | | | 1 (5%) | | |
| Insomnia | 1 (5%) | | | | |
| Leukopenia | 1 (5%)[a] | 2 (10%)[c1] | 3 (15%)[c2] | | |
| Malaise | | 1 (5%)[a] | **1 (5%)** | | |
| Nausea | 1 (5%) | 2 (10%)[b1;c1] | 1 (5%)[c] | | |
| Neutropenia | 1 (5%) | 1 (5%)[c] | 6 (30%)[a1;c5] | | |
| Pain | 1 (5%) | 5 (25%) | | | |
| Poor tolerance | 1 (5%)[c] | | | | |
| Port dislocation | | | 1 (5%) | | |
| Proteinuria | | *1 (5%)[b]* | | | |
| Redness of port region | | 1 (5%) | | | |
| Respiratory failure | | | | | **1 (5%)** |
| Thrombocytopenia | | 3 (15%)[c] | 1 (5%)[c] | | |
| Thrombosis V. subclavia | | *1 (5%)[b]* | | | |
| Vomiting | | 2 (10%)[b1;c1] | 1 (5%)[c] | | |
| Weight loss | | 1 (5%) | | | |
| Worsening of enterothorax | | | **1 (5%)** | | |
| Worsening of general condition | | 2 (5%) | | | |
| Worsening of tumor pain | | 1 (5%) | | | |

*Note*: AEs classified as serious are displayed in bold. AEs classified as of special interest are displayed in italics. a—at least possibly related to ramucirumab and TAS-102; b—at least possibly related to ramucirumab; c—at least possibly related to TAS-102, enclosed number indicates the number of AEs that were classified as related, if not all were related; #—for one of the two patients it was classified as serious.

nonhematological as well as hematological adverse events were rare, which was in line with the observations for TAS-102 monotherapy in the TAGS trial.[9] However, only 25% of the patients treated showed an SAE. Thus, regarding the primary safety endpoint, our trial showed a numerically lower SAE incidence compared to the historical data of TAS-102 monotherapy in the TAGS trial (25% vs 43%).[9] This numerically lower SAE-rate was potentially due to the efficacy of the combination treatment resulting in a lower rate of tumor-associated complications. The combination treatment resulted in a disease control rate of 45%.

None of the assessable patients achieved complete or partial response. The confirmatory phase III trials revealed only low objective response rates for TAS-102 (4%) and ramucirumab (3%) monotherapies in previously treated advanced stage,[5,9] thus the combination was not expected to have a high response rate. Nevertheless, a disease control rate of 45% was reached with the combination. The median overall survival for the combination of TAS-102 and ramucirumab was 9.1 months (95% CI: [5.4-10.1]), and thus about 3.4 months longer than what was previously achieved for TAS-102 (5.7 months [4.8-5.2]) and ramucirumab (5.2 months [2.3-9.9]) monotherapies.[5,9]

Overall, with an increase of the median overall survival of about 3.4 months compared to historical data of TAS-102 monotherapy, the efficacy signal can be regarded as promising. In addition, ramucirumab plus TAS-102 showed a favorable safety profile in patients with advanced EGA that progressed on prior ramucirumab-containing therapy. Thus, in the context of the good tolerability and promising efficacy the combination of ramucirumab and TAS-102 may result in a longer stabilization of disease without further progression, and thus to fewer tumor-associated symptoms and less impairment of quality of life. Therefore, combination of ramucirumab plus TAS-102 warrants further investigation in future clinical trials.

The implementation of checkpoint-inhibitors alone or in combination with chemotherapy has currently expanded the treatment landscape in patients with advanced esophagogastric adenocarcinoma in first and second-line situation. The landscape will continue to evolve after the recent approval of antibody-drug conjugates like trastuzumab-deruxtecan.[11-15] The integration of these new therapies early on in their treatment course may help more patients to live longer in a good performance status and possibly fit for receiving multiple lines of therapy. This raises the question for the optimal sequence of therapies. Gastrointestinal oncologists have learned a lot from beyond progression concepts evaluated in colorectal cancer, for example, in the phase III TML- or RAISE-trial.[7,8] In addition, in patients with metastatic colorectal cancer refractory to SOC-treatments, TAS-102 in combination with the VEGF-inhibitor bevacizumab was more beneficial compared to TAS-102 monotherapy, with significant improvement in progression-free and overall survival shown in a Danish phase II trial.[16] These promising data were recently confirmed by the latest results of the multinational phase III SUNLIGHT trial,[17] which supports the benefit of continued inhibition of angiogenesis beyond progression and further encouraging the concept of RE-ExPEL in gastric cancer.

Nevertheless, our study had several limitations. First, it was not randomized and provided only a small sample size of patients. Furthermore, it enrolled only European patients with advanced gastric cancer and previous results of a meta-analysis showed better clinical outcome for Western patients receiving antiangiogenic agents compared to Asian patients (HR 0.79; 95% CI: 0.64-0.97 vs HR 0.96; 95% CI: 0.72-1.28), although the interregional difference was not statistically significant.[18] Therefore, the very promising antitumor activity in our results is encouraging but requires confirmation in a larger, randomized study.

To our knowledge, the RE-ExPEL pilot trial is the first to assess the efficacy of the combination TAS-102 plus ramucirumab with a pure beyond progression concept for patients with advanced gastric cancer who were pretreated with ramucirumab. The promising results of RE-ExPEL suggest that beyond progression treatment is feasible and could be a good option not only for colorectal cancer but also for patients with gastric cancer.

## AUTHOR CONTRIBUTIONS

**Thorsten Oliver Goetze:** Original idea, designed the study and were responsible for the protocol development; recruited patients into the study and collect data; had final responsibility for the decision to submit for publication; **Alexander Stein:** recruited patients into the study and collect data; **Sylvie Lorenzen:** recruited patients into the study and collect data; **Timorshah Habibzada:** recruited patients into the study and collect data; **Eray Goekkurt:** recruited patients into the study and collect data; **Peter Herhaus:** recruited patients into the study and collect data; **Maria Loose:** wrote the article together with TOG, performed the literature search and prepared figures and tables; **Disorn Sookthai:** Performed the statistical analysis; **Tanita Brulin:** Responsible for the project management; **Kristina Ihrig:** Responsible for the project management; **Claudia Pauligk:** Responsible for the project management; **Salah-Eddin Al-Batran:** Original idea, designed the study and were responsible for the protocol development; had final responsibility for the decision to submit for publication; All authors contributed to data interpretation and revising the article. The work reported in the article has been performed by the authors, unless clearly specified in the text.

## ACKNOWLEDGMENT

Open Access funding enabled and organized by Projekt DEAL.

## FUNDING INFORMATION

The sponsor of this trial (IKF-t028) is the Institute for Clinical Cancer Research IKF GmbH. The study was supported by grants from Lilly Deutschland GmbH.

## CONFLICT OF INTEREST STATEMENT

Thorsten Oliver Goetze: Consulting: Amgen, AstraZeneca, Bayer, BMS, Daiichi Sankyo, Foundation One Medicine, Lilly, MCI, MSD, Novartis, Roche, Boehringer Ingelheim; Honorary: Amgen, BMS, Lilly, MSD, Novartis, Roche, GSK. Alexander Stein: Advisory Board: Servier; Institutional Research Funding: Servier; Institutional Speaker Honoraria: Lilly. Salah-Eddin Al-Batran: is the CEO/founder of Institute for Clinical Cancer Research IKF; Advisory Board: BMS, Immutep,

Lilly, MacroGenics, MSD; Research grants: AstraZeneca, BMS, Celgene, Eurozyto, Hospira, Immutep, Ipsen, Lilly, Medac, MSD, Roche, Sanofi, Vifor; Speaker: AIO Studien gGmbH, BMS, Lilly, MCI. Other authors have no conflict to disclose.

## DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

## ETHICS STATEMENT

The trial was conducted in accordance with the principles of the Declaration of Helsinki. All versions of the trial protocol were approved by the Ethik-Kommission der Landesärztekammer Hessen (2020-1707-fAM/03.08.2020) as coordinating ethic committee and subsequently by the respective ethics committees of each participating center. This trial is registered with ClinicalTrials.gov number NCT04517747. Study management and coordination were done by the Institute for Clinical Cancer Research IKF GmbH. All patients provided written informed consent to participate in this trial.

## ORCID

*Maria Loose* https://orcid.org/0000-0003-2319-7734

## REFERENCES

1. Ishak NS, Rahman HA, Lee SHF, et al. Incidence, survival and prognostic factors of oesophagogastric cancer. *J Gastrointest Cancer*. 2022;53(1):130-143.
2. Wagner AD, Grothey A, Haerting J. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol*. 2006;24(18):2903-2909.
3. Carmeliet P. VEGF as key mediator of angiogenesis of cancer. *Oncology*. 2005;69:4-10.
4. Oholendt AL, Zadlo JL. Ramucirumab: a new therapy for advanced gastric cancer. *J Adv Pract Oncol*. 2015;6:71-75.
5. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2014;383:31-39.
6. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol*. 2014;15:1224-1235.
7. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol*. 2013;14(1):29-37.
8. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol*. 2015;16(5):499-508.
9. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2018;19(11):1437-1448.
10. Tabernero J, van Cutsem E, Lakomý R, et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. *Eur J Cancer*. 2014;50(2):320-331.
11. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398(10294):27-40.
12. Janjigian YY, Kawazoe A, Yañez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Nature*. 2021;600(7890):727-730.
13. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab Deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med*. 2020;382(25):2419-2430.
14. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2021;398(10302):759-771.
15. Ku GY, Di Bartolomeo M, Smyth E, et al. Updated analysis of DESTINY-Gastric02: A phase II single-arm trial of trastuzumab deruxtecan (T-DXd) in western patients (Pts) with HER2-positive (HER2+) unresectable/metastatic gastric/gastroesophageal junction (GEJ) cancer who progressed on or after trastuzumab-containing regimen. Presented at ESMO Annual Meeting 2022, Abstract 1205MO.
16. Pfeiffer P, Yilmaz M, Möller S, et al. TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open-label, randomised, phase 2 trial. *Lancet Oncol*. 2020;21(3):412-420.
17. Tabernero J, Prager GW, Fakih M, et al. Trifluridine/tipiracil plus bevacizumab for third-line treatment of refractory metastatic colorectal cancer: The phase 3 randomized SUNLIGHT study. Presented at ASCO Gastrointestinal Cancer Symposium 2023. Abstract 4.
18. Zhang Z, Liu Z, Chen Z. Comparison of treatment efficacy and survival outcomes between Asian and Western patients with unresectable gastric or gastro-esophageal adenocarcinoma: a systematic review and meta-analysis. *Front Oncol*. 2022;7(12):831207.

**How to cite this article:** Goetze TO, Stein A, Lorenzen S, et al. Ramucirumab beyond progression plus TAS-102 in patients with advanced or metastatic esophagogastric adenocarcinoma, after treatment failure on a ramucirumab-based therapy. *Int J Cancer*. 2023;153(10):1726-1733. doi:10.1002/ijc.34652