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

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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.

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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		