NON-INTERVENTIONAL STUDY REPORT

TITLE:

AVASTIN® first line in metastatic Renal Cancer

Study Number:	ML21519
Clinical Phase:	Post-Marketing
Investigational Medicinal Product:	AVASTIN® (Bevacizumab)
Indication Studied:	Advanced and/or metastatic renal cell cancer
Study Initiated:	08 January 2008 (First Patient In)
Study Completed:	26 September 2014 (Last Patient Follow-Up)

Scientific Coordinator

[redacted]

Sponsor

Medical Manager, Roche, Grenzach:

[redacted]

Statistician:

Non-interventional study – AVASTIN® first line in metastatic Renal Cancer

SIGNATURES

By signing this report we certify that it provides a true and accurate record of the conduct of this study and its results.

[redacted]

[redacted]

[redacted]

Non-interventional study – AVASTIN® first line in metastatic Renal Cancer

ORIGINAL

SIGNATURES

By signing this report we certify that it provides a true and accurate record of the conduct of this study and its results.

2. SYNOPSIS

Name of Sponsor/Company: [redacted]	Individual Study Table Referring to Part of the Dossier: NA Volume: NA Page: NA	(For National Authority Use only)
Name of Finished Product: Avastin®		
Name of Active Substance: Bevacizumab		

Title of study:
Non-interventional study AVASTIN® first line in metastatic Renal Cancer

Protocol ID:
The study was based on the consolidated observational plan version 6.0 dated 18.11.2010. This protocol version included amendment 01, version 2.0 dated 20.05.2008 and amendment 02, version 2.2 dated 18.11.2010

Study Number: ML21519

Scientific Coordinator:
[redacted]

Study centres:
The study was performed by 136 medical oncologists and urologists in hospitals and private practices, qualified in anti-tumour therapy, throughout Germany

Publication (reference): **NA**

Studied period (months):	81 months	**Clinical phase:** Post-marketing
(date of first enrolment)	08 January 2008	
(date of last follow-up)	26 September 2014	

Objectives:
The objective of this non-interventional study (NIS) was the collection and documentation of data on safety and effectiveness of Avastin® in combination with interferon alpha-2a immunotherapy for first-line treatment in patients with advanced and/or metastatic renal cell cancer (mRCC) in daily routine.

Methodology:
Non-interventional, multi-centre, defined population, prospective cohort observation

Number of patients (planned and analysed):

Planned: 400 patients

Although 407 inclusion faxes were received, 38 documentation folders were not returned by the respective investigators. Four patients with no valid informed consent form were excluded from the analysis sets as determined in the data review meeting.

Analysed: 365 patients were documented in the all patients set and
359 patients included in the safety set (SAF);
354 patients were analysed in the full analysis set (FAS);
353 patients were analysed in the per protocol set (PPS).

Diagnosis and main criteria for selection:

- Age ≥18 years
- Histologically confirmed advanced and/or metastatic renal cell cancer
- No contraindications to Avastin® and concomitant medication according to the current Summary of Product Characteristics (SmPC) for Avastin®
- Therapeutic decision for Avastin® as first line treatment in combination with immunotherapy (interferon alpha-2a) was taken individually and independent of the non-interventional study

Name of Sponsor/Company: Roche Pharma AG	Individual Study Table Referring to Part of the Dossier: NA Volume: NA Page: NA	(For National Authority Use only)
Name of Finished Product: Avastin®		
Name of Active Substance: Bevacizumab		

Product, dose and mode of administration:

Application of immunotherapy and Avastin should follow recommendations given in the current SmPC. The recommended dose for Avastin was 10 mg/kg body weight given once every 2 weeks as intravenous infusion. IFN alfa-2a could be given until disease progression at a recommended starting dose of 9 MIU three times a week allowing a dose reduction to 3 MIU in 2 steps.

Normal merchandise was to be used and was reimbursed by the respective national or private health insurance.

Main parameters of interest:

- Effectiveness (response rate, progression free survival [PFS]) in large patient populations
- Administration of immunotherapy and Avastin® (dose, regimen, duration etc.) and cumulative doses in daily routine
- Adverse drug reactions: type, course, measures taken, with special interest on wound healing disorder, gastrointestinal perforation, arterial and venous thromboembolic events, cerebral and other haemorrhage.
- Collection of any new information or changes of already known adverse drug reactions with Avastin® in routine clinical practice
- Reasons for treatment discontinuation or modifications

Statistical methods:

Based on the AVOREN study results with 327 patients treated with bevacizumab + IFN and on the planned sample size of the current study with 400 patients, the therapeutic effectiveness in terms of overall response rate (ORR) with 95% confidence intervals (CI) was expected to be:
ORR = 30.6%, 95% CI = (26.1% - 35.1%).

The estimate for progression free survival (PFS) was 10.2 months, 95% CI = (9.5 – 10.9 months).
The estimate for 12 months PFS was 44.2%, 95% CI = (41.7% - 46.6%).

The data were evaluated using descriptive statistical methods. No explicit statistical testing was specified. Time-to-event analyses were performed using Kaplan-Meier-methodology.

SUMMARY

The safety set included 359 mRCC patients from 136 centres in Germany who were evaluated in the current NIS. 354 patients were evaluable in the FAS. One patient was excluded from the per protocol sample due to the protocol violation 'no combination treatment with interferon alpha' classified as major deviation. The total mean observation duration for patients with data available in the safety set (n=359) was 286.7 days (SD=227.2) and median duration was 217.5 days (range 1 to 985).

Mean (±SD) patient age was 65.5 (±10.1) years. 59.6% of the patient population was 65 years of age or older. Male patients accounted for 68% of the study population. The mean body weight (BW) at inclusion was 81.8 kg (±16.5) for all patients, mean BMI was 27.7 (±4.9). About 36% of patients had a Motzer score of 0 (favourable risk) and 50.3% had 1-2 risk factors (intermediate risk). Mean Karnofsky performance index at baseline was 85.7 (±11.7). 71.9% of the patients were diagnosed with advanced stage IV disease at the start of the observation; 69.3% had metastases spread lung, lymph nodes (26.4%), and/or bones (23.2%). Most of the patients (87.2%) had histologically confirmed clear cell carcinoma. 91% underwent surgery with a mean time since operation of 34.1 months.
On average, Avastin® was administered for a mean duration of 266.1 days (SD=223.7) during 16.6

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cycles (SD=14.0). The median dose per infusion throughout all cycles was 10 mg/kg BW. The main combination used at least once for patients evaluated in the FAS was Avastin® with interferon (99.7%). Interferon alpha-2a was administered at a median dose of 3 million IU throughout all treatment cycles. About 45% of patients received second line therapies during the 12-month follow-up phase. Most of them (36.2%) were treated with antineoplastic agents.

EFFECTIVENESS RESULTS:

Best tumour response over time (assessed as per clinical routine of the individual centre) showed that complete response (CR) was achieved by 18 (5.3%) of the patients. 74 (21.9%) of patients obtained partial remission (PR) and 132 (39.1%) were assessed with stable disease (SD). The disease control rate (DCR), defined as percentage of patients who have achieved complete response, partial response or stable disease during the course of the observation was 66.3% for the FAS population. The mean Karnofsky performance status at the end of the study was 78.3 (±16.5), median 80.0.

ORR calculated as percentage of patients with CR and PR was 27.2%. The Kaplan-Meier estimate of time until progression resulted in a median PFS of 10.2 months (95%CI: 8.6; 12.6). 50% of the patients were within the range of 4.2 and 18.5 months until estimated disease progression. The event rate was 62.5% in the FAS and 62.3% for the PP population. The Kaplan-Meier survival distribution function estimate for 12 months PFS was 45% (95%CI: 39%; 51%). All three parameters are in line with expected values.

The median overall survival estimate for patients observed in the FAS and PPS was 28.7 months (95%CI: 24.5; 38.3) with an event rate of 38.8% in the FAS and 39.0% for the PPS. The Kaplan-Meier survival distribution function estimate for 12 months overall survival was 76% (95%CI: 71%; 80%).

SAFETY RESULTS:

11377 adverse events (AEs) were observed in 334 patients (incidence of 93.0%). Out of these, 72 patients (20.1%) experienced serious AEs and for 70 patients (19.5%) the AE was classified as AE of special interest.

AEs (any causality) with grade ≥3 toxicity according to the NCI Common Toxicity criteria (version 3.0) were reported for 132 patients (36.8%). The most frequently affected SOC was 'Blood and lymphatic system disorders' with 13.1%, followed by 'General disorders' with 10.9%. The most frequent reported preferred term was anaemia in 28 (7.8%) patients, a common side effect of interferon therapy.

Incidences for AEs of special interest were: epistaxis 9.7% (grade ≥3: 0.1%), haemorrhage 4.7% (none grade ≥3), gastrointestinal perforation 0.8% (none grade ≥3) and diverticular perforation 0.3% (grade 3), impaired healing 0.8% (none grade ≥3) and pulmonary embolism 0.3% (grade 4).

Serious AEs ≥3 were reported for 6.7% of the study population. Four patients (1.2%) had hypertension, 2 patients (0.6%) a hypertensive crisis, 2 patients (0.6%) suffered from diarrhoea and 4 patients (1.1%) from anaemia. Two patients experienced SAEs with fatal outcome (multi-organ failure and pulmonary embolism) considered as related to Avastin® by the investigators.

The main reason for end of study was cancer progression of the underlying disease in 51.8% of the patients. 143 patients (40.9%) died during the course of the observational study, 120 patients died from the underlying disease and for 18 patients the investigator stated death from other cause (causality unknown) as reason for the end of treatment. For 5 patients no information about the cause of death was received.

Name of Sponsor/Company: Roche Pharma AG	Individual Study Table Referring to Part of the Dossier: NA Volume: NA Page: NA	(For National Authority Use only)
Name of Finished Product: Avastin®		
Name of Active Substance: Bevacizumab		

DISCUSSION:

The current observational study was already planned in 2007 with the objective to collect data on safety and effectiveness of Avastin® in combination with interferon alpha immunotherapy in a large, unselected patient population. The advantage of a non-interventional descriptive study design is the collection of 'real world data' under daily routine practice conditions, as allocation of exposure is not determined by a pre-defined protocol. Following the applicable guidelines at that time, no source data verification or selective monitoring of the main outcome parameters was performed. This can lead to incomplete and sometimes inconsistent data and therefore hampers direct comparison to controlled clinical trials (RCTs). In addition other confounding factors, the lack of in and exclusion criteria and differences in response measurements lead to non-comparability of populations.

Nevertheless, the observed PFS of 10.2 months together with the PFS event free rate of 45% at 12 months in this study replicate the results from the AVOREN trial (4). The overall response rate published for AVOREN is slightly higher with 31% vs 27.2% in the current NIS.

The median OS time of 28.7 is within the range of values reported in the literature. Median OS time was 23.3 months in the Avastin plus IFN arm of the AVOREN trial (4), 18.3 months (Avastin plus IFN group) for CALGB (5) and 30.7 months in the BEVLiN study, a single-arm phase II trial investigating Avastin with low-dose IFN (6).

The comparison of baseline characteristics with results for AVOREN revealed no relevant differences to the pivotal AVOREN trial with regard to gender distribution, mean age (ML 21519: 65.5 years vs AVOREN: 61 years), risk score (ML 21519: favourable + intermediate risk 86.4% vs AVOREN: 83%), localisation of metastases (ML 21519: lung 69%, lymph nodes 26%, bone 23% vs AVOREN: 62%, 34% and 18%). Only the baseline Karnofsky performance index assessed as further prognostic score was higher for AVOREN patients, probably due to the fact that performance status of 70% or more was one of the eligibility criteria. 76% of patients in the AVOREN Avastin plus IFN arm patients had baseline scores of 90-100 vs 55% in the current NIS.

No sub-group analyses according to risk scores as described in AVOREN were performed in ML21519 to allow direct comparison to the results of the BEVLiN trial.

However, there is a noticeable difference in median treatment duration regarding the Avastin® plus IFN arm of previous clinical trials and the current study. The median duration of Avastin® treatment was 9.7 months for AVOREN, 10 months with 22.5 cycles in the BEVLiN trial, 8.2 cycles of 28 days duration in the CALGB trial, and 6.5 months during 13 cycles in the current NIS It might be speculated that investigators in the real life setting do not use Avastin® until diseases progression while still meaningful efficacy parameters similar to AVOREN were observed.

Overall AE and SAE incidences of 93% and 20% were similar to those reported for AVOREN (AE:97%, SAE:29%) (4) and CALGB (AE:99%, no SAEs specified) (5). Incidences for grade ≥3 toxicities were distinctly lower (ML 21519: 36.8%, AVOREN 84.2%, CALGB: 80%), probably due to the general risk of under-reporting of AEs in uncontrolled observational studies.

CONCLUSION:

In general, results from this non-interventional study replicate the results of the phase III AVOREN study which demonstrated that Avastin® in combination with interferon alpha immunotherapy improves overall response and time to progression in patients with advanced and/or metastatic renal cell cancer (mRCC).

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The safety profile is comparable to those found in RCTs and previously published data (4,5). No new safety signals were detected in patients treated within the mRCC NIS. The NIS data replicate the favourable results for Avastin® demonstrated in AVOREN and provide real word data support for the utility of Avastin® in the treatment of advanced mRCC.		
Date of report: 08 February 2016		

3. TABLE OF CONTENTS

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3.2 Directory of Text Figures

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse event of special interest
ALL	All Patients Set
AMG	Arzneimittelgesetz (German Drug Law)
AMS	AMS Advanced Medical Services GmbH (CRO)
ATC	Anatomical Therapeutic Chemical Classification System
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CHF	Congestive heart failure
CI	Confidence Interval
CNS	Central nervous system
CRF	Case Report Form
CRO	Contract Research Organisation
CTC	Common Toxicity Criteria
EC	European Community
EM(E)A	European Agency for the Evaluation of Medicinal Products
FAS	Full Analysis Set
GCP	Good clinical Practice
GI	Gastrointestinal
Hb	Haemoglobin
HLGT	High level group terms
HLT	High level term
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFN	Interferon
IU	International unit
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mRCC	Metastatic renal cell cancer
NCI	National Cancer Institute
ORR	Overall Response rate
OS	Overall Survival
PEI	Paul-Ehrlich-Institut
PPS	Per Protocol Set
PT	Preferred term
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
UICC	Union for International Cancer Control
WHO-ART	World Health Organization Adverse Reaction Terminology

5. ETHICS

5.1 Independent Ethics Committee (IEC)

The observational plan was submitted to the Ethics Committee of the 'Albert-Ludwigs-Universität' in Freiburg prior to start of the observation. A formal approval was received on 04 December 2007.

The study was announced to the Competent Authority (PEI) according to German Drug Law (§ 67 Abs. 6 AMG) and to the umbrella organizations of the German health insurance system.

5.2 Ethical Conduct of the Study

The study was conducted according to established regulations and recommendations relating to the conduct of a non-interventional study, such as the Declaration of Helsinki and to Good Clinical Practice guidelines, where applicable to a non-interventional study, and according to relevant local laws, regulations and organisations.

5.3 Patient Information and Consent

All patients were informed about documentation of their treatment data within a non-interventional study. The patients' written consent to collecting and processing of their treatment data according to the current data protection law was obtained by Roche Pharma AG prior to inclusion. Only patients who had consented to the processing of their data with their signature were evaluated in the current analysis.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was sponsored by [redacted] The sponsor authorized the contract research organisation [redacted] to perform the project-coordination and data management of the study. In March 2012 this task was transferred to another [redacted] took over the data management, statistical evaluation and medical writing of the non-interventional study. Overall project-management was performed by the sponsor.

The management of adverse event data (acceptance, cleaning and maintenance of the clinical database) was performed by the respective CRO [redacted] Notification forms were forwarded to [redacted] Medical Affairs/ Drug Safety Department within 24 hours. A reconciliation of serious adverse events (SAEs) and adverse events of special interest (AESIs) was performed on a regular basis.

Due to the non-interventional character of the observation, no principal or coordinating investigator had to be nominated. Scientific study coordinator was [redacted]

6.1 Study Sites

Overall 137 oncological centres throughout Germany participated in the study. Centre no 284 had to be excluded from the analyses due to missing patient informed consent forms, thus data from136 centres were evaluated.

6.2 Sponsor's Representatives

The project management at [redacted] was performed by [redacted] from September 2012 until August 2013, [redacted] until December 2014 and Dr. [redacted] from January 2015.

The sponsor's medical managers were [redacted] was responsible for project coordination, data-management, statistical analyses, and for medical writing of the study report from March 2012 to the end of the study. The statistical analyses were performed by [redacted]

Names and functions of all staff involved will be supplied upon request.

7. INTRODUCTION

The renal cell carcinoma comprises approximately 85% of all malignant kidney tumours. In Germany, the rate of newly diagnosed diseases is estimated to be at 15,000 /year. Men are about 1.5-times more often afflicted than women. Together with the carcinomas of the renal pelvis and the ureters, renal cell carcinomas account for 3.6% and 2.5% of the newly diagnosed malignancies in men and women, respectively. The incidence rate increased until the middle of the 1990s and has since remained fairly constant. The median age of the patients at diagnosis ranges between 65 and 70 years for men, and lies over 70 years for women [1].

Common risk factors are obesity, chronic renal insufficiency, smoking, antihypertensive therapy, occupational exposure to halogenated hydrocarbons and long-term exposure to X-rays.

Avastin contains the active substance bevacizumab, a recombinant humanised monoclonal antibody. Bevacizumab binds selectively to the human vascular endothelial growth factor (VEGF).

The safety and efficacy of Avastin, in combination with interferon alfa-2a for the first-line treatment of advanced and/ or metastatic renal cell cancer was investigated in the Phase III trial BO17705 (AVOREN Trial). The average progression-free survival was 10.2 months in the patients receiving Avastin and 5.4 months in those receiving placebo (SmPC Section 5.1).

BO17705

This was a phase III randomised double-blind trial conducted to evaluate the efficacy and safety of Avastin in combination with interferon (IFN) alfa-2a versus IFN alfa-2a alone as first-line treatment in mRCC. The 649 randomised patients (641 treated) had Karnofsky Performance Status (KPS) of ≥ 70%, no CNS metastases and adequate organ function. Patients were nephrectomised for primary renal cell carcinoma. Avastin 10 mg/kg was given every 2 weeks until disease progression. IFN alfa-2a was given up to 52 weeks or until disease progression at a recommended starting dose of 9 MIU three times a week, allowing a dose reduction to 3 MIU three times a week in 2 steps. Patients were stratified according to country and Motzer score and the treatment arms were shown to be well balanced for the prognostic factors.

The primary endpoint was overall survival, with secondary endpoints for the trial including progression-free survival. The addition of Avastin to IFN-alpha-2a significantly increased PFS and objective tumour response rate. These results have been confirmed through an independent radiological review. However, the increase in the primary endpoint of overall survival by 2 months was not significant (HR= 0.91). Although the primary end point of the AVOREN trial was overall survival, progression-free survival was used to evaluate efficacy and to support regulatory submissions because second-line therapies that became available while the trial was ongoing could have confounded OS analyses resulting in the prolongation of overall survival in both experimental and control arms [4].

A high proportion of patients (approximately 63% IFN/placebo; 55% Avastin/IFN) received a variety of non-specified post-trial anti-cancer therapies. Tyrosine-kinase inhibitors (TKIs) were the most common post-protocol therapy, received by 113 (35%)

and 120 (37%) patients in the bevacizumab + IFN and IFN + placebo arms, respectively, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 14 of the SmPC [3]

Efficacy results for trial BO17705

	Placebo + IFN[a]	Bv[b] + IFN[a]
Number of patients	322	327
Progression-free survival		
Median (months)	5.4	10.2
Hazard ratio	0,63	
95 % CI	0.52; 0.75	
	(p-value < 0.0001)	
Objective response rate (%) in patients with measurable disease		
N	289	306
Response rate	12.8%	31.4%
	(p-value < 0,0001)	

a Interferon alfa-2a 9 MIU 3x/week
b Bevacizumab 10 mg/kg q 2 wk

Overall survival		
Median (months)	21.3	23.3
Hazard ratio	0.91	
95 % CI	0,76, 1.10	
	(p-value 0.3360)	

An exploratory multivariate Cox regression model using backward selection indicated that the following baseline prognostic factors were strongly associated with survival independent of treatment: gender, white blood cell count, platelets, body weight loss in the 6 months prior to trial entry, number of metastatic sites, sum of longest diameter of target lesions, Motzer score. Adjustment for these baseline factors resulted in a treatment hazard ratio of 0.78 (95% CI [0.63; 0.96], p=0.0219), indicating a 22% reduction in the risk of death for patients in the Avastin + IFN alfa-2a arm compared to IFN alfa-2a arm.

Ninety seven (97) patients in the IFN alfa-2a arm and 131 patients in the Avastin arm reduced the dose of IFN alfa-2a from 9 MIU to either 6 or 3 MIU three times a week as pre-specified in the protocol. Dose-reduction of IFN alfa-2a did not appear to affect the efficacy of the combination of Avastin and IFN alfa-2a based on PFS event free rates over time, as shown by a sub-group analysis. The 131 patients in the Avastin + IFN alfa-2a arm who reduced and maintained the IFN alfa-2a dose at 6 or 3 MIU during the

trial, exhibited at 6, 12 and 18 months PFS event free rates of 73, 52 and 21% respectively, as compared to 61, 43 and 17% in the total population of patients receiving Avastin + IFN alfa-2a.

The open-label, phase III Cancer and Leukemia Group B (CALGB) 90206 trial comparing bevacizumab plus IFN with IFN monotherapy also showed significant PFS and ORR benefits for bevacizumab plus IFN (median PFS, 8.4 v 4.9 months, respectively; HR = 0.71; P < .001, stratified; ORR, 25.5% v 13.1%, respectively, stratified). Differences in the patient populations of these trials do not allow direct comparisons with AVOREN. Median OS has also been reported for the CALGB 90206 trial (18.3 months for bevacizumab plus IFN v 17.4 months for IFN monotherapy; HR = 0.86; P = .069, stratified). Reasons for the nonsignificant improvement in OS may also include the impact of postprogression therapies [5].

BEVLiN was an open-label, single-arm, multinational, phase II trial to evaluate bevacizumab with low-dose IFN in mRCC patients. A total of 146 patients were treated; the median follow-up was 29.4 months. Any-grade and grade ≥3 IFN-associated AEs occurred in 53.4% and 10.3% of patients, respectively. The median PFS and overall survival were 15.3 [95% confidence interval (CI): 11.7-18.0] and 30.7 months (95% CI: 25.7-not reached), respectively. The ORR was 28.8%. Compared with a historical control AVOREN subgroup, low-dose IFN with bevacizumab resulted in a reduction in incidence rates of IFN-related AEs, without compromising efficacy [6].

In December 2007 the marketing authorization for Avastin® as first line therapy in the treatment of advanced RCC was granted for the EU.

The present post authorisation non-interventional study was planned as a prospective cohort study enrolling patients with advanced and/or metastatic renal cell cancer (mRCC) treated with Avastin® under routine conditions in a widespread use.

8. STUDY OBJECTIVES

The objective of this non-interventional study was the collection and documentation of data on safety and effectiveness of i.v. Avastin® in combination with interferon alpha-2a for first-line treatment of patients with advanced and/or metastatic renal cell cancer (mRCC) in daily routine.

The following questions were addressed:

- Effectiveness (response rate, overall survival (OS) and progression free survival [PFS]) in a large real-world patient population
- Administration of immunotherapy (interferon alpha-2a) and Avastin® (dose, regimen, duration etc.) and cumulative doses in daily routine
- Adverse events: type, course, measures taken, with special focus on wound healing disorder, gastrointestinal perforation, arterial and venous thromboembolic events, cerebral and other haemorrhage
- Collection of any new information or changes of already known adverse drug reactions with Avastin® in routine clinical practice
- Reasons for treatment discontinuation or modifications

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan Description

The study was performed by 136 medical oncologists and urologists in hospital and private practices, qualified in the treatment of mRCC, throughout Germany between January 2008 and September 2014. Total study duration was 81 months. First patient, first visit (informed consent signed) was on January 08, 2008; last patient, end of follow-up was on September 26, 2014.

Patients were treated with Avastin® according to the current SmPC section 4.1 and 4.2 of Avastin®.

The decision about the duration of treatment with Avastin® was at the discretion of the physician and was independent from participation in this non-interventional study. Within this study the treatment observation was planned to be 52 weeks per patient (6 x 3 bi-weekly cycles of immunotherapy in addition to Avastin® until progression).

All patients were to be observed until progression or intolerable toxicity, whichever occurred first. A final documentation was to be performed within 4 weeks after end of treatment with Avastin®, regardless of further therapy options. 12 months after the end of the study a follow-up visit was to be performed to evaluate 2nd line treatment, tumour response and survival status.

Only patients receiving standard treatment with Avastin® were included in the study following the schedule below.

Table 9-1 Overview of observations

Type of assessment	Start of observation	ongoing (every 2 weeks)	Final examination
Demographic data (year of birth, gender)	X		
Cancer history (Initial diagnosis, surgery, recurrence, tumour stage, distant metastases)	X		
Relevant pre-and coexisting conditions	X		
Vital signs (body weight, height, body surface area, Motzer-Score, blood pressure)	X		
Laboratory parameters	X		
General condition (Karnofsky Performance Status)	X	X	X
Systemic therapy (therapy administered, dose deviations, therapy interruption, discontinuation)		X	
Combination Therapy		X	
Current tumour status		X	
Adverse Events (Toxicity)		X	
End of therapy (date, reason)			X
Best tumour response (over time)			X
Subsequent therapy			X

Serious Adverse events and Adverse events of special interest were to be reported on the additional forms 'Meldeformular: Schwerwiegende unerwünschte Arzneimittelwirkung (Beobachtungsstudie)' and 'Formular zum Berichten von unerwünschten Ereignissen (Beobachtungsstudie)', Pregnancy were to be reported on 'Clinical Trial Pregnancy Reporting Form'.
12 month after end of study: Follow-up documentation of 2nd-line therapies and assessment of survival status

9.2 Discussion of Study Design

In clinical trials, where physicians and patients have to follow a predefined diagnostic and therapeutic regimen, subjects have to be informed extensively about modalities and have to provide their informed consent before inclusion. Therefore, a selection bias cannot be fully excluded. In contrast, a non-interventional study reflects the routine use of medication and the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice. It is the appropriate tool to generate representative data for effectiveness and tolerability of a listed drug under routine conditions.

A non-interventional, multi-centre, defined population, prospective study design was chosen following current guidance documents: 'Empfehlungen zur Planung und Durchführung von Anwendungsbeobachtungen' of the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM), 7.Juli 2010.

9.3 Selection of Study Population

- Suitable patients for this non-interventional study were selected after the physician had chosen this treatment in his daily routine. Patients with diagnosed histologically confirmed advanced and/or metastatic renal cell cancer could be included in the observation. All patients were informed about documentation of their treatment data within a non-interventional study. The patients' written consent to collecting and processing of their treatment data according to the current data protection law by Roche Pharma AG was obtained prior to inclusion.

Patients were eligible for enrolment if the following applied:

- Avastin® is given according to the SmPC, in combination with interferon alpha-2a immunotherapy for first-line treatment of adult patients with histologically confirmed advanced and/or metastatic renal cell cancer
- No contraindications to Avastin® according to the current SmPC section 4.3.
- Signed written informed consent

Patients presenting the following conditions should not be included in the observational study:

- Treatment not according to current Avastin® SmPC
- Contraindication to Avastin® according to the current SmPC section 4.3.
- No signed written informed consent

Patients could withdraw their consent at their own request without providing any reason. Decisions on treatment discontinuation or changes were solely based on medical reasons, which were in the best interest of the patients. These decisions were made independent from considerations of continuation in the observation.

9.4 Treatments

Patients were treated with Avastin® (active ingredient bevacizumab) 25 mg/ml concentrate for solution for infusion.

The dose and administration schedule of Avastin® was at the discretion of the treating physician. The investigator should however follow recommendations given in the package leaflet or according to section 4.2 of the current SmPC (see below):

Advanced and/or metastatic renal cell cancer (mRCC)

The recommended dose of Avastin is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion.

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Normal merchandise was to be used and was reimbursed by the respective national or private health insurance.

9.5 Effectiveness and Safety Variables

9.5.1 Effectiveness and Safety Measurements Assessed

The current study focused on the recording of data on safety and effectiveness of Avastin® in combination with immunotherapy. The following parameters were collected within the observational study as part of the clinical routine:

Baseline data

- Demographic data (year of birth, gender)
- Cancer history (Initial diagnosis, tumour stage, surgery, recurrence, current status, distant metastases)
- Relevant pre-and coexisting conditions
- Vital signs:
  - Body weight, height, body surface area, Karnofsky score, Motzer score, blood pressure
- Laboratory parameters:
  - Haemoglobin, Platelets, Leukocytes, Granulocytes, Creatinine, SGPT, SGOT, Bilirubin

Systemic Therapy:

- Description of therapy with Avastin®
- Description of immunotherapy and other combination partner(s)
- Dose deviations
- Therapy interruption
- Permanent discontinuation

Current tumour status

- Staging
- Karnofsky Perfomance Status

Adverse Events (including toxicity based on NCI/CTC (version 3.0)

Incidence rate of the following adverse events of special interest (AESI) according to Amendment 2:

- Wound healing complications
- Gastrointestinal perforation/ fistula
- Haemorrhage (cerebral and/or other)
- Thromboembolism

Progression free survival (PFS)

Overall survival (OS)

Best Tumour Response (over time)

Other parameters:

- End and duration of the observation
- General condition (Karnofsky Performance Status)
- Deaths
- Subsequent therapy

Follow up (12 months after end of non-interventional study)

- Results of 2nd line therapy (if applicable)

9.5.2 Appropriateness of Measurements

All effectiveness and safety parameters measured in this study are accepted standards used in clinical studies.

9.5.3 Main Effectiveness Variables

Effectiveness endpoints were

- Tumour response –Disease Control Rate
- Progression Free Survival defined as time (months) between start of therapy and progression or death
- Overall Survival defined as time (months) between start of therapy and date of death.

9.5.4 Safety Variables

Safety parameters included the occurrence, frequency, nature and severity of adverse events and adverse events of special interest. The type and severity of adverse events were to be assessed on the basis of NCI-CTC-AE criteria (version 3.0) to allow a standardised documentation

Adverse Events

Starting at the first therapy cycle and every visit thereafter, the investigator had to document all adverse events in the CRF giving the following information:

- Description of event,
- Severity
- Seriousness,
- Causal attribution

A Serious Adverse Event (SAE) was defined as any untoward medical occurrence or effect that at any dose:

- Results in death,
- Is life-threatening,
- Requires hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect, or
- Is another medically important condition

Adverse Events of special interest included haemorrhages, gastrointestinal perforation/ fistula, wound healing complications, and thromboembolism.

Serious AEs and AEs of special interest were to be reported on separate report forms within one working day. The report form included: description of event, start date, outcome, causal attribution, and action with regard to study treatment.

9.6 Data Quality Assurance

Appropriate quality control procedures were applied to each stage of data entry and data handling to ensure that all data were reliable and have been processed correctly. The SOP systems of the Sponsor and AMS GmbH were applied.

9.6.1 Case Report Forms

All steps related to the selection and enrolment of patients and the treatment of these patients were in accordance with standard medical care and the current SmPC of Avastin®. Each site received a case report form (CRF) titled "Avastin® first-line beim metastasierten Nierenzellkarzinom", to document baseline characteristics, treatment and its results for each patient. Relevant missing information and discrepancies were to be followed up by queries. The investigator confirmed the accuracy of the data with his signature.

9.6.2 Data Management

The database for this study was maintained by [redacted]. A Data Handling Manual including the description of processes such as handling of CRFs, data cleaning, coding, SAE Reconciliation, CIOMS II Listings and database lock was issued.

The CRFs were entered into the CDMS (Clincase) by data entry staff of [redacted] using single data entry. Guidelines for the data entry staff were detailed in Data Entry Conventions and an Obvious Correction Sheet. Plausibility checks and listings for manual data review are described in the respective Data Validation Plan.

Data handling and storing was done using Microsoft®Windows 7 Ultimate. Data regarding adverse events, previous and concomitant diseases were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1.

Medications were coded using the WHO drug dictionary (WHO DD), version 4.1. The coding was checked subsequently by qualified personnel. Queries resulting from the plausibility checks and the manual data review were forwarded to the investigational sites for clarification. The database was corrected according to the answers of the queries, documented by an audit trail and the filed query answers.

The database was controlled by the Data Management Department of [redacted]. It was also validated according to the corresponding validation SOP of the [redacted]

9.6.3 Biometrics

All statistical analyses were performed by the Biometrics Department of [redacted] using SAS® version 9.4, based on the Statistical Analysis Plan (SAP). The outputs of the statistical programs were quality controlled by the project statistician. Statistical tables and listings were created as write-protected pdf-files and are included in appendix 16 (available on request).

9.6.4 Data Review Meeting

A data review meeting (DRM) was held prior to database lock. AMS and sponsor representatives checked and assessed the data for the purpose of finalizing the planned analysis. They decided on unclear data issues and defined the analysis population.

Four patients (no.1093, 1347, 1560, and 2064) with no valid informed consent (ICF) were excluded from the analysis populations. The respective data were stored in the clinical and safety databases but no further processing will be performed. Further protocol deviations such as missing date of birth, missing date for start of therapy, missing tick for renal cell cancer, incorrect documentation of combination partners were discussed and the assignment to the respective analysis sets is described in section 10 **Figure 10-1**.

Due to the fact that only one patient was excluded from the per-protocol set, the PPS analyses were limited to the parameters PFS and OS.

Further data issues included the handling of inconsistent or incomplete documentation of Avastin doses and adverse events. Explanatory footnotes should be added to the respective tables.

The DRM Meeting Minutes dated 08 May 2015 and Addendum dated 18 May 2015 are included in appendix 16.3.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

The statistical analysis was carried out by [redacted], in accordance with the respective biostatistics SOPs of [redacted] The specification of the complete analysis is laid down in detail in the final version 1.0 of the SAP, dated April 20th, 2015, compiled and signed by [redacted] and approved in writing by [redacted] The SAP was finalized prior to data base lock.

9.7.1.1 Populations for Analysis

Four study populations were defined for analysis:

All Patients Set: Comprises all patients included in the observational study and having signed the ICF, regardless whether they finished the study or not.

Safety set (SS): Comprises all patients who have received at least once one dose of Avastin.

Full-Analysis Set (FAS): Comprises all patients who received at least one dose of study medication and have at least one post dose efficacy assessment, following the intention-to-treat principle.

Per-protocol Set (PPS): Consists of all patients of the FAS without major protocol deviations as assessed in the DRM-meeting (see 9.6.4)

9.7.1.2 General Methodology

In general, all available data were included in the analyses and were to be summarized descriptively. The statistical analyses were to be carried out by means of the SAS® package (version 9.4).

Quantitative data (e.g. age) was to be analysed by the statistical parameters valid N, mean, standard deviation (SD), minimum, 25% quantile, median, 75% quantile, and maximum. Missing values were not to be replaced.

Qualitative (e.g. gender) and categorical variables (e.g. score values) were to be presented by means of absolute and relative frequency distributions. Percentages for relative frequencies were based on all non-missing values (=100%). Percentages were rounded to one decimal place, thus, there may be occasions where the total of the percentages does not equal 100% exactly.

The description of single cycles was limited to the planned observation period of 104 weeks.

Events were analysed on a patient and not on an event basis, i.e. number and percentage of patients with at least one (specific) event/ side-effect is displayed (incidence).

Adverse events and medical history were coded by AMS using MedDRA Version 15.1. The cytostatic combination partners and subsequent therapies were coded according to WHO DD Version 4.1.

9.7.1.3 Demographic Data and other Baseline Characteristics

Baseline information on demography, disease history and comorbidities were evaluated descriptively.

9.7.1.4 Effectiveness Analysis

Survival endpoints (PFS and OS) were estimated using the Kaplan-Meier approach with corresponding 95% confidence intervals.

9.7.1.5 Safety Analysis

The number of patients with (serious) adverse events, (serious) adverse events of special interest and toxicities were displayed in summary tables by MedDRA Primary System Organ Class and Preferred Term.

Relative frequencies are based on the total number of patients.

9.7.2 Determination of Sample Size

A patient number of 400 was estimated to allow a 99% probability to record an adverse drug reaction with a true incidence of 2.5% at least four times.

Based on the AVOREN study results (Escudier et al in J Clin Oncol 25, 2007) with 327 patients treated with bevacizumab + IFN and of the current study including 400 patients, the therapeutic effectiveness in terms of overall response rate (ORR) with 95% confidence intervals (CI) was expected to be:

ORR = 30.6%, 95% CI = (26.1% - 35.1%).

The estimate for progression free survival (PFS) was calculated as:

Median PFS = 10.2 months, 95% CI = (9.5 months – 10.9 months).

The estimate for 12 months PFS was:

12 month-PFS = 44.2%, 95% CI = (41.7% - 46.6%).

9.7.3 Bias

Blinding was not applicable; this was a non-comparative observational study. To minimize underreporting of adverse drug reactions and adverse events of special interest, the physician had to document in the CRF at each patient visit, if an AE or ADR had occurred in the period since the previous visit. Monitoring only was to be performed in exceptional cases to ensure completeness and plausibility.

Demographic and disease related variables were recorded to assess their potential influence on treatment results and adverse drug reactions, thus the influence of co-variables as potential confounders can be accounted for using stratified analyses.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Amendments

Two amendments to the final study protocol Version 5.3 dated 26 November 2007 were implemented.

Amendment 1, Version 2.0 dated 20 May 2008 accounted for new safety results that hypertension and proteinuria grade 1 and 2 were no longer regarded as adverse events of special interest with respective expedited reporting times.

In addition interim reports regarding treatment regimen and safety data were planned every 6 months requiring changes in the description of the process.

Administrative changes included an update of the payment scheme, the clarification of terms and procedures and spelling mistakes.

Amendment 2, Version 2.2 dated 18 November 2010 was issued to extend the recruitment period and prolong the total study duration by 2 years.

The description of safety analyses, data management and payment was refined and legal basics were adjusted.

The Consolidated Protocol Version 6.0, dated 18.11.2010 including Amendment 1 Version 2.0, 20.05.2008 and Amendment 2, Version 2.2, 18.11.2010 will be supplied upon request.

10. STUDY PATIENTS

10.1 Disposition of Patients

Selection of patients for this observational study took place in 136 oncological centres which were representative of the spectrum of clinical settings in Germany where patients with mRCC are diagnosed and treated. These centres included hospitals and private practices across Germany and were selected to obtain a representative sample of mRCC patients in Germany. From originally received 407 inclusion faxes 38 CRFs were not returned by the respective investigators.

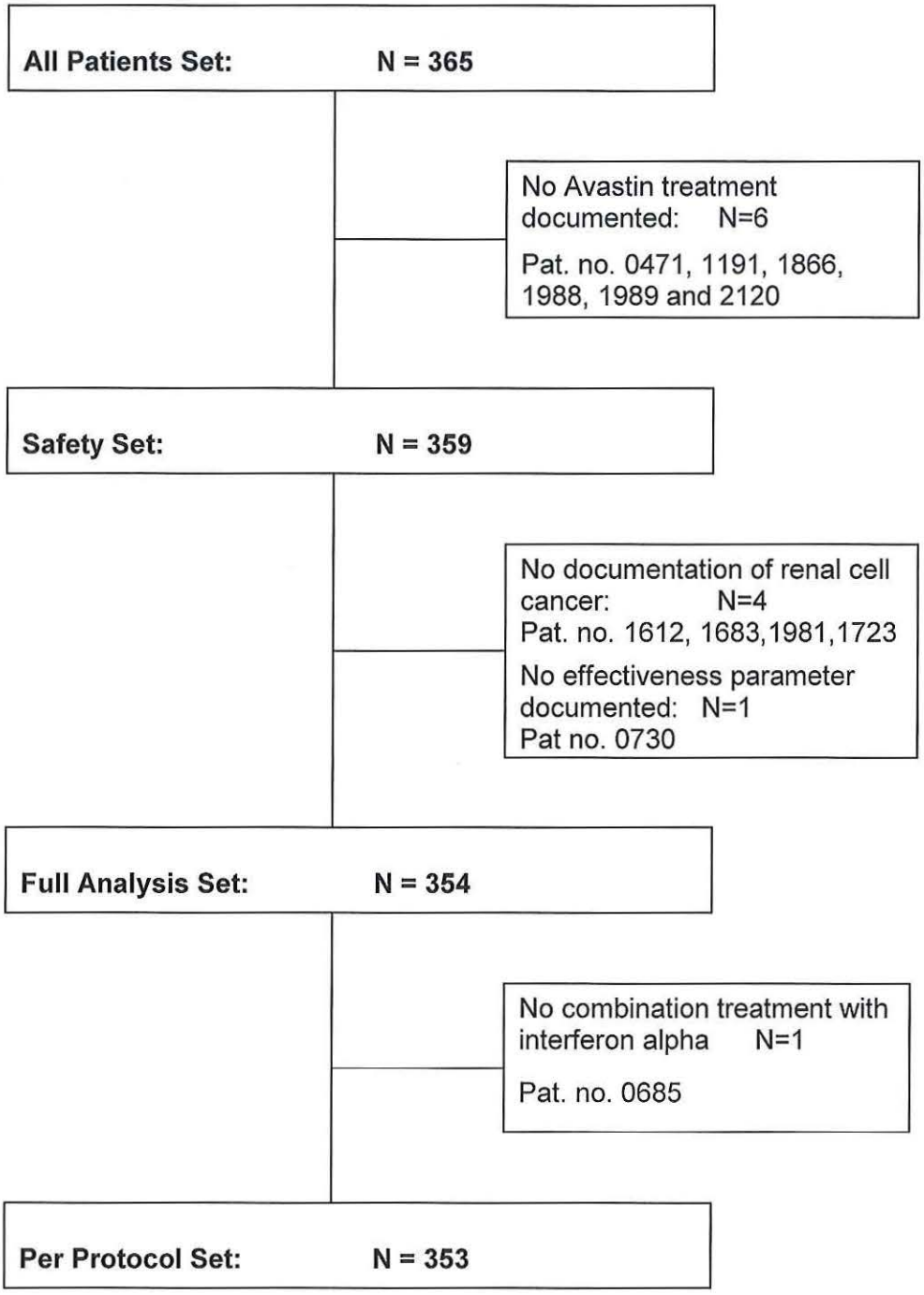
Four patients with no valid informed consent form were excluded from the analysis sets as determined in the data review meeting (see also section 9.6.4.).

A total of 365 patients provided written consent to collection and processing of their data in the observational study and were included in the 'All Patients Set'. Of these 359 patients were analysed in the safety set (SAF) and 354 patients were evaluable in the full analysis set (FAS). One patient was excluded from the per protocol sample due to major protocol violation.

The first patient was entered in the study on January 08 2008 (date of enrolment first patient on registration fax) and last patient follow-up was on September 26, 2014.

Figure 10-1 summarizes the numbers of patients enrolled and analysed in the study, including the reasons for exclusion of the respective analysis set.

Figure 10-1 Flowchart of patients analysed



Source: Appendix Table 1.1 and DRM minutes

The reasons for end of therapy for patients included in the safety set are provided in **Table 10-1**. The main reason for end of study was cancer progression of the underlying disease in 51.8% of the patients, followed by administrative reasons reported for 24.6% of the patients and poor compliance in 12.0%. Administrative reasons included mainly adverse drug reactions and deterioration of the general condition, stable disease or complete remission, planned end of observation period and other treatment options (see also listing 8.3.). For the total number of deaths at the end of follow-up, please refer to section 12.2.1.

Table 10-1 Reason for End of Therapy[1], SAF

Category*	Total (N=359)
n (missing)	342 (17)
Cancer progression of underlying disease	177 (51.8%)
Administrative reasons / Other	84 (24.6%)
Refusal of treatment / poor cooperation	41 (12.0%)
Death from cancer	35 (10.2%)
Serious adverse events	32 (9.4%)
Loss of contact (lost to follow-up)	15 (4.4%)
Death from other cause	10 (2.9%)

Appendix Table 7.1.a, *multiple counts are possible,
[1]assessed at the end of regular observation period, excluding follow-up

A listing with free text comments for end of therapy is provided in appendix 16, listing 8.3.

10.2 Demographic and Other Baseline Characteristics

The demographic and baseline characteristics of the study population are shown in Table 10-2. The analysis set included 359 patients from 136 centres in Germany who were evaluated in the mRCC NIS. Mean patient age was 65.5 (±10.1) years. The major proportion of patients (59.6%) was 65 years of age or older. Male patients accounted for 68% of the study population. The mean weight at inclusion was 81.8 kg (±16.5) for all patients, mean BMI was 27.7 (±4.9). About 36% of patients had a Motzer score of 0 (favourable risk) and 50.3% had 1-2 risk factors (intermediate risk).

Table 10-2 Study Population Baseline Characteristics[1] SAF

Characteristics	Total (N=359)
Years of Age [Mean (SD)]	65.5 (10.1)
Age group	
n/missing	357/2
< 65 years	144 (40.3%)
65 to < 70 years	64 (17.9%)
70 to < 75 years	89 (24.9%)
≥ 75 years	60 (16.8%)
Gender	
n/missing	356/3
female / male	114 (32.0%)/ 242 (68.0%)
Body weight (kg)	
n/missing	354/5
Mean (SD)	81.8 (16.5)
Height (cm)	
n/missing	348/11
Mean (SD	171.3 (9.7)
Surface area (/ m^2)	
n/missing	258/101
Mean (SD	1.95 (0.32)
BMI (kg/ m^2)	
n/missing	347/12
Mean (SD	27.71 (4.90)
Motzer Score	
n/missing	316/43
0	114 (36.1%)
1-2	159 (50.3%)
3-5	21 (6.6%)
NA	22 (7.0%)

[1] Number (%) of patients with non-missing data is presented, unless stated otherwise.
SD=standard deviation, Appendix Tables 1.2b, 1.5,

Tables 1.2a - c and 1.5 in appendix 16 give the demographic data and vital parameters for the analysis populations.

10.2.1 Cancer history and previous treatment

The initial diagnosis and tumour classification is shown in table 10-3. Mean time since initial diagnosis of renal cell carcinoma in the study population was 33.8 (±49.3) months, median duration was 11 months. For patients with recurrence of their disease, the mean time since diagnosis of recurrence was 9.3 (±16.8) months with a median time of 2 months.

In 190 (87.2%) of patients with available data the tumour was classified as clear cell carcinoma. The majority of the patients (59.1%) were initially diagnosed with stage IV according to TNM (UICC) classification. 323 patients (91%) underwent surgery, mean time since operation was 34.1 (±48.4) months, median time was 12 months.

Table 10-3 Cancer History - SAF

Initial diagnosis	Total (N=359)
Time since initial diagnosis (months)	
n/missing	331/28
Mean (SD)	33.8 (49.3)
Median	11.0
Range	0 - 293
Time since diagnosis of recurrence (months)	
n/missing	305/54
Mean (SD)	9.3 (16.8)
Median	2.0
Range	0 - 94
Renal cell cancer	
Yes	354
Missing entry	5
Type of renal cell cancer	
Clear cell	190 (87.2%)
Papillary	7 (3.2%)
Chromophobe	3 (1.4%)
Collecting duct carcinoma	1 (0.5%)
Missing entry	141
TNM-Staging (seventh edition)	
Stage I	22 (9.3%)
Stage II	24 (10.1%)
Stage III	51 (21.5%)
Stage IV	140 (59.1%)
Missing entry	122
Surgery yes	323 (91.0%)

Initial diagnosis	Total (N=359)
Time since operation (months)	
n/missing	301/58
Mean (SD)	34.1 (48.4)*
Median	12.0
Range	0 - 293
Surgical area n/missing	181/178
Primary tumour	176 (97.2%)
Metastases	5 (2.8%)

Appendix Table 1.3b, *as documented in the CRF

The tumour stages and sites of distant metastases are displayed in table 10-4 and appendix table 1.3b for the SAF. At the start of the observational study 71.9% of the patients had advanced stage IV disease with metastases spread into lung (69.3%), lymph nodes (26.4%) and/or bones (23.2%).

Table 10-4 Tumour Stage and Metastatic Sites, SAF

	Total (N=359)
Current Tumour stage	
n/missing	278 / 81
Local advanced, Stage III	78 (28.1%)
Stage IV	200 (71.9%)
Metastatic sites*	
n/missing	349 / 10
Lung	242 (69.3%)
Lymph nodes	92 (26.4%)
Bones	81 (23.2%)
Brain	14 (4.0%)
Other	69 (19.8%)

Appendix Table 1.3b,* multiple counts possible

Cancer history for the 'all patients set' is given in appendix table 1.3.a, for the FAS in table 1.3.c.

10.2.2 Comorbidities at Baseline

The most common comorbidities reported by patients at baseline were 'vascular disorders' with hypertension in 194 patients (54.0%), 'cardiac disorders' in 85 patients (23.7%), and 'metabolism and nutrition disorders' with diabetes mellitus in 62 patients (17.3%). In the SOC 'renal and urinary disorders' nephropathy was listed in 69 (19.2%) patients (Table 10-5).

Table 10-5 Prevalence of Comorbidities at Baseline (>3% total), SAF

Pre- and coexisting conditions Primary System Organ Class (SOC) and Preferred Term	**Total (N=359)**
Patients with pre- and coexisting conditions	276 (76.9%)
Vascular disorders	196 (54.6%)
Hypertension	194 (54.0%)
Embolism	11 (3.1%)
Cardiac disorders	85 (23.7%)
Cardiac disorder	85 (23.7%)
Metabolism and nutrition disorders	83 (23.1%)
Diabetes mellitus	62 (17.3%)
Renal and urinary disorders	70 (19.5%)
Nephropathy	69 (19.2%)
Nervous system disorders	21 (5.8%)
Nervous system disorder	14 (3.9%)
Endocrine disorders	19 (5.3%)
Hypothyroidism	13 (3.6%)
Respiratory, thoracic and mediastinal disorders	19 (5.3%)
Chronic obstructive pulmonary disease	13 (3.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	16 (4.5%)
Gastrointestinal disorders	14 (3.9%)
Immune system disorders	13 (3.6%)

Appendix Table 1.4

Relevant pre- and coexisting conditions at baseline for the analysis population by Primary System Organ Class and Preferred Term is displayed in table 1.4, appendix 16.

10.2.3 Vital Signs and Laboratory

Descriptive statistics for systolic and diastolic blood pressure (BP) measures at the beginning of the observation are given in table 10-6 and appendix table 1.5. Mean systolic BP was 132.9 (±16.4) and mean diastolic BP was 79.1 (±9.4) mmHg.

Table 10-6 Vital Signs at Baseline, SAF

Parameter	**Total (N=359)**
Blood pressure, systolic (mmHg)	
n (missing)	288 (71)
Mean (SD)	132.9 (16.4)
Median	130.0

Parameter	Total (N=359)
Range	90 - 195
Blood pressure, diastolic (mmHg)	
n (missing)	288 (71)
Mean (SD)	79.1 (9.4)
Median	80.0
Range	56 - 110

Appendix Table 1.5

Summary statistics for haematological and biochemical parameters determined at baseline such as haemoglobin, platelets, leukocytes, granulocytes, creatinine, SGPT, SGOT and bilirubin are displayed in appendix table 1.6.

10.3 Systemic Therapy

The mean total number of cycles was 16.6 ±14.0 (median 13.0), about 33% of the patients received 20 or more treatment cycles with Avastin® (Table 10-7).

Table 10-7 Number of Cycles – Systemic Therapy

Parameter	Total (N=359)
Total number of cycles	
Mean (SD)	16.6 (14.0)
Median	13.0
Min – Max	1 - 71
Number of Avastin treatment cycles - categories	
< 4	46 (12.8%)
4 to < 6	42 (11.7%)
6 to < 8	33 (9.2%)
8 to < 10	28 (7.8%)
10 to < 12	17 (4.7%)
12 to < 15	41 (11.4%)
15 to < 20	32 (8.9%)
≥ 20	120 (33.4%)

Appendix Table 2.7

The number of patients per cycle decreased from 354 (98.6%) at baseline to 89 (24.8%) at the end of the first year (week 51-52). At the end of the second year (week 103-104 treatment data for 15 patients (4.2%) were collected. From week 105 onwards 4 patients received Avastin treatment, and from week 131 onwards only 2 patients were still treated (table 10-8).

Table 10-8 Number of Patients per Cycle

Treatment weeks	Total (N=359)
1-2	354 (98.6%)
3-4	338 (94.2%)
7-8	305 (85.0%)
9-10	287 (79.9%)
11-12	265 (73.8%)
13-14	246 (68.2%)
15-16	236 (65.7%)
17-18	218 (60.7%)
21-22	194 (54.0%)
25-26	178 (49.6%)
29-30	152 (42.3%)
32-34	137 (22.3%)
39-40	119 (33.1%)
47-48	99 (27.6%)
51-52	89 (24.8%)
55-56	69 (19.2%)
61-62	57 (15.9%)
69-70	46 (12.8%)
79-80	32 (8.9%)
89-90	22 (6.1%)
99-100	16 (4.5%)
103-104	15 (4.2%)
105-106	4 (1.1%)

Source Table 2.2.1

The mean dose per infusion over all cycles was 10.6 mg/kg BW (±7.0), the median dose was 10 mg/kg BW (appendix table 2.2).

Table 10-9 Mean dose of Avastin per cycle, FAS

Parameter	Statistic	Total (N=359)
Mean dose of Avastin per cycle during entire study (mg/kg BW)	n (missing)	359 (0)
	Mean (SD)	10.6 (7.0)
	Median	10.0
	Min - Max	4 – 100*

Appendix Table 2.2
*as documented by the investigator, no obvious correction performed

As shown in table 10-10 more than 90% of patients with data available were on the 10 mg dose regimen throughout the observation, few patients (between 3 and 11) received the 5 mg dose until week 19 to 20, afterwards only 1 patient stayed on the 5mg dose. 7 patients were treated with 15mg at week 1-2, between 1 and 5 patients received 15mg until treatment week 103-104.

Table 10-10 Single Dose of Avastin per infusion, SAF N=359

Infusion dose of Avastin	Treatment weeks	n (%)	Treatment weeks	n (%)
Missing n	1-2	5	17-18	141
5 mg/kg BW		11 (3.1%)		4 (1.8%)
7.5 mg/kg BW		1 (0.3%)		NA
10 mg/kg BW		330 (93.2%)		208 (95.4%)
15 mg/kg BW		7 (2.0%)		2 (0.9%)
Missing n	3-4	21	19-20	150
5 mg/kg BW		10 (3.0%)		3 (1.4%)
7.5 mg/kg BW		1 (0.3%)		NA
10 mg/kg BW		317 (93.8%)		202 (96.7%)
15 mg/kg BW		5 (1.5%)		2 (1.0%)
Missing n	5-6	33	21-22	165
5 mg/kg BW		7 (2.1%)		1 (0.5%)
7.5 mg/kg BW		1 (0.3%)		NA
10 mg/kg BW		309 (94.8%)		188 (96.9%)
15 mg/kg BW		5 (1.5%)		2 (1.0%)
Missing n	7-8	54	23-24	172
5 mg/kg BW		5 (1.6%)		1 (0.5%)
10 mg/kg BW		290 (95.1%)		182 (97.3%)
15 mg/kg BW		4 (1.3%)		2 (1.1%)
Missing n	9-10	72	25-26	181
5 mg/kg BW		5 (1.7%)		1 (0.6%)
10 mg/kg BW		272 (94.8%)		172 (96.6%)
15 mg/kg BW		4 (1.4%)		3 (1.7%)
Missing n	11-12	94)	51-52	270
5 mg/kg BW		5 (1.9%)		1 (1.1%)
10 mg/kg BW		251 (94.7%)		81 (91.0%)
15 mg/kg BW		2 (0.8%)		5 (5.6%)
Missing n	13-14	113	103-104	344
5 mg/kg BW		4 (1.6%)		NA
10 mg/kg BW		232 (94.3%)		14 (93.3%)
15 mg/kg BW		4 (1.6%)		1 (6.7%)
Missing n	15-16	123		
5 mg/kg BW		4 (1.7%)		
10 mg/kg BW		226 (95.8%)		
15 mg/kg BW		2 (0.8%)		

Appendix Table 2.2.1

The infusion doses per treatment cycle by categories and as documented in the CRF are displayed in appendix table 2.2.1.

At least one dose deviation in relation to the planned therapy with Avastin® was documented for 39 (10.9%) of the patients (appendix table 2.4.1). The number of patients with dose deviations per cycle is displayed as shift table in appendix table 2.4.

The majority of patients had no therapy interruptions in their Avastin® treatment. Appendix table 2.5 gives the shift table for number of patients with Avastin® therapy interruption versus interruption of combination partners per cycle.

The infusion time for Avastin® per cycle is shown in appendix table 2.1. The mean duration of the infusion time decreased from 83.2 min ± 32.6 (median 90 min) at the first cycle to 55.4 min ± 22.8 (median 60 min) in treatment weeks 51 to 52. Median values remained constant with 60.0 min from week 3-4 until week 139-140.

The frequencies of combinations (at least one cycle) as documented in the CRF are given in appendix table 2.8. The most frequently documented combination was Avastin / Interferon administered in 96.7% of the patients included in the SAF population. 99.7% of patients (353/354) in the FAS were treated at least once as per label.

Appendix table 2.3 gives the doses per cycle of the combination partners. Interferon alpha-2a used as main combination partner was administered at a median dose of 3.0 million IU throughout all treatment cycles. Mean values for interferon administration were 5.0 MIU (SD 5.5) at the beginning und 3.8 MIU (SD 2.0) in week 54 (Appendix Table 2.3 Dose per application of combination partners (SAF))

Concomitant medication was documented for 39 patients (10.9%). Table 10-12 summarizes the most commonly prescribed drugs (>3%) for patients included in the SAF.

Table 10-11 Concomitant medication (>3% total), SAF

ATC Class (Level 2) Preferred Term	Total (N=359)
Patients with concomitant medications	39 (10.9%)
DRUGS FOR TREATMENT OF BONE DISEASES	16 (4.5%)
Zoledronic acid	15 (4.2%)
ANALGESICS	13 (3.6%)
Paracetamol	12 (3.3%)

Appendix Table 2.9

Concomitant medications were coded using WHO DD 4.1 (2004)

Further statistics on systemic therapy and combination partners per treatment cycle are given in appendix 16:

Table 2.1 Systemic therapy: Infusion time of Avastin (SAF)
Table 2.2 Systemic therapy: Avastin dose per cycle (SAF)

10.4 Observation and treatment duration

Table 10-12 Treatment duration, SAF

Parameter	Statistic	Total (N=359)
Duration of therapy with Avastin (Days)	n (missing)	347 (12)
	Mean (SD)	266.1 (223.7)
	Median	192.0
	Min - Max	1 - 998
Observation period (Days)	n (missing)	322 (37)
	Mean (SD)	286.7 (227.2)
	Median	217.5
	Min - Max	1 - 985

Appendix Table 7.1a

The total mean observation duration for patients with data available (n=322) was 286.7 days (SD=227.2). The median duration was 217.5 days with a range from 1 to 985 days. Mean treatment duration with Avastin® (n=347) was 266.1 days (SD=223.7) and median treatment duration was 192 days (range 1-998).

Descriptive parameters on duration of therapy and observation period for the FAS are given in appendix table 7.1b.

10.5 Subsequent Therapies and Follow-up

Subsequent therapies at the end of the observation period were planned or initiated for 194 (54%) of the patients in the SAF (appendix table 7.1.1a) and 192 (54.2%) in the FAS (appendix table 7.1.1b). Patients with any subsequent therapy by ATC class and preferred term are listed in Table 10-14 below..

Table 10-13 Subsequent therapies, FAS and SAF

ATC Class (Level 2) Preferred Term	FAS Total (N=354)	SAF Total (N=359)
Patients with subsequent therapies	192 (54.2%)	194 (54.0%)
ANTINEOPLASTIC AGENTS	130 (36.7%)	131 (36.5%)
Other antineoplastic agents (Undefined)	105 (29.7%)	106 (29.5%)
Sorafenib	17 (4.8%)	17 (4.7%)
Bevacizumab	5 (1.4%)	5 (1.4%)
Antineoplastic agents (Undefined)	1 (0.3%)	1 (0.3%)
Fluorouracil	1 (0.3%)	1 (0.3%)
Monoclonal antibodies (Undefined)	1 (0.3%)	1 (0.3%)
IMMUNOSUPPRESSIVE AGENTS	40 (11.3%)	41 (11.4%)
Everolimus	40 (11.3%)	41 (11.4%)
IMMUNOSTIMULANTS	8 (2.3%)	8 (2.2%)
Interferon*	5 (1.4%)	5 (1.4%)
Interferon alfa*	3 (0.8%)	3 (0.8%)
THERAPEUTIC RADIOPHARMACEUTICALS	8 (2.3%)	8 (2.2%)
Therapeutic radiopharmaceuticals (Undefined)	8 (2.3%)	8 (2.2%)
DRUGS FOR TREATMENT OF BONE DISEASES	3 (0.8%)	3 (0.8%)
Zoledronic acid	2 (0.6%)	2 (0.6%)
Bondronat (Ibandronate sodium,Ibandronic acid)	1 (0.3%)	1 (0.3%)
ALL OTHER THERAPEUTIC PRODUCTS	1 (0.3%)	1 (0.3%)
Folinic acid	1 (0.3%)	1 (0.3%)
ENDOCRINE THERAPY	1 (0.3%)	1 (0.3%)
Exemestane	1 (0.3%)	1 (0.3%)

Appendix Table 7.1.1b and 7.1.1a
* Combination partner documented erroneously as subsequent therapy by respective investigators

10.5.1 Follow-up

Information on second line therapies and best tumour response, collected 12 months after the end of the observational study are presented in tables 10-15 and 10-16 below.

163 (45.4%) of patients in the SAF and 161 (45.5%) of the patients in the FAS sample had received second line therapies during the follow-up phase. Most of the patients (36.2%) were treated with antineoplastic agents (table 10-15).

Table 10-14 Follow-up 2nd line therapies, FAS and SAF

ATC Class (Level 2) Preferred Term	FAS Total (N=354)	SAF Total (N=359)
Patients with subsequent therapies	161 (45.5%)	163 (45.4%)
ANTINEOPLASTIC AGENTS	128 (36.2%)	130 (36.2%)
Other antineoplastic agents (Undefined)	108 (30.5%)	110 (30.6%)
Sorafenib	21 (5.9%)	21 (5.8%)
Bevacizumab	9 (2.5%)	9 (2.5%)
Antineoplastic agents (Undefined)	2 (0.6%)	2 (0.6%)
Monoclonal antibodies (Undefined)	2 (0.6%)	2 (0.6%)
Fluorouracil	1 (0.3%)	1 (0.3%)
Vinorelbine	1 (0.3%)	1 (0.3%)
IMMUNOSUPPRESSIVE AGENTS	41 (11.6%)	41 (11.4%)
Everolimus	41 (11.6%)	41 (11.4%)
IMMUNOSTIMULANTS	7 (2.0%)	7 (1.9%)
Interferon	5 (1.4%)	5 (1.4%)
Interferon alfa	1 (0.3%)	1 (0.3%)
Interferon alfa-2a	1 (0.3%)	1 (0.3%)
THERAPEUTIC RADIOPHARMACEUTICALS	4 (1.1%)	4 (1.1%)
Therapeutic radiopharmaceuticals (Undefined)	4 (1.1%)	4 (1.1%)
DRUGS FOR TREATMENT OF BONE DISEASES	2 (0.6%)	2 (0.6%)
Zoledronic acid	2 (0.6%)	2 (0.6%)
ALL OTHER THERAPEUTIC PRODUCTS	1 (0.3%)	1 (0.3%)
Folinic acid	1 (0.3%)	1 (0.3%)

Appendix Table 7.2.1b

Best tumour response during 2nd line therapy is displayed in table 10-16 for the FAS and SAF. At the end of follow-up 113 patients were reported as cases of death (any cause) in the SAF and 111 patients in the FAS. 20 patients in the SAF were documented twice as cases of death, once at the end of observation (table 7.1.a section 10.1) and at the end of follow-up (table 7.2.a), for 5 patients no reason of death was given resulting in an overall death rate of 40.9% (143/359, table 7.3a)

Table 10-15 Tumour response, FAS and SAF

Parameter	Category	FAS Total (N=354)	SAF Total (N=359)
Best tumour response (during 2nd-line therapy)	n/missing	166/188	169/190
	CR	8 (4.8%)	8 (4.7%)
	PR	32 (19.3%)	32 (18.9%)
	NC*	38 (22.9%)	38 (22.5%)
	PD	45 (27.1%)	46 (27.2%)
	NE	43 (25.9%)	45 (26.6%)
Cause of death	n/missing	111/243	113/246
	Death from cancer	99 (89.2%)	101 (89.4%)
	Death from other cause	12 (10.8%)	12 (10.6%)

Appendix Table 7.2.a and 7.2b

* as erroneously printed in the CRF- NC = no change, used equivalent to term SD = stable disease

Further descriptive statistics on follow-up parameters and subsequent are given in appendix 16:

Table 7.1.1a Subsequent therapies by ATC Class and WHO DD Preferred Term (SAF)
Table 7.1.1b Subsequent therapies by ATC Class and WHO DD Preferred Term (FAS)
Table 7.2.1a Subsequent therapies 2nd-line by ATC Class and WHO DD Preferred Term (SAF)
Table 7.2.1b Subsequent therapies 2nd-line by ATC Class and WHO DD Preferred Term (FAS)
Table 7.2a Follow-up (SAF)
Table 7.2b Follow-up (FAS)

11. EFFECTIVENESS EVALUATION

11.1 Effectiveness Results

Tumour Response

Tumour status was assessed according to the categories CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE for not evaluable. Best tumour response over time (assessed as per clinical routine of the individual centre) showed that complete response was achieved by 18 (5.3%) of the patients. 74 (21.9%) of patients obtained partial remission and 132 (39.1%) were assessed with stable disease. ORR calculated as percentage of patients with CR and PR was 27.2% (table 11-1). Karnofsky performance status at the end of the observation was 80 to 100% in 67.1% of the patients.

Table 11-1 End of Observation Assessment of Tumour Response and Performance Status, FAS

Parameter	Category	Total (N=354)
Best tumour response over time	Missing	16
	CR	18 (5.3%)
	PR	74 (21.9%)
	SD	132 (39.1%)
	PD	56 (16.6%)
	NE	58 (17.2%)
Karnofsky Performance status (KPS)	Missing	53
	100 %	37 (12.3%)
	90 %	76 (25.2%)
	80 %	89 (29.6%)
	70 %	51 (16.9%)
	60 %	24 (8.0%)
	50 %	12 (4.0%)
	40 %	4 (1.3%)
	30 %	3 (1.0%)
	20 %	3 (1.0%)
	10 %	2 (0.7%)

Appendix Table 7.1b, 3.2.1

The tumour evaluation over time is shown below in table 11-2 and appendix table 3.1.

Karnofsky Performance Status by treatment cycle is displayed in appendix table 3.2.1. Descriptive statistics by treatment weeks is given in table 3.2.

Table 11-2 Current Tumour Status, FAS (N=354)

Tumour status	Treatment weeks	n (%)	Treatment weeks	n (%)
Missing	1-2	14	17-18	136
PR		1 (0.3%)		21 (9.6%)
SD		30 (8.8%)		26 (11.9%)
PD		14 (4.1%)		9 (4.1%)
NE		48 (14.1%)		8 (3.7%)
No new restaging		247 (72.6%)		154 (70.6%)
Missing	3-4	19	19-20	153
PR		2 (0.6%)		15 (7.5%)
SD		25 (7.5%)		33 (16.4%)
PD		8 (2.4%)		5 (2.5%)
NE		40 (11.9%)		7 (3.5%)
No new restaging		260 (77.6%)		141 (70.1%)
Missing	5-6	28	21-22	161
PR		8 (2.5%)		20 (10.4%)
SD		39 (12.0%)		30 (15.5%)
PD		11 (3.4%)		5 (2.6%)
NE		38 (11.7%)		8 (4.1%)
No new restaging		230 (70.6%)		130 (67.4%)
Missing	7-8	53	23-24	170
CR		1 (0.3%)		NA
PR		12 (4.0%)		15 (8.2%)
SD		43 (14.3%)		32 (17.4%)
PD		15 (5.0%)		5 (2.7%)
NE		23 (7.6%)		6 (3.3%)
No new restaging		207 (68.8%)		126 (68.5%)
Missing	9-10	68	25-26	178
CR		2 (0.7%)		1 (0.6%)
PR		21 (7.3%)		20 (11.4%)
SD		50 (17.5%)		40 (22.7%)
PD		12 (4.2%)		6 (3.4%)
NE		20 (7.0%)		7 (4.0%)
No new restaging		181 (63.3%)		102 (58.0%)
Missing	11-12	89	51-52	260
CR		3 (1.1%)		NA
PR		28 (10.6%)		9 (9.6%)
SD		55 (20.8%)		14 (14.9%)
PD		15 (5.7%)		4 (4.3%)
NE		16 (6.0%)		3 (3.2%)
No new restaging		148 (55.8%)		64 (68.1%)
Missing	13-14	111	103-104	339
CR		1 (0.4%)		NA
PR		18 (7.4%)		2 (13.3%)
SD		54 (22.2%)		1 (6.7%)
PD		10 (4.1%)		NA
NE		10 (4.1%)		NA
No new restaging		150 (61.7%)		12 (80.0%)
Missing	15-16	121		

Tumour status	Treatment weeks	n (%)	Treatment weeks	n (%)
CR		3 (1.3%)		
PR		27 (11.6%)		
SD		37 (15.9%)		
PD		7 (3.0%)		
NE		8 (3.4%)		
No new restaging		151 (64.8%)		

Appendix Table 3.1

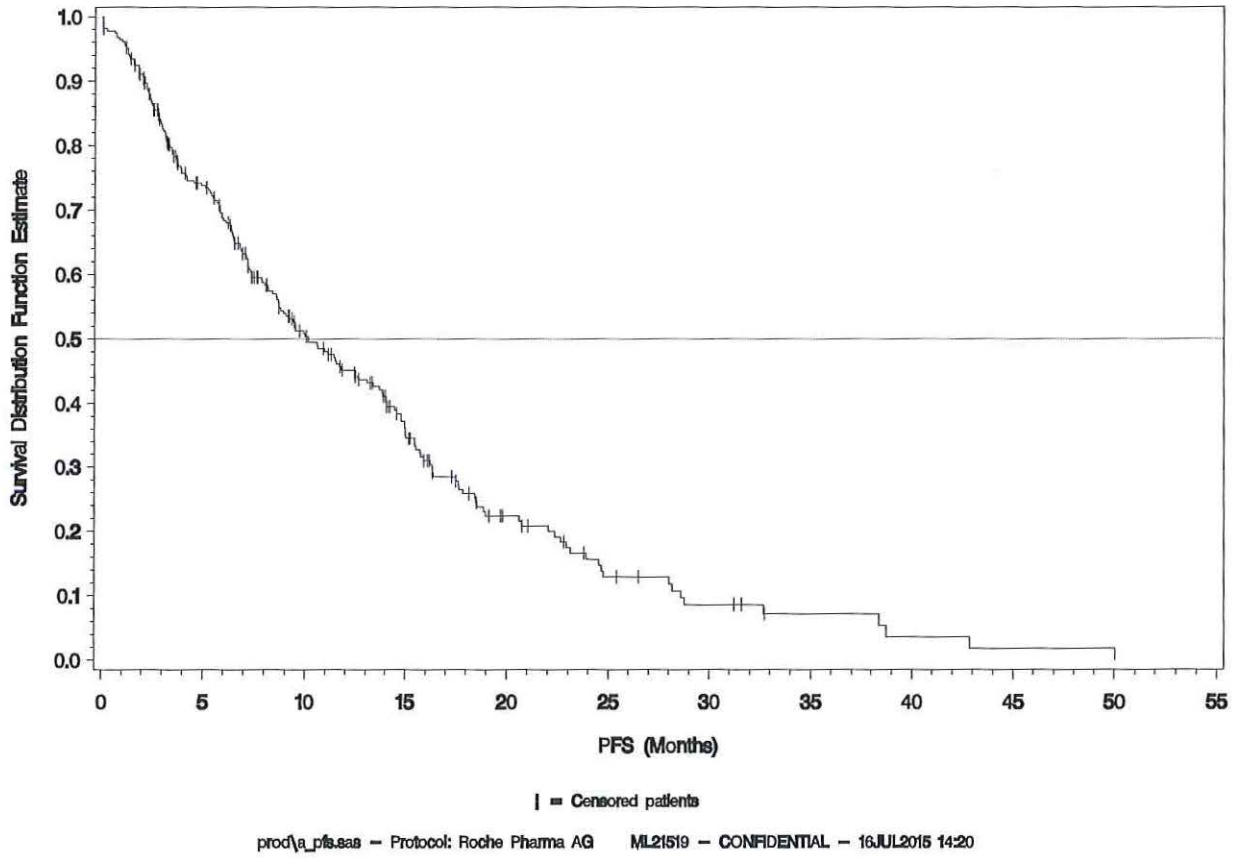
Disease control rate (DCR)

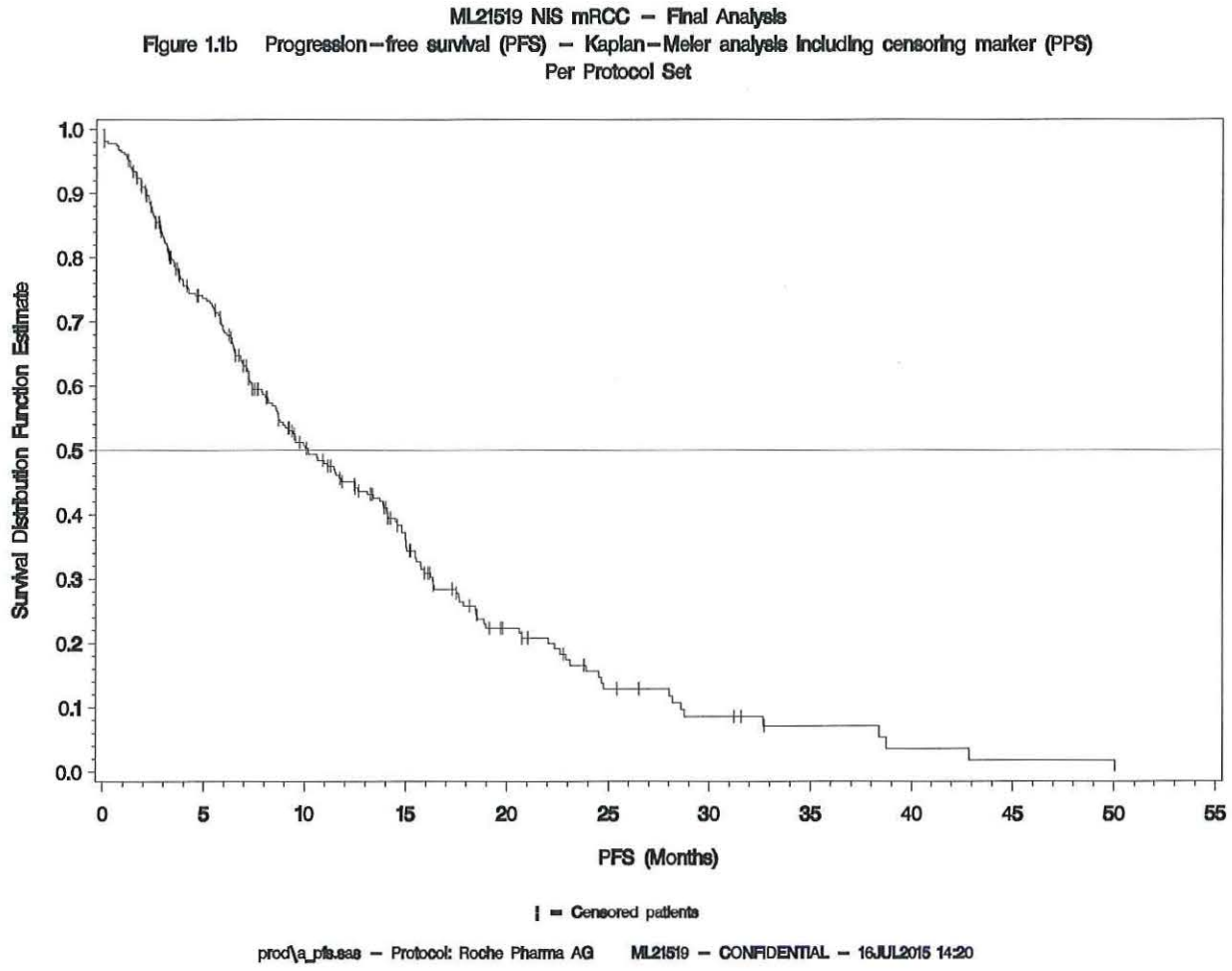
The disease control rate, defined as percentage of patients who have achieved complete response, partial response and/or stable disease during the course of the observation was 66.3% for patients in the full analysis set (appendix table 3.3).

Progression-free Survival

The Kaplan-Meier estimate of time until progression resulted in a median PFS of 10.2 months (95%CI: 8.6; 12.6) in the FAS and PP population. 50% of the patients were within the range of 4.2 and 18.5 months until estimated disease progression (see Figure 1.1a and 1.1b). The event rate, defined as proportion of patients with the events progression or death, was 62.3% in the FAS and 62.5% for the PPS (appendix tables 5.1a and 5.1.b).

ML21519 NIS mRCC – Final Analysis
Figure 1.1a Progression–free survival (PFS) – Kaplan–Meier analysis including censoring marker (FAS)
Full Analysis Set





The number of patients at risk at selected timepoints is shown in table 11-3 and appendix tables 5.1.a (FAS) and 5.1.b (PPS).

Table 11-3 PFS – Number of patients at risk for selected timepoints (FAS)

Selected Timepoints (Months)	PFS (Months)	Patients at risk
6	5.98	177
12	11.84	94
18	17.85	40
24	23.90	18
30	28.77	9
36	32.71	5

Appendix Table 5.1a

The survival distribution function estimates with respective 95% confidence intervals are displayed in 11-4 and appendix table 5.2.a (FAS) and 5.2.b (PPS).

Table 11-4 PFS - Survival distribution function estimate (Kaplan-Meier) for selected timepoints (FAS)

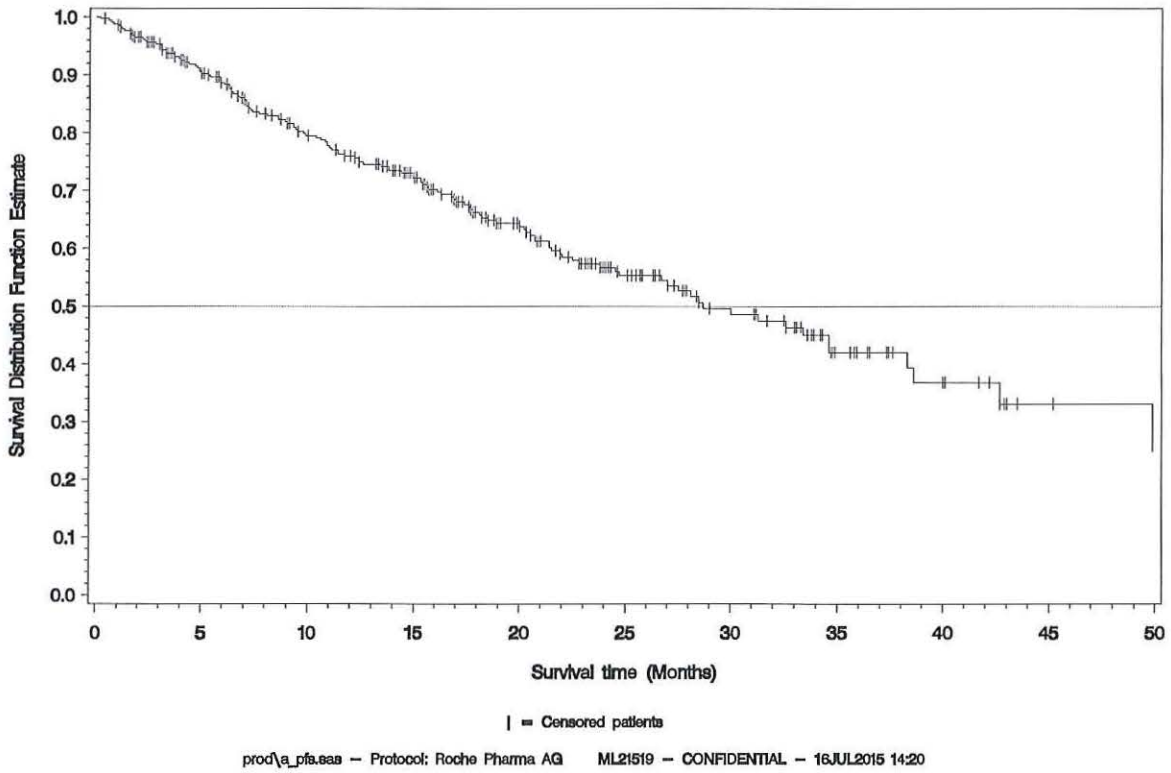
Selected Timepoints (Months)	PFS (Months)	Survival Distribution Function Estimate	95% Confidence Interval	
			Lower	Upper
6	5.98	0.68	0.63	0.74
12	11.80	0.45	0.39	0.51
18	17.85	0.26	0.20	0.32
24	23.90	0.16	0.10	0.22
30	28.77	0.09	0.04	0.14
36	32.68	0.07	0.03	0.13

Appendix Table 5.2a

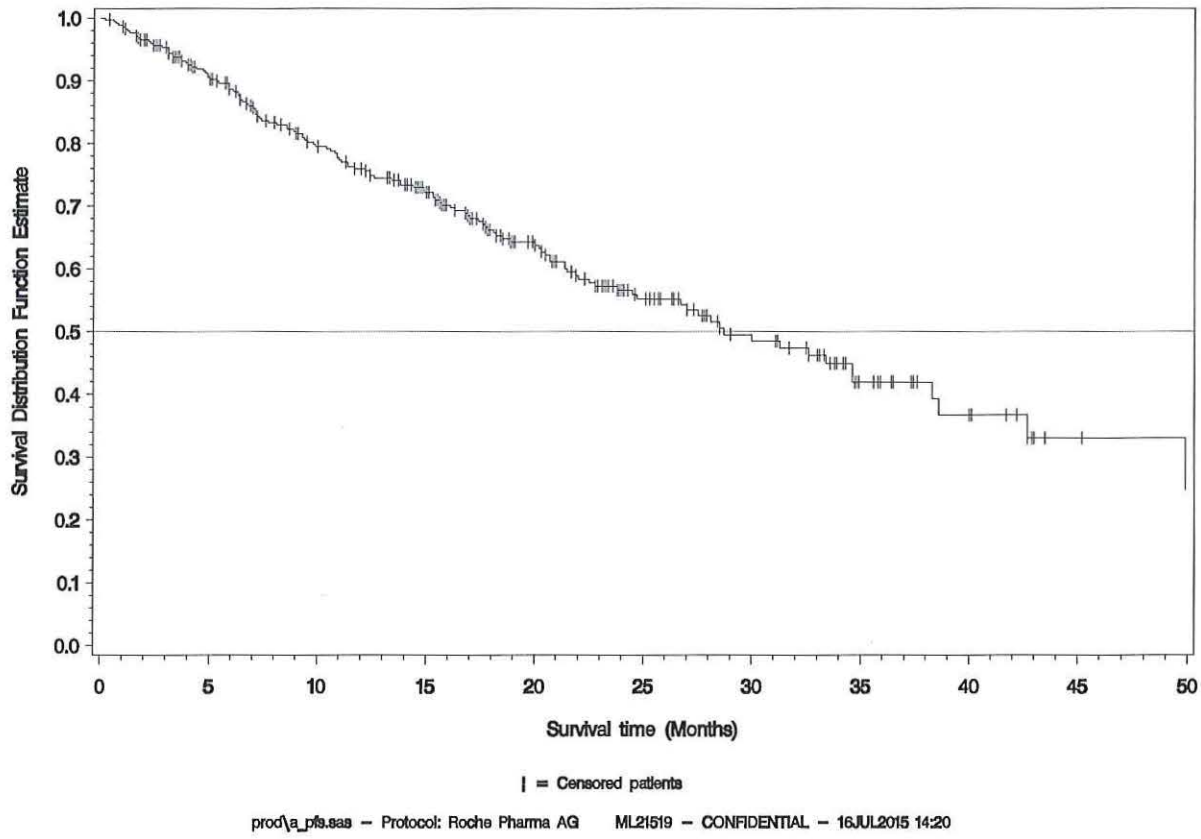
Overall Survival

The median overall survival estimate for patients observed in the FAS and PPS was 28.7 months (95%CI: 24.5; 38.3) see appendix tables 6.1a and 6.1.b and Figure 2a and 2b. The event rate was 38.8% in the FAS and 39.0% for the PPS.

ML21519 NIS mRCC – Final Analysis
Figure 2.1a Overall survival (OS) – Kaplan–Meier analysis including censoring marker (FAS)
Full Analysis Set



ML21519 NIS mRCC – Final Analysis
Figure 2.1b Overall survival (OS) – Kaplan–Meier analysis including censoring marker (PPS)
Per Protocol Set



The number of patients at risk at selected timepoints is shown in table 11-4 and appendix tables 6.1.a (FAS) and 6.1.b (PPS).

Table 11-5 OS – Number of patients at risk for selected timepoints (FAS)

Selected Timepoints (Months)	Survival time (Months)	Patients at risk
6	5.90	274
12	11.70	217
18	17.90	144
24	23.90	88
30	30.00	47
36	35.90	22

Appendix Table 6.1a

The survival distribution function estimates with respective 95% confidence intervals are displayed in 11-6 and appendix tables 6.2.a (FAS) and 6.2.b (PPS).

Table 11-6 OS - Survival distribution function estimate (Kaplan-Meier) for selected timepoints (FAS)

Selected Timepoints (Months)	Survival time (Months)	Survival Distribution Function Estimate	95% Confidence Interval	
			Lower	Upper
6	5.90	0.89	0.85	0.92
12	11.70	0.76	0.71	0.80
18	17.80	0.66	0.60	0.71
24	23.80	0.57	0.50	0.63
30	30.00	0.49	0.41	0.56
36	34.60	0.42	0.34	0.50

Appendix Table 6.2a

11.2 Effectiveness Conclusions

Best tumour response over time (assessed as per clinical routine of the individual centre) showed that complete response (CR) was achieved by 18 (5.3%) of the patients. 74 (21.9%) of patients obtained partial remission (PR) and 132 (39.1%) were assessed with stable disease (SD). The disease control rate (DCR), defined as percentage of patients who have achieved complete response, partial response or stable disease during the course of the observation was 66.3% for the FAS population. The mean Karnofsky performance status at the end of the study was 78.3 (±16.5), median 80.0.

ORR calculated as percentage of patients with CR and PR was 27.2%. The Kaplan-Meier estimate of time until progression resulted in a median PFS of 10.2 months (95%CI: 8.6; 12.6). 50% of the patients were within the range of 4.2 and 18.5 months until estimated disease progression. The event rate was 62.5% in the FAS and 62.3% for the PP population. The Kaplan-Meier survival distribution function estimate for 12 months PFS was 45% (95%CI: 39%; 51%) which confirms the expected value.

The median overall survival estimate for patients observed in the FAS and PPS was 28.7 months (95%CI: 24.5; 38.3). The event rate was 38.8% in the FAS and 39.0% for the PPS. The Kaplan-Meier survival distribution function estimate for 12 months overall survival was 76% (95%CI: 71%; 80%).

163 (45.4%) of patients in the SAF and 161 (45.5%) of the patients in the FAS sample received second line therapies during the 12-month follow-up phase. Most of the patients (36.2%) were treated with antineoplastic agents (**Table 10-14**).

12. SAFETY EVALUATION

The safety evaluations are based on all patients included in the safety set (SAF) (N=359).

12.1 Adverse Events

12.1.1 Summary of Adverse Events

A total of 11377 adverse events were observed in 334 patients; this corresponds to an AE incidence of 93.0%. Out of these, 72 patients (20.1%) experienced serious AEs and for 70 patients (19.5%) the AE was classified as AE of special interest.

Table 12-1 presents the summary of adverse events for the SAF.

Table 12-1 Summary of Adverse Events, SAF

	Total (N= 359)
Patients with adverse events	334 (93.0%)
Adverse events (AE)	11377
Patients with serious AE	72 (20.1%)
Patients with AE of special interest	70 (19.5%)

Appendix Tables 4.1

12.1.2 Display of Adverse Events

The incidence of events by MedDRA primary System Organ Class (SOC) and Preferred Term (PT) is presented in Table 12-2 displaying the SOCs and PTs with an overall incidence of at least 3.0% and in table 4.2, appendix 16, for all incidences.

The most often affected MedDRA SOC is 'blood and lymphatic system disorders', with an incidence of 70.2%. Within this SOC, anaemia and leukopenia occurred with an incidence of 55.2% and 41.8%, respectively. Thrombocytopenia occurred in 32.9% of the patients and neutropenia in 23.1%.

63.5% of the patients had AEs classified as 'general disorders and administration site condition': influenza like illness was reported for 40.7% of the patients, pyrexia for 32.3%. 51.8% of the patients had 'gastrointestinal disorders', most often nausea (39.3%) and diarrhoea (22.3%). Hypertension was observed in109 (30.4%) patients.

Table 12-2 Adverse Events with Overall Incidence ≥ 3% (SAF)

Primary System Organ Class ≥ 3% Preferred Term incidence ≥ 3%	**Total (N=359)**
Patients with adverse events	334 (93.0%)
Blood and lymphatic system disorders	252 (70.2%)
Anaemia	198 (55.2%)
Leukopenia	150 (41.8%)

Primary System Organ Class ≥ 3% Preferred Term incidence ≥ 3%	**Total (N=359)**
Thrombocytopenia	118 (32.9%)
Neutropenia	83 (23.1%)
General disorders and administration site conditions	228 (63.5%)
Influenza like illness	146 (40.7%)
Pyrexia	116 (32.3%)
Pain	85 (23.7%)
Fatigue	42 (11.7%)
Spinal pain	18 (5.0%)
Chills	13 (3.6%)
Mucosal inflammation	12 (3.3%)
Gastrointestinal disorders	186 (51.8%)
Nausea	141 (39.3%)
Diarrhoea	80 (22.3%)
Vomiting	66 (18.4%)
Constipation	13 (3.6%)
Vascular disorders	117 (32.6%)
Hypertension	109 (30.4%)
Haemorrhage	17 (4.7%)
Musculoskeletal and connective tissue disorders	109 (30.4%)
Back pain	36 (10.0%)
Pain in extremity	34 (9.5%)
Arthralgia	27 (7.5%)
Bone pain	24 (6.7%)
Musculoskeletal pain	12 (3.3%)
Flank pain	11 (3.1%)
Nervous system disorders	100 (27.9%)
Peripheral sensory neuropathy	44 (12.3%)
Headache	37 (10.3%)
Dizziness	22 (6.1%)
Renal and urinary disorders	94 (26.2%)
Proteinuria	90 (25.1%)
Skin and subcutaneous tissue disorders	76 (21.2%)
Palmar-plantar erythrodysaesthesia syndrome	54 (15.0%)
Respiratory, thoracic and mediastinal disorders	69 (19.2%)
Epistaxis	35 (9.7%)
Dyspnoea	18 (5.0%)
Cough	11 (3.1%)
Investigations	41 (11.4%)

Primary System Organ Class ≥ 3% Preferred Term incidence ≥ 3%	**Total (N=359)**
Weight decreased	25 (7.0%)
Cardiac disorders	33 (9.2%)
Cardiac failure	28 (7.8%)
Infections and infestations	30 (8.4%)
Metabolism and nutrition disorders	22 (6.1%)
Decreased appetite	16 (4.5%)
Psychiatric disorders	20 (5.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18 (5.0%)
Malignant neoplasm progression	11 (3.1%)
Injury, poisoning and procedural complications	16 (4.5%)

Appendix Table 4.2

Table 12-3 shows AEs with toxicity grade ≥3 with an incidence of at least 1%. Appendix table 4.3 gives all incidences.

AEs with grade ≥3 were reported for 132 patients (36.8%). As already seen for the total number of AEs, the most frequently affected SOC was 'Blood and lymphatic system disorders' with 13.1%, followed by 'General disorders' with 10.9%.

Table 12-3 Adverse Events with Toxicity Grade ≥3, (SAF)

Primary System Organ Class ≥ 1% Preferred Term incidence ≥ 1%	**Total (N=359)**	
	Grade 3	**Grade 4**
Patients with adverse events	112 (31.2%)	20 (5.6%)
Blood and lymphatic system disorders	41 (11.4%)	6 (1.7%)
Anaemia	23 (6.4%)	5 (1.4%)
Leukopenia	7 (1.9%)	0 (0.0%)
Neutropenia	10 (2.8%)	0 (0.0%)
Thrombocytopenia	6 (1.7%)	1 (0.3%)
General disorders and administration site conditions	37 (10.3%)	2 (0.6%)
Fatigue	7 (1.9%)	1 (0.3%)
Influenza like illness	14 (3.9%)	0 (0.0%)
Pain	14 (3.9%)	0 (0.0%)
Gastrointestinal disorders	12 (3.3%)	3 (0.8%)
Diarrhoea	4 (1.1%)	1 (0.3%)
Nausea	8 (2.2%)	0 (0.0%)
Vomiting	4 (1.1%)	0 (0.0%)
Vascular disorders	9 (2.5%)	3 (0.8%)
Hypertension	9 (2.5%)	2 (0.6%)

Primary System Organ Class ≥ 1% Preferred Term incidence ≥ 1%	**Total (N=359)**	
	Grade 3	**Grade 4**
Musculoskeletal and connective tissue disorders	20 (5.6%)	1 (0.3%)
Bone pain	4 (1.1%)	0 (0.0%)
Pain in extremity	5 (1.4%)	1 (0.3%)
Nervous system disorders	12 (3.3%)	1 (0.3%)
Headache	5 (1.4%)	0 (0.0%)
Renal and urinary disorders	8 (2.2%)	0 (0.0%)
Bladder pain	1 (0.3%)	0 (0.0%)
Proteinuria	7 (1.9%)	0 (0.0%)
Skin and subcutaneous tissue disorders	4 (1.1%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	4 (1.1%)	3 (0.8%)
Cardiac disorders	5 (1.4%)	0 (0.0%)
Cardiac failure	4 (1.1%)	0 (0.0%)
Psychiatric disorders	3 (0.8%)	1 (0.3%)

Appendix Table 4.3

12.1.3 Adverse Events of Special Interest

The incidences for AEs of special interest are presented in Table 12-4 and appendix table 4.2.2.

AESIs were reported for 70/359 (19.5%) patients, regardless of their causal relationship to treatment.

The most often affected SOC was 'Respiratory, thoracic and mediastinal disorders', with an overall incidence of 10.6%. The highest incidence rate within this SOC was reported for epistaxis in 9.7% of the patients. 'Vascular disorders' was the second most affected SOC with an overall incidence of 5.6%. Haemorrhage was reported in 4.7% of the patients; gastrointestinal perforation, haematuria and impaired healing in 0.8% each.

Table 12-4 Adverse Events of Special Interest by primary SOC and PT (SAF)

Primary System Organ Class Preferred Term	**Total (N=359)**
Patients with adverse events of special interest	70 (19.5%)
Respiratory, thoracic and mediastinal disorders	38 (10.6%)
Epistaxis	35 (9.7%)
Haemoptysis	2 (0.6%)
Pulmonary embolism	1 (0.3%)
Vascular disorders	20 (5.6%)
Haemorrhage	17 (4.7%)
Arterial thrombosis	2 (0.6%)
Venous thrombosis	1 (0.3%)
Gastrointestinal disorders	13 (3.6%)
Gingival bleeding	4 (1.1%)
Gastrointestinal perforation	3 (0.8%)
Mouth haemorrhage	2 (0.6%)
Anal haemorrhage	1 (0.3%)
Colitis ulcerative	1 (0.3%)
Diverticular perforation	1 (0.3%)
Diverticulum intestinal haemorrhagic	1 (0.3%)
Intestinal haemorrhage	1 (0.3%)
Large intestinal haemorrhage	1 (0.3%)
Nervous system disorders	4 (1.1%)
Cerebral haemorrhage	4 (1.1%)
General disorders and administration site conditions	3 (0.8%)
Impaired healing	3 (0.8%)
Renal and urinary disorders	3 (0.8%)
Haematuria	3 (0.8%)
Urinary bladder haemorrhage	1 (0.3%)

Primary System Organ Class Preferred Term	**Total (N=359)**
Blood and lymphatic system disorders	1 (0.3%)
Haemorrhagic anaemia	1 (0.3%)
Eye disorders	1 (0.3%)
Eye haemorrhage	1 (0.3%)
Retinal exudates	1 (0.3%)
Retinal haemorrhage	1 (0.3%)
Infections and infestations	1 (0.3%)
Diverticulitis	1 (0.3%)
Injury, poisoning and procedural complications	1 (0.3%)
Post procedural haemorrhage	1 (0.3%)
Reproductive system and breast disorders	1 (0.3%)
Menorrhagia	1 (0.3%)

Appendix Table 4.2.2

The majority of patients in the SAF (47 (13.1%)) had grade 1 toxicities.

AEs of special interest with toxicity grade ≥3 occurred in 5 (1.4%) patients (Table 12-5). Frequencies by MedDRA Primary SOC, Preferred Term and corresponding grade of toxicity (0-4) are given in appendix table 4.3.2.

Table 12-5 Adverse Events of Special Interest with toxicity ≥3 (SAF)

Primary System Organ Class **Preferred Term**	**Grade 3**	**Grade 4**
Patients with adverse events	3 (0.8%)	2 (0.6%)
Respiratory, thoracic and mediastinal disorders	1 (0.3%)	1 (0.3%)
Epistaxis	1 (0.3%)	0
Pulmonary embolism	0	1 (0.3%)
Vascular disorders	0	0
Gastrointestinal disorders	1 (0.3%)	1 (0.3%)
Diverticular perforation	0	1 (0.3%)
Large intestinal haemorrhage	1 (0.3%)	0
Nervous system disorders	1 (0.3%)	0
Cerebral haemorrhage	1 (0.3%)	0
Infections and infestations	0	1 (0.3%)
Diverticulitis	0	1 (0.3%)
Injury, poisoning and procedural complications	0	1 (0.3%)
Post procedural haemorrhage	0	1 (0.3%)

Appendix Tables 4.3.2

12.1.4 Listing of Adverse Events by Patient

Adverse events with respective NCI/CTC toxicity grading for each patient, are given in appendix 16, listing 4.4.

12.2 Serious Adverse Events and Deaths

Serious AEs were reported for 72 patients (20.1%). Incidences of serious AEs by primary SOC and Preferred Term are displayed in Table 12-6 and appendix table 4.2.1.

The most often affected primary SOC was 'Nervous system disorders' with an incidence of 5%. The most frequent reported preferred term within this class was 'cerebral haemorrhage' for 4 (1.1%) of the patients.

3.9% of the patients had SAEs classified as 'general disorders and administration site conditions' or 'respiratory, thoracic and mediastinal disorders'. 3.6% of the patients had 'vascular disorders', most often hypertension (1.7%) or hypertensive crisis (0.6%).

Table 12-6 Serious Adverse Events, SAF

Primary System Organ Class ≥ 0.5% Preferred Term incidence ≥ 0.5%	**Total (N=359)**
Patients with serious adverse events	72 (20.1%)
Nervous system disorders	18 (5.0%)
Cerebral haemorrhage	4 (1.1%)
Posterior reversible encephalopathy syndrome	3 (0.8%)
Epilepsy	2 (0.6%)
Syncope	2 (0.6%)
Transient ischaemic attack	2 (0.6%)
General disorders and administration site conditions	14 (3.9%)
General physical health deterioration	6 (1.7%)
Asthenia	2 (0.6%)
Death	2 (0.6%)
Dyspnoea	3 (0.8%)
Haemoptysis	2 (0.6%)
Pulmonary embolism	2 (0.6%)
Vascular disorders	13 (3.6%)
Hypertension	6 (1.7%)
Hypertensive crisis	2 (0.6%)
Gastrointestinal disorders	11 (3.1%)
Gastrointestinal perforation	3 (0.8%)
Diarrhoea	2 (0.6%)
Nausea	2 (0.6%)
Anaemia	6 (1.7%)
Pancytopenia	2 (0.6%)

Primary System Organ Class ≥ 0.5% Preferred Term incidence ≥ 0.5%	**Total (N=359)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (2.8%)
Malignant neoplasm progression	7 (1.9%)
Metastases to bone	2 (0.6%)
Infections and infestations	7 (1.9%)
Diverticulitis	2 (0.6%)
Peritonitis	2 (0.6%)
Sepsis	2 (0.6%)
Psychiatric disorders	6 (1.7%)
Confusional state	4 (1.1%)
Cardiac disorders	5 (1.4%)
Atrial fibrillation	2 (0.6%)
Cardiac failure	2 (0.6%)
Injury, poisoning and procedural complications	4 (1.1%)
Metabolism and nutrition disorders	4 (1.1%)
Hyponatraemia	4 (1.1%)
Musculoskeletal and connective tissue disorders	4 (1.1%)
Pain in extremity	3 (0.8%)
Renal and urinary disorders	4 (1.1%)
Haematuria	2 (0.6%)
Weight decreased	2 (0.6%)
Eye disorders	2 (0.6%)
Hepatobiliary disorders	2 (0.6%)

Appendix Table 4.2.1

Serious AEs ≥3 were reported for 24 (6.7%) patients. 'Gastrointestinal disorder' and 'Vascular disorders' were the SOCs with the highest frequency of 1.6%. Four patients (1.2%) had hypertension, 2 patients (0.6%) a hypertensive crisis, 2 patients (0.6%) suffered from diarrhoea and 4 patients (1.1%) from anaemia.

Two patients experienced SAEs with fatal outcome considered as related to Avastin® treatment by the investigators: patient no. 527 died from multi-organ failure and patient no. 2054 from pulmonary embolism and sepsis. Three patients had fatal events considered as not related/not applicable by the investigator and assessed as relationship unknown by Roche Drug Safety: patient no. 703 with preferred term pain, patient no 1586 with death cause unknown and patient 1651 with myocardial infarction and pulmonary embolism.

Serious adverse drug reactions by MedDRA Primary System Organ Class and Preferred Term and NCI/CTC grade (0-4) are displayed in appendix table 4.3.1.

Table 12-7 Serious Adverse Events with toxicity ≥3 (SAF)

Primary System Organ Class Preferred Term	Grade 3	Grade 4
Patients with serious adverse events	10 (2.8%)	14 (3.9%)
Vascular disorders	3 (0.8%)	3 (0.8%)
Hypertension	2 (0.6%)	2 (0.6%)
Hypertensive crisis	1 (0.3%)	1 (0.3%)
Gastrointestinal disorders	3 (0.8%)	3 (0.8%)
Abdominal pain	0	1 (0.3%)
Diarrhoea	1 (0.3%)	1 (0.3%)
Diarrhoea haemorrhagic	1 (0.3%)	0
Diverticular perforation	0	1 (0.3%)
Large intestinal haemorrhage	1 (0.3%)	0
Blood and lymphatic system disorders	1 (0.3%)	3 (0.8%)
Anaemia	1 (0.3%)	3 (0.8%)
Nervous system disorders	3 (0.8%)	0
Cerebral haemorrhage	1 (0.3%)	0
Orthostatic intolerance	1 (0.3%)	0
Sciatica	1 (0.3%)	0
Syncope	1 (0.3%)	0
General disorders and administration site conditions	0	1 (0.3%)
Gait disturbance	0	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	0	2 (0.6%)
Dyspnoea	0	1 (0.3%)
Pulmonary embolism	0	1 (0.3%)
Cardiac disorders	1 (0.3%)	0
Cardiac failure	1 (0.3%)	0
Infections and infestations	0	1 (0.3%)
Diverticulitis	0	1 (0.3%)
Injury, poisoning and procedural complications	0	1 (0.3%)
Post procedural haemorrhage	0	1 (0.3%)
Psychiatric disorders	0	1 (0.3%)
Confusional state	0	1 (0.3%)
Renal and urinary disorders	1 (0.3%)	0
Bladder pain	1 (0.3%)	0
Hepatobiliary disorders	0	1 (0.3%)
Hepatic failure	0	1 (0.3%)
Musculoskeletal and connective tissue disorders	0	1 (0.3%)
Pain in extremity	0	1 (0.3%)

Appendix Table 4.3.1

12.2.1 Deaths

Out of 359 patients with data available 143 patients (40.9%) died during the course of the observation including the 12-month follow-up period (appendix table 7.3.a). Of these 120 patients died from the underlying disease and 18 patients died from other causes (appendix table 7.2.a and 7.1). For 5 patients no information about the cause of death was received.

The causes for death are given in listings 8.3 End of observation – free text, and 8.4 Follow-up – free text, appendix 16.

13. SUMMARY OF RESULTS, DISCUSSION AND OVERALL CONCLUSIONS

The non-interventional study was performed to examine the safety and effectiveness of Avastin® in combination with interferon alpha 2a in a large, unselected patient population with advanced and/or metastatic renal cell cancer (mRCC).

The safety set included 359 mRCC patients from 136 centres in Germany who were evaluated in the current NIS. 354 patients were evaluable in the FAS. One patient was excluded from the per protocol sample due to the protocol violation 'no combination treatment with interferon alpha' classified as major deviation.

Mean (±SD) patient age was 65.5 (±10.1) years. 59.6% of the patient population was 65 years of age or older. Male patients accounted for 68% of the study population. The mean body weight (BW) at inclusion was 81.8 kg (±16.5) for all patients, mean BMI was 27.7 (±4.9). About 36% of patients had a Motzer score of 0 (favourable risk) and 50.3% had 1-2 risk factors (intermediate risk). Mean Karnofsky performance index at baseline was 85.7 (±11.7).

71.9% of the patients were diagnosed with advanced stage IV disease at the start of the observation. 69.3% had metastases spread lung, lymph nodes (26.4%), and/or bones (23.2%). Most of the patients (87.2%) had histologically confirmed clear cell carcinoma. 91% underwent surgery with a mean time since operation of 34.1 months.

On average, Avastin® was administered for a mean duration of 266.1 days during 16.6 cycles, median duration was 198 days (range 1 to 998) during 13 cycles. The median dose per infusion throughout all cycles was 10 mg/kg BW. The main combination used at least once for patients evaluated in the FAS was Avastin® with interferon alpha (99.7%) administered at a median dose of 3.0 million IU.

About 45% of patients received second line therapies during the 12-month follow-up phase. Most of them (36.2%) were treated with antineoplastic agents.

EFFECTIVENESS RESULTS:

Best tumour response over time (assessed as per clinical routine of the individual centre) showed that complete response (CR) was achieved by 18 (5.3%) of the patients. 74 (21.9%) of patients obtained partial remission (PR) and 132 (39.1%) were assessed with stable disease (SD). The mean Karnofsky performance status at the end of the study was 78.3 (±16.5), median 80.0.

The disease control rate (DCR), defined as percentage of patients who have achieved complete response, partial response or stable disease during the course of the

observation was 66.3% for the FAS population. The Kaplan-Meier estimate of time until progression resulted in a median PFS of 10.2 months (95%CI: 8.6; 12.6). 50% of the patients were within the range of 4.2 and 18.5 months until estimated disease progression. The event rate was 62.5% in the FAS and 62.3% for the PP population. The Kaplan-Meier survival distribution function estimate for 12 months PFS was 45% (95%CI: 39%; 51%) which confirms the expected value.

The median overall survival estimate for patients observed in the FAS and PPS was 28.7 months (95%CI: 24.5; 38.3). The event rate was 38.8% in the FAS and 39.0% for the PPS. The Kaplan-Meier survival distribution function estimate for 12 months overall survival was 76% (95%CI: 71%; 80%).

SAFETY RESULTS:

11377 adverse events (AEs) were observed in 334 patients (incidence of 93.0%). Out of these, 72 patients (20.1%) experienced serious AEs and for 70 patients (19.5%) the AE was classified as AE of special interest.

AEs (any causality) with grade ≥3 toxicity according to the NCI Common Toxicity criteria (version 3.0) were reported for 132 patients (36.8%). The most frequently affected SOC was 'Blood and lymphatic system disorders' with 13.1%, followed by 'General disorders' with 10.9%. The most frequent reported preferred term was anaemia in 28 (7.8%) patients, a common side effect of interferon therapy.

Incidences for AEs of special interest were: epistaxis 9.7% (grade ≥3: 0.1%), haemorrhage 4.7% (none grade ≥3), gastrointestinal perforation 0.8% (none grade ≥3) and diverticular perforation 0.3% (grade 3), impaired healing 0.8% (none grade ≥3) and pulmonary embolism 0.3% (grade 4) which were similar to frequencies reported for the AVOREN trial (arterial thromboembolic event, gastrointestinal perforation, wound healing complications 1% each).

Serious AEs ≥3 were reported for 6.7% of the study population. Four patients (1.2%) had hypertension, 2 patients (0.6%) a hypertensive crisis, 2 patients (0.6%) suffered from diarrhoea and 4 patients (1.1%) from anaemia. Two patients experienced SAEs with fatal outcome (multi-organ failure and pulmonary embolism) considered as related to Avastin® by the investigators.

The main reason for end of study was cancer progression of the underlying disease in 51.8% of the patients. 143 patients (40.9%) died during the course of the observational study, 120 patients died from the underlying disease and for 18 patients the investigator stated death from other cause (causality unknown) as reason for the end of treatment. For 5 patients no information about the cause of death was received.

DISCUSSION:

The current observational study was already planned in 2007 with the objective to collect data on safety and effectiveness of Avastin® in combination with interferon alpha immunotherapy in a large, unselected patient population. The advantage of a non-interventional descriptive study design is the collection of 'real world data' under daily routine practice conditions, as allocation of exposure is not determined by a pre-defined protocol. Following the applicable guidelines at that time, no source data verification or selective monitoring of the main outcome parameters was performed. This can lead to incomplete and sometimes inconsistent data and therefore hampers direct comparison

to controlled clinical trials (RCTs). In addition other confounding factors, the lack of in and exclusion criteria and differences in response measurements lead to non-comparability of populations.

Nevertheless, the observed PFS of 10.2 months together with the PFS event free rate of 45% at 12 months in this study replicate the results from the AVOREN trial (4). The overall response rate published for AVOREN is slightly higher with 31% vs 27.2% in the current NIS.

The median OS time of 28.7 is within the range of values reported in the literature. Median OS time was 23.3 months in the Avastin plus IFN arm of the AVOREN trial (4), 18.3 months (Avastin® plus IFN group) for CALGB (5) and 30.7 months in the BEVLiN study, a single-arm phase II trial investigating Avastin® with low-dose IFN (6).

The comparison of baseline characteristics with results for AVOREN revealed no relevant differences to the pivotal AVOREN trial with regard to gender distribution, mean age (ML 21519: 65.5 years vs AVOREN: 61 years), risk score (ML 21519: favourable + intermediate risk 86.4% vs AVOREN: 83%), localisation of metastases (ML 21519: lung 69%, lymph nodes 26%, bone 23% vs AVOREN: 62%, 34% and 18%). Only the baseline Karnofsky performance index assessed as further prognostic score was higher for AVOREN patients probably due to the fact that performance status of 70% or more was one of the eligibility criteria. 76% of patients in the AVOREN Avastin® plus IFN arm patients had baseline scores of 90-100 vs 55% in the current NIS.

No sub-group analyses according to risk scores as described in AVOREN were performed in ML21519 to allow direct comparison to the results of the BEVLiN trial.

However, there is a noticeable difference in median treatment duration regarding the Avastin® plus IFN arm of previous clinical trials and the current study. The median duration of Avastin treatment was 9.7 months for AVOREN, 10 months with 22.5 cycles in the BEVLiN trial, 8.2 cycles of 28 days duration in the CALGB trial, and 6.5 months during 13 cycles in the current NIS. It might be speculated that investigators in the real life setting do not use Avastin® until diseases progression while still meaningful efficacy parameters similar to AVOREN were observed.

Overall AE and SAE incidences of 93% and 20% were similar to those reported for AVOREN (AE:97%, SAE:29%) (4) and CALGB (AE:99%, no SAEs specified) (5). Incidences for grade ≥3 toxicities were distinctly lower (ML 21519: 36.8%, AVOREN 84.2%, CALGB: 80%), probably due to the general risk of under-reporting of AEs in uncontrolled observational studies.

CONCLUSION:

In general, results from this non-interventional study replicate the results of the phase III AVOREN study which demonstrated that Avastin® in combination with interferon alpha immunotherapy improves overall response and time to progression in patients with advanced and/or metastatic renal cell cancer (mRCC). The safety profile is comparable to those found in RCTs and previously published data (4,5). No new safety signals were detected in patients treated within the mRCC NIS. The NIS data replicate the favourable results for Avastin demonstrated in AVOREN and provide real word data support for the utility of Avastin in the treatment of advanced mRCC.

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16. APPENDICES

16.1 Beobachtungsplan

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Supplied upon request