Treatment of Metastatic Colorectal Carcinoma with Bevacizumab in First-Line and beyond First Progression: The KORALLE Non-Interventional Cohort Study

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Abstract

Introduction: The non-interventional study (NIS) KORALLE evaluated the effectiveness and safety of bevacizumab in patients with metastatic colorectal carcinoma (mCRC) treated with bevacizumab in combination with fluoropyrimidine-based chemotherapy in the first-line setting and beyond first progression in routine clinical practice. Methods: This prospective, multicenter NIS observed adult patients with mCRC who started first-line bevacizumab therapy. The planned maximum duration of observation per patient was 21 months. The primary effectiveness variable was progression-free survival in the first-line therapy setting (PFS-1). Secondary effectiveness variables included PFS after first progression as well as overall survival and overall response rate. All analyses were carried out descriptively for the full analysis population set (FAS). Effectiveness analyses were also assessed for predefined subgroups based on therapy goals. Results: Between December 2012 and July 2016, 2,429 eligible patients were observed at 314 sites in Germany. In the first-line setting in the FAS, the median PFS-1 was 10.3 months (95% CI: 9.9; 10.8), the median overall survival was 16.9 months (95% CI: 16.3; 17.5), and the overall response rate (ORR-1) was 44.2% (95% CI: 41.6%; 46.8%). Effectiveness results of all subgroups were similar to the FAS. Overall, 80.9% of patients experienced any adverse events, 36.6% of patients experienced serious adverse events, and 8.8% of patients experienced fatal adverse events. Conclusion: The NIS KORALLE provided broad real-world evidence on effectiveness and safety of bevacizumab. Despite different treatment intentions, the combination of bevacizumab plus fluoropyrimidine-based chemotherapy was similarly effective in all subgroups in routine clinical practice. The safety information reported in this study is consistent with the known safety profile of bevacizumab.

Keywords
Metastatic colorectal carcinoma · Bevacizumab · Non-interventional study · First- and second-line setting · Subgroups according to therapy goals

Introduction

In all new cancer cases in Germany, the colon and rectum are currently the second and third most frequent tumor localization in women and men [1]. In 2020, the prospected incidence of colorectal cancer was 24,100 in women and 31,300 in men [1]. Approximately 25% of patients with colorectal carcinoma present with metastatic disease at the time of diagnosis; up to a further 35% of patients experience emergence of metastases following resection of the primary tumor [2].

ClinicalTrials.gov identifier: NCT01775644.
Based on previous phase 2 and 3 studies [3–7], bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of adult patients with metastatic carcinoma of the colon or rectum and has become the standard of care [8]. The additional results obtained in the Treatment Multiple Lines (TML) study (ML18147), in which patients were treated with bevacizumab beyond first progression [9], as well as two further marketing authorization studies in 2012 and 2013 for treatment of metastatic colorectal carcinoma (mCRC) offer further treatment options in mCRC [10, 11].

Treatment of advanced colorectal carcinoma follows the treatment goal depending on the clinical and individual situation of the patient [12–14]. Treatment guidelines in Germany, i.e., the S3 guidelines of the German Cancer Society, first included treatment goals in 2010 as a criterion to determine the intensity of mCRC therapy.

The non-interventional study (NIS) KORALLE aimed to evaluate the effectiveness and safety of bevacizumab in patients with mCRC treated with bevacizumab in combination with any fluoropyrimidine-based chemotherapy in the first-line setting and beyond first progression, i.e., in second-line as a continuation of first-line, in German routine clinical practice. Effectiveness data were analyzed for subgroups defined by the therapy goal following the S3 guidelines in addition to the overall patient population.

Materials and Methods

Patients and Study Design

KORALLE is a non-interventional, prospective, multicenter, cohort study (ClinicalTrials.gov identifier: NCT01775644). Patients were recruited between December 2012 and July 2016 (dates of informed consent) at 314 sites across Germany, including oncolo-gists and gastroenterologists in hospitals, outpatient clinics, and independent oncology practices. End of data collection (last patient, last visit) was in September 2018. Eligible patients were ≥18 years of age, diagnosed with mCRC, and received first-line therapy with bevacizumab (Avastin®) in combination with fluoropyrimidine-based chemotherapy according to the decision of their treating physicians and the summary of product characteristics of bevacizumab. The planned maximum duration of observation per patient was 21 months, including therapy in first-line and beyond first progression. Regular capturing of data started from the initial dose of first-line chemotherapy with bevacizumab and was continued monthly for each bevacizumab cycle, but ended if a second progression occurred or if bevacizumab therapy was discontinued. In case of an early end, a further documentation step (final visit) and a follow-up documentation step, 21 months after the start of first-line therapy with bevacizumab, were carried out. Retrospective inclusion and documentation of patients were accepted for up to 90 days after start of first-line therapy. The study protocol was approved by the Ethics Committee of the Medical Association Hamburg (Ärztekammer Hamburg), Germany, on November 13, 2012 (reference PV4214).

Statistics

All variables were analyzed descriptively. Time-to-event variables were evaluated using the Kaplan-Meier method, including the median with a corresponding 95% confidence interval (CI) according to Brookmeyer and Crowley [15, 16]. For response rates, 95% CI was calculated according to Clopper and Pearson [17]. Missing values were not replaced; for partially unknown dates, the most conservative imputation method was used.

Analyses were carried out for the full analysis population set (FAS), which comprised all patients considered eligible in a data review meeting on December 17, 2018, and for the following three predefined subgroups by therapy goal: “RES”, patients with liver and/or lung metastases, potentially resectable following a response to systemic therapy and clinically operable; “AGGR”, patients with tumor-related symptoms, risk for (organ) complications or rapid progression for whom quick proliferation control is needed (i.e., “aggressive” tumor biology, as assessed by the treating physician); “INDO”, asymptomatic patients (“indolent” tumor biology) without the option of resection of metastases (rapid remission not required) for whom the goal of therapy is proliferation control. Furthermore, patients who received second-line therapy with bevacizumab or without bevacizumab were analyzed as additional subgroups. The National Cancer Institute’s standardized definitions for Common Terminology Criteria for Adverse Events (CTCAE) v4.03 were used for severity grading of all adverse events and Medical Dictionary for Regulatory Activities (MedDRA) v21.0 for classification of reported terms within respective system organ class and preferred term.

Results

Patient Characteristics at Baseline

The NIS KORALLE enrolled 3,003 patients at 314 sites. 2,429 patients met all selection criteria and were included in the FAS (online suppl. Fig. S1; for all online suppl. ma-
Of these, 1,443 (59.4%) patients had a regular termination of the study including 245 (17.0%) who completed the 21-month documentation period, 959 (66.5%) who terminated due to tumor progression, and 239 (16.6%) who died. Conversely, 891 (36.7%) patients had a non-regular study termination, mostly due to the patient’s wish for termination (245 patients) (online suppl. Table S1).

In the FAS, the median age was 69 years (range: 27–89), 60.5% of patients were men, and the majority of the patients had ECOG performance status 0 (38.1%) or 1 (50.4%) at baseline (online suppl. Table S2). The most frequent primary tumor location was the rectum (34.8%), and most patients were reported with left-sided tumors (64.9%). The most common metastatic sites were the liver (68.7%) and the lung (35.8%). Overall, baseline characteristics were balanced in the subgroups (Fig. 1; online suppl. Table S2).

**Bevacizumab Therapy**

In the FAS, the median total dose of bevacizumab per patient over all cycles was 4,500 mg (range: 250–40,090) (online suppl. Table S3). Median time between the first and last bevacizumab administration was 6.0 months (range: 0–48.2). The most commonly used chemotherapy regimens in combination with bevacizumab were folinic acid/5-fluorouracil/irinotecan (FOLFIRI; 37.5%), folinic acid/5-fluorouracil/oxaliplatin (FOLFOX; 36.8%), and folinic acid/5-fluorouracil (FL; 10.0%) (Fig. 2a; online suppl. Table S3).

The primary therapy goal by predefined categorization was “long OS” for 35.8% of patients of the FAS, “long PFS” for 22.0% of patients, and “control of tumor” for 16.5% of patients (Fig. 2b; online suppl. Table S3). Overall, 26.3% of patients were reported with continuation of bevacizumab therapy after first progression. The two major reasons for continuing bevacizumab therapy in the total population were “principle of therapy”
(61.3%) and “tolerability of therapy” (49.6%) (online suppl. Table S3). Bevacizumab therapy, concomitant chemotherapy, and primary therapy goal differed only slightly between the FAS and the predefined subgroups RES, AGGR, and INDO (for definitions of subgroups, see Materials and Methods, Statistics) (Fig. 2; online suppl. Table S3).

**Effectiveness Outcomes**

During first-line bevacizumab therapy, 60.5% of patients experienced the onset of progression or death. The median PFS-1, i.e., the time from the first dose of bevacizumab to the first progression or death due to any cause, was 10.3 months (95% CI: 9.9; 10.8) in the FAS (Table 1; online suppl. Fig. S2a). No descriptive difference was observed in the analyzed subgroups.

The results for the secondary endpoints PFS-2 and OS are shown in Table 1 (for definitions of variables, see Materials and Methods, Variables; for OS, see online suppl. Fig. S2b). Again, no substantial differences were observed between the FAS and the predefined subgroups.

ORR-1 was evaluated using the best tumor response during first-line bevacizumab therapy. In the FAS, 1,473 patients had a documented tumor assessment during first-line bevacizumab therapy. Among them, 57 (3.9%) patients had a CR and 594 (40.3%) a PR, resulting in an ORR-1 of 44.2% (95% CI: 41.6%; 46.8%) (Table 1). Results for ORR-2 and DCR are shown in Table 1 (for definitions of variables, see Materials and Methods, Variables).

**Safety Outcomes**

Overall, 80.9% of patients experienced an adverse event during treatment, and 36.6% of patients experienced a serious adverse event (Table 2). For 14.6% of patients, the treating physician judged an adverse event to be related to bevacizumab or capcitabine and for 3.0% of patients, a serious adverse event to be related to bevacizumab or capcitabine. During treatment, 8.8% of patients died due to a fatal adverse event. For each category, the most common adverse events (preferred terms) are shown in Table 2. No new safety signals were identified.
Table 1. Main effectiveness outcomes (FAS and subgroups)

|                                | Baseline subgroups | RES n = 670 | AGGR n = 821 | INDO n = 768 | Post-baseline subgroups¹ | patients with 2L chemotherapy |
|--------------------------------|--------------------|-------------|--------------|--------------|---------------------------|-----------------------------|
|                                |                    |             |              |              |                           | with bevacizumab             | without bevacizumab           |
|                                |                    |             |              |              |                           | n = 759                     | n = 60                        |
| Median PFS-1, months (95% CI)² | 10.3 (9.9; 10.8) n = 2,429 | 10.3 (9.7; 11.2) n = 670 | 9.9 (9.2; 10.6) n = 821 | 10.4 (9.7; 11.4) n = 768 | –                          | –                           |
| Median PFS-2, months (95% CI)² | 4.9 (4.3; 5.7) n = 1,007 | 5.1 (4.0;6.5) n = 296 | 4.2 (3.6; 5.3) n = 335 | 6.0 (4.9; 6.5) n = 311 | 4.5 (4.2; 5.4) n = 466 | 3.9 (1.8; 8.9) n = 31         |
| Median OS, months (95% CI)²   | 16.9 (16.3; 17.5) n = 2,429 | 17.6 (16.3; 18.3) n = 670 | 15.4 (14.5; 16.5) n = 821 | 18.5 (17.1; 19.5) n = 768 | –                          | –                           |
| Best response before first progression, n (%) |                    |             |              |              |                           |                             |                              |
| CR                             | 57 (3.9)           | 20 (5.1)    | 18 (3.6)     | 15 (3.0)     | 19 (3.7)                  | 0                           |
| PR                             | 594 (40.3)         | 150 (38.6)  | 203 (40.5)   | 208 (41.8)   | 227 (44.4)                | 17 (44.7)                   |
| SD                             | 458 (31.1)         | 114 (29.3)  | 142 (28.3)   | 174 (34.9)   | 145 (28.4)                | 9 (23.7)                    |
| PD                             | 364 (24.7)         | 105 (27.0)  | 138 (27.5)   | 101 (20.3)   | 120 (23.5)                | 12 (31.6)                   |
|                                | n = 1,473          | n = 389     | n = 501      | n = 498      | n = 511                   | n = 38                       |
| ORR-1, % (95% CI)³             | 44.2 (41.6; 46.8) n = 1,473 | 43.7 (38.7; 48.8) n = 389 | 44.1 (39.7; 48.6) n = 501 | 44.8 (40.4; 49.3) n = 498 | –                          | –                           |
| Best response after first progression, n (%) |                    |             |              |              |                           |                             |                              |
| CR                             | 1 (0.3)            | 1 (1.3)     | 0            | 0            | 0                         | 1 (11.1)                    |
| PR                             | 14 (4.6)           | 6 (7.5)     | 4 (3.7)      | 4 (3.9)      | 14 (6.4)                  | 0                           |
| SD                             | 67 (21.9)          | 17 (21.3)   | 22 (20.2)    | 27 (26.2)    | 66 (30.1)                 | 1 (11.1)                    |
| PD                             | 224 (73.2)         | 56 (70.0)   | 83 (76.1)    | 72 (69.9)    | 139 (63.5)                | 7 (77.8)                    |
|                                | n = 306            | n = 80      | n = 109      | n = 103      | n = 103                   | n = 9                        |
| ORR-2, % (95% CI)³             | 4.9 (2.8; 8.0) n = 306 | 8.8 (3.6; 17.2) n = 80 | 3.7 (1.0; 9.1) n = 109 | 3.9 (1.1; 9.6) n = 103 | 6.4 (3.5; 10.5) n = 219 | 11.1 (0.3; 48.2) n = 9       |
| DCR, % (95% CI)³               | 75.3 (73.0; 77.5) n = 1,473 | 73.0 (68.3; 77.4) n = 389 | 72.5 (68.3; 76.3) n = 501 | 79.7 (75.9; 83.2) n = 498 | –                          | –                           |

²L, second-line; CI, confidence interval; CR, complete remission; DCR, disease control rate; FAS, full analysis population set; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial remission; RES/AGGR/INDO, predefined subgroups; SD, stable disease. ¹For the post-baseline subgroups, PFS-1, ORR-1, DCR, and OS, which are evaluated from baseline, are not presented as they can only be determined after the occurrence of a post-baseline first progression event. ²95% CI according to Brookmeyer and Crowley. ³95% CI according to Clopper-Pearson.
**Discussion**

**Strengths and Limitations of the Study**

With 2,429 eligible adult mCRC patients observed at 314 study sites in Germany, KORALLE observed a large unselected population, which led to a high generalizability of the results. The study observed treatment with bevacizumab (Avastin®, Roche); the transferability of the results to biosimilars is unknown. Subgroups defined by therapy goal were essentially balanced in terms of size and patient characteristics at first-line decision making. The subgroup of patients with second-line therapy without bevacizumab (n = 60) was much smaller (patients with bevacizumab: n = 759), which limits the comparability.

The study analyzed effectiveness for three predefined subgroups by investigator-assessed therapy goal, taking into account the clinical and individual situation of the patient. Surprisingly, the effectiveness results between the FAS and those subgroups are not markedly different. The documented primary treatment goals also do not clearly show the expected differences corresponding to the subgroups (Fig. 2b). A possible explanation for this is that the allocation of patients to the subgroups according to therapy goal was not implemented in line with the S3 guideline.

In line with this explanation, concomitant chemotherapy did not vary much between subgroups (Fig. 2a). Alternatively, if the optimal chemotherapy intensity was chosen, i.e., intensive for ambitious goals in the "AGGR"

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**Table 2. Overview of adverse events (FAS)**

| Patients, n (%) – Events, n FAS (n = 2,429) |
|-----------------------------------------------|
| Any adverse event                              | 1,965 (80.9) – 11,245 |
| CTCAE grade 3                                  | 935 (38.5) – 1,729    |
| CTCAE grade 4                                  | 95 (3.9) – 116        |
| CTCAE grade 5                                  | 211 (8.7) – 271       |
| Preferred terms reported for ≥10% of patients: |
| Diarrhea                                       | 728 (30.0) – 1,158    |
| Nausea                                         | 454 (18.7) – 649      |
| Fatigue                                        | 338 (13.9) – 430      |
| Serious adverse events                         | 888 (36.6) – 1,786    |
| Preferred terms reported for ≥2% of patients:  |
| Diarrhea                                       | 106 (4.4) – 123       |
| General physical health deterioration          | 99 (4.1) – 102        |
| Pulmonary embolism                             | 66 (2.7) – 66         |
| Adverse events related to bevacizumab or capecitabine² |
| Preferred terms reported for ≥1% of patients:  |
| Proteinuria                                    | 92 (3.8) – 121        |
| Hypertension                                   | 77 (3.2) – 92         |
| Diarrhea                                       | 31 (1.3) – 32         |
| Pulmonary embolism                             | 29 (1.2) – 29         |
| Nausea                                         | 26 (1.1) – 26         |
| Serious adverse events related to bevacizumab or capecitabine² |
| Preferred terms reported for ≥0.5% of patients: |
| Pulmonary embolism                             | 23 (0.9) – 23         |
| Adverse events leading to discontinuation of study medication |
| Preferred terms reported for ≥1% of patients:  |
| General physical health deterioration          | 51 (2.1) – 52         |
| Diarrhea                                       | 36 (1.5) – 37         |
| Pulmonary embolism                             | 36 (1.5) – 36         |
| Fatal adverse events                           | 214 (8.8) – 274       |
| Preferred terms reported for ≥0.5% of patients: |
| Death                                          | 44 (1.8) – 44         |
| General physical health deterioration          | 42 (1.7) – 42         |
| Ileus                                          | 11 (0.5) – 11         |

Only treatment-emergent adverse events are shown. CTCAE, Common Terminology Criteria for Adverse Events; FAS, full analysis population set. ¹Three additional patients had a fatal event without documented CTCAE severity grade. ²Underreporting expected for adverse events related to capecitabine for technical reasons (no predefined entry fields in electronic case report form); no separate analysis of adverse events related to bevacizumab or to capecitabine available.
group versus lower intensity (e.g., monotherapy) in “INDO” patients, similarly favorable results would be expected in these groups. So, the similar effectiveness results of these groups might imply that the right intensity was generally chosen.

The NIS observed clinical practice without giving the treating physicians any specifications regarding monitoring or treating the disease. Tumor assessment was not standardized by the protocol; assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) was therefore optional and no confirmation was required. This may have affected, to some extent, the results on PFS and ORR, but it reflects routine clinical practice. There was a high number of patients (n = 956; 39.4%) without tumor assessment for ORR-1. Although assessment of treatment course is done generally, only 306 (12.6%) patients had a documented tumor assessment for ORR-2.

The relatedness of adverse events to bevacizumab and/or capecitabine was only assessed collectively and not separately. Before November 2017, only bevacizumab was specified in the electronic case report form (eCRF), while capecitabine could only be entered manually as a possible causal drug. An underreporting especially of capecitabine-related adverse events has to be assumed.

Although queries were sent to the study sites to complete missing data, a considerable number of data remained missing until database lock. A high number of missing data were related to the time of the second onset of progressive disease, potentially affecting the outcome of PFS-2.

It is noticeable that in KORALLE, a high proportion of patients had left-sided tumors (64.9%), which is associated with a better prognosis than right-sided tumors [18]. With RAS testing and the knowledge of the sidedness-dependent efficacy for anti-EGFR inhibitors nowadays [19], this percentage would probably be markedly lower. The mutation status of primary tumors was documented in this study (online suppl. Table S2). However, a high proportion of patients without assessment of the mutation status or with the mutation status “unknown” (RAS: 30.7% of the FAS; BRAF: 81.4% of the FAS) limits the interpretability of the corresponding data. In the time-to-event analyses, a high number of cases were censored (online suppl. Fig. S2).

KORALLE Results in the Context of Other Studies

A direct comparison between the results of a NIS and randomized controlled trials is limited by differences in patient characteristics and the study setting based on the narrowness of selection criteria and the specification of assessment schemes by the protocol. Nevertheless, we place the data obtained in this NIS in the context of pivotal trials to see how the clinical efficacy documented in clinical trials is reflected in routine clinical practice in Germany.

Median PFS-1 observed in the FAS of KORALLE (10.3 months; n = 2,429) was similar to the median PFS (10.6 months; n = 402) in the bevacizumab arm of the double-blind, controlled phase III trial [3] on first-line therapy of mCRC treated with bevacizumab (5 mg/kg BW every 2 weeks) in combination with irinotecan, bolus 5-fluorouracil and leucovorin. The same applies to the ORR (KORALLE FAS, ORR-1 44.2%; bevacizumab arm of phase III trial [3], ORR 44.8%). Median OS (16.9 months) in the FAS of this NIS, however, was shorter than median OS (20.3 months) in the bevacizumab arm of the phase III trial.

Median PFS-2 in patients with second-line chemotherapy with (4.5 months; n = 466) or without bevacizumab (3.9 months; n = 31) in KORALLE (Table 1) was shorter than median PFS (5.7 months; n = 409) in the bevacizumab plus chemotherapy group reported in the randomized, open-label phase III trial ML18147, in which patients were treated with bevacizumab beyond first progression (either 5 mg/kg BW every 2 weeks or 7.5 mg/kg BW every 3 weeks; oxaliplatin- or irinotecan-based second-line chemotherapy; starting point of PFS and OS was randomization) [9].

With second-line bevacizumab in KORALLE, 14 (6.4%) patients were assessed with CR or PR (Table 1), similar to the ML18147 trial (22/404 patients; 5.4%). Overall, ORR-2 in this NIS and ORR in the ML18147 trial were similar for patients having received continued bevacizumab therapy (beyond first progression) in the second-line setting [9], although the number of patients in the KORALLE subgroup of patients with second-line bevacizumab who had a documented tumor assessment after first progression (n = 219; 28.9%) was low (Table 1).

In the context of the pivotal controlled trials, it is worth noting that patient age in the real-world population of NIS KORALLE was expectedly higher: While the mean age was 59.5 years in the bevacizumab cohort (n = 402) of Hurwitz et al. [3] and the median age was 63 years (range: 27–84) in the bevacizumab cohort (n = 409) of Bennouna et al. [9], in the FAS of the NIS KORALLE the median age was 69 years (range: 27–89; online suppl. Table S2) and 687 (28.3%) patients were aged ≥75 years.

Conclusions

KORALLE showed that first-line bevacizumab therapy and bevacizumab therapy beyond first progression is effective in a large, unselected population in routine clinical practice. Despite different treatment intentions, the combination of bevacizumab plus fluoropyrimidine-based chemotherapy was similarly effective in all subgroups. The results of the NIS KORALLE are in line with
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Statement of Ethics

The study was approved by the Ethical Committee of the Medical Association Hamburg (Ärztekammer Hamburg), Germany, on November 13, 2012 (reference PV4214). All patients gave signed, informed consent to participate in the study.

Conflict of Interest Statement

Dirk Arnold: Consultancies: Astra Zeneca, Bayer, BMS, Boston Scientific, Eli Lilly, Merck Serono, Mologen, Oncolytics, MSD, Roche, Sanofi, Servier, Sirtex, and Terumo; Honoraria: Amgen, Astra Zeneca, Bayer, BMS, Boston Scientific, Merck Serono, Roche, Sanofi, Servier, Sirtex, Terumo, Art Tempi, PriME Oncology, and TRM Oncology; Grants: Astra Zeneca, InCyte, MSD, Roche, and Sanofi. Egbert Eggers: Consultancies: Dres. Schlegel + Schmidt and iOMEDICO; Grants: Amgen, Eugastro, Pharm-Allegeran, Biotest, Merck, Novartis, and Sanofi. Jens Uhlig: Consultancies and Honoraria: Roche, Amgen, Servier, MSD, Bristol-Myers Squibb, Sanofi, Merck, Novartis, Janssen-Cilag, Boehringer-Ingelheim, and Bayer. Dietmar Reichert: Grants: Amgen/Onyx, Baxter, Bayer, Biotest, Bristol-Myers Squibb, Celgene, Janssen-Cilag Ltd, Kedrion Biopharma, Eli Lilly, Merck Serono, Novartis, Octapharma, Pfizer, Pharma Mar, Puma Biotechnology, Roche, Sanofi, Teva Pharmaceutical, Abbvie, Ipsen, and Servier.

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Author Contributions

Dirk Arnold, Egbert Eggers, Jens Uhlig, Dietmar Reichert, Lars Becker, and Lars Thiebach conceptualized and designed the study. Dirk Arnold, Egbert Eggers, Jens Uhlig, Dietmar Reichert acquired data. Dirk Arnold, Egbert Eggers, Jens Uhlig, Dietmar Reichert, Lars Becker, and Lars Thiebach analyzed and interpreted data. All the authors wrote, reviewed, and/or revised the manuscript. All the authors approved the final manuscript.

Data Availability Statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivi.org/). Further details on Roche’s criteria for eligible studies are available here (https://vivi.org/members/ourmembers/). For further details on Roche’s Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/criteria_for_eligible_studies.htm). For further details on Roche’s criteria for eligible studies are available here (https://www.roche.com/research_and_development/who_we_are_how_we_work/criteria_for_eligible_studies.htm). For further details on Roche’s criteria for eligible studies are available here (https://www.roche.com/research_and_development/who_we_are_how_we_work/criteria_for_eligible_studies.htm).

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