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Non-Interventional Final Study Report (CPZP034ADE15)

Non-Interventional Study to Assess Effectiveness and Safety of Pazopanib and Everolimus in a Real Life Setting: Reflecting a Changing mRCC Treatment Landscape (PAZOREAL)

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Research question and objectives	This non-interventional study was designed to observe the real-world use of 1st-line pazopanib and 2nd-line everolimus for mRCC patients. After regulatory approval of the checkpoint-inhibitor (CPI) nivolumab for the second (or later) line, this study also allowed documentation of patients treated with nivolumab in 2nd-line or everolimus in 3rd-line after 2nd-line treatment with nivolumab. Any decisions on treatment were made by the treating physician, independently of the study. Objectives: – Evaluate effectiveness of pazopanib in 1st-line and everolimus (also in the approved combination with lenvatinib) in 2nd- or 3rd-line therapy of mRCC patients in real-life setting, by measuring the duration of treatment in the specific therapies. – Test further parameters of effectiveness, safety, and quality of life in mRCC patients treated with pazopanib in 1st-line, everolimus (also in the approved combination with lenvatinib) in 2nd- and 3rd-line and nivolumab in 2nd-line in real-life setting
Country(-ies) of study	Germany
Author	[redacted]

Marketing authorization holder

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1 Abstract

Title

Non-Interventional Study to Assess Effectiveness and Safety of Pazopanib and Everolimus in a Real Life Setting: Reflecting a Changing mRCC Treatment Landscape (PAZOREAL)

Version and date

FINAL v2.0, 18 November 2021

Name and affiliation of main author

[redacted]

Keywords

mRCC, Pazopanib, Everolimus, non-interventional study, Germany

Rationale and background

In 2015, one of the standard treatment options for patients with metastatic RCC (mRCC) was sequential 1st-line pazopanib, a vascular endothelial growth factor receptor (VEGFR) inhibitor, followed by 2nd-line everolimus, an mammalian target of rapamycin (mTOR) inhibitor (Escudier et al., 2014; Ljungberg et al., 2015). With the approvals of new agents, like nivolumab (an immune checkpoint [PD-1] inhibitor), and the multikinase inhibitors cabozantinib and lenvatinib (lenvatinib in combination with everolimus), the treatment algorithms for patients with mRCC have changed markedly in recent years ("Kurzversion S3-Leitlinie Nierenzellkarzinom," 2020). It is important to evaluate real-life utilization of drugs and treatment sequencing to achieve better outcomes with respect to efficacy and safety of the medicines.

Research question and objectives

The primary objective of the PAZOREAL study was to evaluate the effectiveness of pazopanib in 1st-line therapy and everolimus (also in the approved combination with lenvatinib) in 2nd-line and 3rd-line therapy as well as nivolumab in 2nd-line therapy in patients with mRCC in the real-life setting, by measuring the respective treatment duration (time on drug (ToD) as primary variable).

Further objectives were to test further parameters of effectiveness, safety, and quality of life (QoL) in mRCC patients treated with pazopanib in 1st-line, everolimus (also in the approved combination with lenvatinib) in 2nd- and 3rd-line and nivolumab in 2nd-line in real-life setting.

Study design

PAZOREAL was a prospective, multi-center, non-interventional observational study to evaluate effectiveness, tolerability, safety, and QoL in patients with mRCC treated with pazopanib in the 1st-line, nivolumab or everolimus in 2nd-line, or everolimus (also in the approved combination with lenvatinib) in 3rd-line after 2nd-line nivolumab. Data on QoL were collected and analyzed using the EQ-5D-5L questionnaire for patients having consented in the data collection via questionnaire and having obtained their 1st questionnaire before the respecitive treatment started (i.e., QoL data was available for a subset of patients).

Setting

PAZOREAL was conducted in 167 sites all over Germany including oncologists in hospitals and outpatient clinics, and independent oncology practices. Patients were selected between 10 December 2015 (first-patient-in; FPI) and 22 December 2017 (last-patient-in; LPI). Patients were followed until death, loss to follow-up, withdrawal of consent or study end date (whichever occured earlier). The follow-up period comprised follow-up visits every 6 months and lasted until End of study (EOS; last-patient-last-visit; 28 February 2021). Database lock (DBL) was performed on 11 June 2021.

Subjects and study size, including dropouts

Eligible patients were adults with advanced/mRCC and a life expectancy of ≥ 6 months who started treatment with 1st-line pazopanib or 3rd-line everolimus maximum 8 weeks prior to informed consent. All enrolled patients were assigned to either Cohort I or Cohort II as follows:

- Cohort I: 1st-line treatment with pazopanib
- Cohort II: 3rd-line treatment with Everolimus after 2nd-line nivolumab.

It was planned to enroll 450 patients (400 patients in 1st-line pazopanib and 50 patients in 3rd-line everolimus) in about 150 study sites in Germany. Recruitment of patients in 1st-line was stopped on 31 August 2017 when 420 patients were enrolled. Due to end of recruitment period, recruitment of patients in 3rd-line was stopped on 01 March 2018 when 7 patients[1] were enrolled.

After enrollment, 29 patients were excluded from study due to following reasons i) violation of IC/EC criteria (12 patients), ii) not treated (6 patients), and iii) IC withdrawn (11 patients). In sum, 398 patients were treated and of these 16 subjects were omitted (9 due to participation in another clinical trial, 7 due to inspection findings). The full analysis set (FAS) of final study report comprises 382 study subjects with signed informed consent form (as documented in EDC) enrolled in 119 sites.

Variables and data sources

PAZOREAL collected clinical routine data on patient demographics, concomitant disease, medical history, performance status, concomitant medication, exposure to pazopanib, nivolumab and everolimus, disease assessment, subsequent therapies, and survival status. (S)AEs, special situations and safety laboratory data were collected. Toxicities were classified and documented according to CTCAE criteria. Patient reported otcome (PRO) including QoL was assessed using the standardized EQ-5D-5L questionnaire.

All data were collected prospectively, with the following exceptions:

- Retrospective documentation of 1st-line treatment with pazopanib (cohort I) was allowed for up to 8 weeks after first intake of pazopanib, but only after informed consent of the respective patient. In this case, data were collected retrospectively from the 1st-line treatment period that had already elapsed.

[1] After enrollment, one patient was excluded due to the exclusion criteria ‘participation in another clinical trial’. Thus 6 patients were assigned to FAS-II, cohort II, i.e. treated with everolimus in 3rd-line setting.

- For patients in cohort II, 2nd-line treatment with nivolumab was documented retrospectively in all cases. Data collection of treatment with nivolumab was only allowed after informed consent of the respective patient and if treatment with nivolumab had been carried out in the approved indication, i.e. outside of clinical trials. Retrospective documentation of 3rd-line treatment with everolimus was allowed for up to 8 weeks after first intake of everolimus after 2nd-line treatment with nivolumab. In this case, data for everolimus were collected retrospectively from the 3rd-line treatment period that had already elapsed.

The electronic data capture (EDC) system (iostudy office edc) used in this study was provided to the study sites by iOMEDICO AG. The data were derived from entries in the electronic case report forms (eCRFs) made by the study sites as part of routine clinical practice. Data was transferred from source documents (i.e., patient's medical records) to the eCRF. Data was fully pseudonymized and all information collected in this study was treated strictly confidentially. Captured data was validated by source data verification. The database quality was reviewed by onsite and remote monitoring of data entered in the eCRF. Completed eCRF data-entries were checked for compliance with the protocol and for completeness, consistency, and accuracy. For patients who filled in QoL questionnaires (EQ-5D-5L), these questionnaires were also used as a data source.

Statistical methods

The statistical methods were applied according to the final SAP v4.1 dated 14 November 2019 (Annex 1 – List of Stand-Alone Documents). The following analysis populations were used in the final analysis:

- Full analysis set (FAS): The primary analysis population included all patients for whom the documentation was started in the 1st-line (pazopanib treatment) or in the 3rd-line (everolimus treatment following 2nd-line nivolumab) and who received at least one dose of study drug in the respective therapy line (pazopanib or everolimus, respectively). All patients included in the primary analysis population were distributed to two different analysis sets. Patients who entered the study in the 1st-line treatment with pazopanib were included in the full analysis set – cohort I (FAS - cohort I). Patients who entered the study in the 3rd-line setting (study medication: everolimus after 2nd-line nivolumab) were included in the full analysis set – cohort II (FAS - cohort II). The FAS - cohort I and the FAS - cohort II were the relevant populations for the effectiveness evaluation as well as exposure data.
- Safety Set (SAF): The second analysis population - the SAF - included all patients from the FAS who received at least one dose of study drug (pazopanib, everolimus or nivolumab) and for whom at least one further post-baseline information (e.g. laboratory) was available. This population was relevant for laboratory parameters and adverse events (AEs).

Subgroup analyses by gender, age, Body mass index (BMI), Memorial Sloan-Kettering Cancer Center (MSKCC) score, histology, trial-eligibility, local factors, nephrectomy and local distance were conducted for ToD, overall survival (OS) and safety analyses, if each specification of the respective subgroup consisted of at least 5 patients.

Key Results

Between 10 December 2015 and 22 December 2017, 427 patients were enrolled in PAZOREAL and 398 patients were treated. In the analysis population FAS, 376 patients were assigned to cohort I (FAS – cohort I) and were treated with pazopanib in 1st-line setting (FAS(P)), while 6 patients were assigned to cohort II (FAS – cohort II and were treated with everolimus in 3rd-line setting). After 1st-line pazopanib, 163 patients were treated with nivolumab in 2nd-line (FAS(N)) and of these 9 patients received the 3rd-line treatment everolimus. [2] In addition, after 1st-line pazopanib, 5 patients were treated with 2nd-line everolimus. However, due to the small number of patients treated with either everolimus in 2nd-line (cohort I) or everolimus in 3rd-line (after nivolumab 2nd-line documented retrospectively, cohort II) present effectiveness results and analyses are focused on cohort I and respective FAS and SAF cohorts with patients receiving 1st-line pazopanib and/or 2nd-line nivolumab.

During the course of the study, 174 patients of cohort I and 5 patients of cohort II died. The median observation time (first prescription of pazopanib for cohort I until last contact or death) was 44.6 (95% CI: 43.2 – 47.1) months.

In cohort I, the majority of patients were male (n=257, 68.4%) and had at enrollement a median BMI of 26.4 kg/m² (range 16.8-58.4) (Goebell et al., 2018a). Most of the patients had an ECOG performance status of 0 or 1 (n=301, 80.1%) (Escudier et al., 2014). The majority of the patients presented with metastatic disease (n=353, 93.9%) (Cora N Sternberg et al., 2010; Sternberg et al., 2013). The vast majority of tumors showed a clear cell histology (80.9%) (Cora N. Sternberg et al., 2010). Compared to pivotal studies (Cora N Sternberg et al., 2010; Sternberg et al., 2014, 2013) with reported median age of 59 years (range 28.0-85.0 years, VEG105192, clinicaltrial.gov identifier NCT00334282) and of 65years (range 25.0-80.0 years, VEG107769, clinicaltrial.gov identifier NCT00387764) in PAZOREAL the median age was comparable higher: at baseline, in cohort I the median age was 69.7 years (range 38.5-89.2 years) and most of the patients receiving 1st-line pazopanib, FAS(P) were older than 65 years (n=244, 64.9%). Also, patients receiving subsequent 2nd-line nivolumab (FAS(N)) were mostly older than 65 years (n=114, 69.9%).

The MSKCC risk score was available for 85 (22.6%) patients and could be unambiguously categorized according to the MSKCC criteria. The overall median ToD (mToD) for patients starting with 1st-line pazopanib, administration until end date of last administration of any study medication (i.e. either 1st-line pazopanib, 2nd-line everolimus or nivolumab or 3rd-line everolimus), was 10.0 (8.5-11.7) months.

In the FAS(P), pazopanib 1st-line mToD was 6.3 (95% CI: 5.6-7.4) months and in accordance to previous data (Cora N Sternberg et al., 2010). However mToD observed in other previous studies were comparably longer with 8.1months (COMPARZ-study, clinicaltrials.gov identifier NCT00720941 (Motzer et al., 2014, 2013)) and 9.7 months (Sternberg et al., 2013).The 6-month time on drug rate was 52.2% (95% CI: 47.0 - 57.1%). In the respective trial-eligible population, the mToD was 7.7 (95% CI: 6.1-9.0) months and the 6-month time on drug rate was

[2] Due to small numbers of patients with 2nd- or 3rd-line everolimus (i.e. of cohort I and cohort II) respective data were not described in the present final study report and respective data were provided in appendix.

58.9% (95% CI: 50.5 - 66.4%). Sensititvity analyses revealed no differences between subgroups, e.g. tumor histology seems to have no impact on mToD.

The overall mOS for patients started with 1st-line pazopanib (mOS1) was 35.9 (95% CI: 28.2-48.3) months whereas trial- eligible patients achived a mOS of 53.2 (95% CI: 38.9-NA) months. Of note, 12-month OS rate of both populations were similar with 71.5% (95% CI: 66.4-76.0%) and 77.9% (95% CI: 69.9-84.0%). However, while present mOS1 is longer compared to previous data of the phase III non-inferiority study COMPARZ (comparing pazopanib to sunitinib) with a mOS of 28.3 (26.0, 35.5) months (Motzer et al., 2014), present mOS1 is accordance with previously reported mOS of 34.4 months, (95% CI: 29.5–39.3) of the retrospective, observational study PAMERIT (Mosca et al., 2021). Further, other studies showed a prolongiation of mOS with the sequential use of everolimus (4.9months (Motzer et al., 2010)) or nivolumab (25months (Motzer et al., 2015c)).

Median OS after start of 2nd-line treatment (mOS2) was 30.4 months (95% CI: 22.6-NA) with nivolumab and 26.6 months (95% CI: 9.6-NA) with other 2nd-line treatments. Sensitivity analyses showed no difference between subgoups. Present mOS2 for patients started with 2nd-line nivolumab is similar to previously reported mOS for 2nd-line nivolumab (25.0 months, 95% CI: 21.8-NA) (Motzer et al., 2015a).

Best response was assessed by either radiologic assessment or by clinical assessment. In FAS(P) 36 patients (9.57%) achieved complete response (CR) whereas 178 patients (47.34%) were observed with stable disease (SD, definded as non-CR or non-progressive disease (PD)) as best response. PD was the best response in 81 patients (21.54%). Disease control rate (i.e. sum of rates of patients with CR and SD) was 56.91% (51.86-61.83%) in the 1st-line pazopanib cohort (cohort I).

Of patients with 1st-line pazopanib treatment (cohort I) 212 patients (56.4%) had a progressive disease and of these 127 patients (33.8%) received the subsequent 2nd-line treatment with either nivolumab or everolimus.

The majority of patients (66%, FAS (P)) started with full dose pazopanib (800 mg/day). This is similar to reported real world data showing an initial daily dose of 800mg in 76.4% of patients (Mosca et al., 2021). The lowest documented dose during the course of 1st-line treatment was 800 mg/day in 39.6%, 400 mg/day in 43.6%, while only <10% of patients received less than 400 mg as lowest administered dose. For most of the patients (69.7%) no dose interruption was observed. Dose interruptions were mostly due to adverse events (13.3%) or toxicity (14.9%). Dose reductions mainly resulted from the treating physician’s decisions (42.0%) rather than from adverse events (6.1%) or toxicity (29.0%). End of treatment (EOT) was mainly caused by progressive disease in about half of the patients (52.4%), other EOT reasons were toxicity (13.6%), adverse events (5.9%) and death (5.9%).

In agreement with the Summary of product characteristics (SmPC) of pazopanib (June 2021, Reference ID: 014815-67235) most frequent TEAEs of any grade were gastrointestinal disorders with diarrhoea (36.8%), nausea (22.4%) and vomiting (7.2%) as well as fatigue (19.2%), decreased appetite (12.5%) and hypertension (12.3%).

At baseline (i.e. before treatment start with 1st line pazopanib) 219 (78.5%) health-related QoL questionnaires were available for analysis, after 3 months and 24 months the number of

evaluable questionnaires deceased to 141 (64.4%) and 31 (14.2%), respectively. Health-related QoL assessed by EQ-5D-5L did not change from baseline: patients were mainly bothered by pain/discomfort and the patients' mobility and usual activity were affected by the disease.

In the time period between the first COVID-19 case in Germany (27 January 2020) and date of last-subject-last-visit (28 February 2021), 130 study subjects were observed. No subject visits were delayed or cancelled due to the COVID-19 pandemic. For one subject a COVID-19 infection (CTCAE 2) during treatment with pazopanib has been reported. Validation of the database quality was carried out by onsite monitoring. All planned onsite monitoring visits took place. All study objectives were addressed and evaluated as planned and defined in the study protocol. No protocol amendment was required due to the COVID-19 pandemic. Taken together, the COVID-19 pandemic had no impact on the conduct of the study.

Discussion

Due to the non-interventional character of this study, different limitations of this study type apply also for PAZOREAL. For example the internal validity of the collected data is limited, as no predefined schedule and only minimal inclusion criteria were present. Moreover, a standardized tumor response evaluation (e.g. according to RECIST) was not available as it was not part of the clinical routine. With regard to QoL evaluation, many patients did not complete all questionnaires and did not answer all items of the questionnaires. More importantly, it is reasonable that patients that are doing rather well under therapy were still able to complete questionnaires at later time points. Therefore, results of QoL scores might not be fully representative of the whole patient collective. Nevertheless, non-interventional studies including PAZOREAL have also important advantages compared to clinical trials: As data are coming from a less homogen patient pool, subpopulations of the patient collective may be analysed and compared to obtain a better understanding on treatment options for special patient groups as e.g. older patients. Moreover, due to the non-interventional character more patients can be observed without any additional risk for their well being compared to routine treatment allowing the collection of additional data for effectiveness and safety.

In PAZOREAL 376 patients were assigned to cohort I and were treated with pazopanib in 1st-line setting (FAS(P)), while only 6 patients were assigned to cohort II (i.e. were treated with everolimus in 3rd-line setting after having 2nd-line nivolumab) reflecting that there was a substantially higher number of patients consenting at the beginning of 1st-line pazopanib mRCC treatment than 3rd-line patients treated with everolimus after 2nd-line nivolumab treatment. Accordingly, previous study reported that the sequence of pazopanib followed by nivolumab as 2nd-line treatment is a commonly applied therapy strategy in patients with mRCC (Méndez-Vidal et al., 2018).

Present patient charcteristics were similar to previously reported characteristics of mRCC patients, having a tendency towards male sex, older age and higher BMI (Goebell et al., 2018a). Of note, compared to patients included in the pazopanib pivotal studies baseline characteristics of the PAZOREAL patient collective were more diverse in regard to histologic tumor subtype, ECOG performance status, and age (Motzer et al., 2013; Cora N Sternberg et al., 2010). Further, in PAZOREAL the MSKCC risk score was available in only 23% of patients reflecting that MSKCC risk score determination is not routinely performed in clinical practice and that the risk score does not decide the treatment strategy (Motzer et al., 2013).

Pazopanib 1st-line mToD was 6.3 (5.6-7.4) months in PAZOREAL cohort I, and respective mToD for trial-eligible patients was 7.7 (6.1-9.0) months which is comparable to median exposure duration of 7.4 months in the pazapanib arm of VEG105192 (Sternberg et al., 2013) and of 8.0 months in ((Motzer et al., 2013), Study VEG108844), indicating that pazopanib therapy in the real world setting can be applied somewhat shorter than in the RCT setting (Cora N Sternberg et al., 2010). Similar outcomes in patient subgroup trial-eligible hint to no impact of trial-eligibility on treatment (Motzer et al., 2013; Cora N Sternberg et al., 2010).

In PAZOREAL most patients started with the standard dose 800 mg/day pazopanib. Pazopanib dose interruptions occurred in 30.3% of patients (FAS(P)) and was thus lower than in the randomized controlled trials (Motzer et al., 2013; Sternberg et al., 2019). There, 44% of pazopanib-treated patients had dose interruption and 24% of patients permanently discontinued the study drug because of adverse events (Motzer et al., 2013).

The PAZOREAL safety data is comparable to pivotal studies and current SmPC of pazopanib (June 2021, Reference ID: 014815-67235, (Motzer et al., 2014, 2013; Sternberg et al., 2019)).

QoL assessed by EQ-5D-5L did not relevantly change over the course of treatment in the clinical routine setting confirming previous observations in pivotal studies (Cora N Sternberg et al., 2010). However, previous reported QoL data of nivolumab in 2nd- and 3rd-line setting showed an QoL improvement compared to baseline (Cella et al., 2016). However, in PAZOREAL the number of patients for QoL-analyses was considerably smaller than in the study of Cella et al. 2016 (reporting a number of patients at baseline: 362 (88%) of 410 patients) and present QoL data should be interpreted with caution (Cella et al., 2016).

Conclusion

In real world, the majority of patients started with full dose (i.e., 800 mg per day) pazopanib. Taken the safety data of the PAZOREAL study together, it can be concluded that pazopanib is well tolerated. AE pattern and death rate lie in the expected range. No new or potentially important safety issues were identified during the study. The treatment sequence of pazopanib followed by nivolumab as 2nd-line treatment is commonly applied in Germany. Third-line everolimus following nivolumab is a rather rarely chosen therapy strategy. MSKCC risk score determination is not routinely performed and risk score does not decide the treatment strategy. For patients considered trial-eligible, time on drug was comparable with results from clinical trials.

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2 List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CI	Confidence Intervals
CONSORT	Consolidated Standards of Reporting Trials
CPI	Checkpoint-inhibitor
CRF	Case Report/Record Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
DBL	Database Lock
DCR	Disease Control Rate
DMP	Data Management Plan
EC	Ethic Committee
eCRF	electronic Case Report/Record Form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EMA	European Medicines Agency
EOS	End of Study
EQ-5D-5L	European Quality of Life -5 Dimensions -5 Levels
FAS	Full analysis set
FAS - cohort I	FAS comprised of patients who entered the study in the 1st-line treatment with pazopanib
FAS - cohort II	FAS comprised of patients who entered the study in the 3rd-line setting (study medication: everolimus after 2nd-line nivolumab)
FAS (E)	refers to the total number of patients included in the FAS for 2nd-or 3rd -line treatment with everolimus
FAS^{ext}	extended FAS comprised of patients of FAS patients plus patients who fulfilled all criteria of the FAS except the criterion of participation in any interventional research study (“klinische Prüfung” according to German drug law)
FAS (P)	refers to the total number of patients included in the FAS for 1st-line treatment with pazopanib
FAS (N)	refers to the total number of patients included in the FAS for 2nd-line treatment with nivolumab
FAS (QS,P)	refers to the total number of patients included in the Full Analysis Set who consented to participate in the questionnaire project
FPI	First-patient-in
GCP	Good Clinical Practice
GPP	Good Pharmacovigilance Practices
HA	Health Authority
HIF	Hypoxia-inducible factor
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IQR	interquartile range
KPS	Karnofsky Performance Status
LPI	Last-patient-in
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities

mRCC	Metastatic Renal Cell Carcinoma
MSKCC	Memorial Sloan-Kettering Cancer Center
mTOR	Mammalian target of Rapamycin
mToD	median Time on Drug
NIS	Non-Interventional Study
NVS	Novartis
OS	Overall survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PFS	Progression-free survival
PI3	Phosphoinositide 3-kinase
PD1	Programmed cell death 1
PDL1	Programmed cell death ligand 1
PT	Preferred Term
PRO	Patient-Reported Outcome
QoL	Quality of Life
RCC	Renal cell carcinoma
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAF	Safety Set
'SAF(all)	of cohort I: includes all patients from the Safety Set entering the study in the first-line setting
SAF^{ext}	extended Safety Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
ToD	Time on drug
TEAE	Treatment Emergent Event
TKI	Tyrosine kinase inhibitor
TNMG	Tumor, Lymph Nodes, Metastasis, Grade
VAS	Visual Analogue Scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor
VHL	Von Hippel-Lindau
WHO	World Health Organisation

3 Investigators

A list of all study sites is provided as a stand-alone document in Annex 1 - List of Stand-Alone Documents. A total of 167 study sites participated in this study, among them 48 sites did not enroll any patient.

4 Other responsible parties

Table 4-1 Responsible parties

Responsibility	Name and affiliation
Scientific Leader	[redacted] Managing Senior Physician Clinic for urologyUrologische Klinik Friedrich-Alexander University Rathsberger Straße 57 91054 Erlangen Germany
Sponsor	[redacted] – Medical Advisor [redacted] – Patient Safety Specialist Novartis Pharma GmbH Roonstraße 25 90429 Nürnberg Germany
Contract Research Organization	iOMEDICO AG Ellen-Gottlieb-Straße 19 79106 Freiburg Germany
Medical Director	[redacted] (iOMEDICO AG)
Project Leader	[redacted] (iOMEDICO AG)
Medical Manager	[redacted] (iOMEDICO AG)
Data Manager	[redacted] (iOMEDICO AG)
Trial Statistician	[redacted] (iOMEDICO AG)
Medical Writer	[redacted] (iOMEDICO AG)
Pharmacovigilance Specialist	[redacted] (iOMEDICO AG)

5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	December 2015	10 December 2015	First-patient-in
End of observation period	28 February 2021	28 February 2021	Last patient Last Visit LPLV

Milestone	Planned date	Actual date	Comments
End of data collection (Last date of data collection)	30 April 2021	30 April 2021 Database Soft Lock (end of data collection of follow-up information for adverse events) 11. June 2021 Data base Hard lock	
Registration in the EU PAS register	Not applicable	Not applicable	This stuy was not a PASS
Study progress report	not applicable	not applicable	Progress reports were not planned for this study
Interim report 1	06 April 2016	31 March 2017	Planned timepoint for Interim report 1: one year after market approval of Nivolumab for metastatic Renal Cell Carcinoma (mRCC). Actual date of Interim report 1 corresponds to the date of the respective database cut
Interim report 2	10 November 2017	13 November 2017	Planned timepoint for Interim report 2: one year after enrollment of 200. 1st-line patient Actual date of Interim report 2 corresponds to the date of the respective database cut
Interim report 3	10 November 2018	08 November 2018	Planned timepoint for Interim report 3: two years after enrollment of 200. 1st-line patient Actual date of Interim report 3 corresponds to the date of the respective database cut

Milestone	Planned date	Actual date	Comments
Interim report 4	10 November 2019	30 September 2019	Planned timepoint for Interim report 4: three years after enrollment of 200. 1st-line patient. Actual date of Interim report 4 corresponds to the date of the respective database cut. Due to submission timelines for the results of 4th interim report, data base cut was scheduled earlier
Final report of study results	30 November 2021	18 November 2021	Database lock (DBL) performed on 11 June 2021. Final study report to be provided to Novatis Pharma GmbH by iOMEDICO

6 Rationale and background

6.1 Background

Renal cell carcinoma (RCC) is the most common tumor disease of the kidney. RCC is diagnosed in about 15,500 patients per year in Germany. The most frequent occurrence of the disease is between the ages of 60 and 80 years (Robert Koch Institut, 2017). Up to 30% of patients have metastatic disease at the time of diagnosis, and up to 30% recur after curative therapy (Corgna et al., 2007; Miller et al., 2007). Clear cell RCC is the most common histologic subtype of RCC, accounting for 75% of the cases (Linehan et al., 2007). Approximately 90% of patients with clear cell RCC have decreased expression of VHL protein (Hemminki et al., 2002; Nickerson et al., 2008). Pathogenetically, this results in decreased degradation of the transcription factors HIF-1α and HIF-2α. This leads to an increased expression of proliferation-promoting and proangiogenic factors such as VEGF. Therefore, direct blockade of the VEGF signaling pathway by VEGF antibodies or VEGFR-TKIs (VEGF receptor tyrosine kinase inhibitor) and inhibition of the PI3 kinase/AKT-/mTOR signaling pathway represent promising therapeutic approaches. mTOR is a component of the PI3 kinase/AKT-/mTOR signaling pathway and has a central role in cell proliferation, survival, and metabolism. Inhibition of mTOR in carcinoma cells and endothelial cells leads to cytostasis and apoptosis and decreases angiogenesis through reduced transcription of VEGF.

The introduction of targeted substances represented a milestone in the treatment of advanced RCC. The VEGFR TKIs sorafenib, sunitinib and pazopanib as well as the anti-VEGF antibody Bevacizumab inhibit the VEGF signaling pathway and are approved for 1st-line treatment of mRCC. They showed prolongation of median progression-free survival (PFS) by 6 months (sunitinib), 5 months (bevacizumab), 3 months (sorafenib), and 3 months (pazopanib), respectively, compared with placebo (Escudier et al., 2007a, 2007b; Motzer et al., 2007; Cora N Sternberg et al., 2010). The two VEGFR TKIs sunitinib and pazopanib are now established

as the standard of care in 1st-line therapy of mRCC and are recommended by the relevant guidelines (Escudier et al., 2014; Kirchner et al., 2013). In a head-to-head comparative study (COMPARZ study) for 1st-line treatment of mRCC, non-inferiority of pazopanib versus sunitinib in terms of efficacy (PFS, Overall survival (OS)) was demonstrated (Motzer et al., 2014, 2013). While PFS was around 9 months for sunitinb as well as for pazopanib, median treatment duration (time on drug, ToD) was 8.1 months and 7.6 months for pazopanib and sunitinib, respectively (Motzer et al., 2014, 2013). Thus, ToD appears to be a practicable surrogate parameter for PFS. OS was around 29 months for both substances in this direct comparison (Motzer et al., 2014). In a patient preference study, 70% of patients stated to prefer pazopanib, 22% selected sunitinib as preferred treatment option (Escudier et al., 2014).

Further prolongation of median survival could be shown with sequential use of targeted therapy after TKI-therapy in 1st-line. Everolimus (Afinitor®), an an orally administered inhibitor of the serine threonine kinase mTOR, was the first therapy to show efficacy after failure of targeted therapy in a controlled trial. Everolimus prolonged PFS in 2nd-line therapy vs. placebo (4.9 vs. 1.9 months) (Motzer et al., 2010). Median OS in the RECORD-1 study was 14.8 months (p = 0.18), which showed no difference due to crossover from placebo arm to everolimus arm (Motzer et al., 2010).

Two further TKIs, cabozantinib (as monotherapy) and lenvatinib (in combination with everolimus), have been approved for second and later line treatment of mRCC in 2016. Both substances showed an additional prolongation of PFS compared to everolimus monotherapy in pretreated patients (Choueiri et al., 2016; Motzer et al., 2015b).

Recent progress in the therapy of various cancers was made with activated T-cells. These molecules (“Checkpoint-inhibitors”, CPI), mostly monoclonal antibodies, binding to PD1 (programmed cell death 1), PDL1 (programmed cell death ligand 1) or CTLA-4 (cytotoxic T-lymphocyte associated protein 4) have shown clinical activity by blocking an inhibitory signal for T-cells, thus activating the patient’s immune system against tumor cells. This intervention in the regulation of T-cells has been tested on several tumor types in parallel and lead to the first approval of the CTL-4 antibody ipilimumab for treatment of metastasized melanoma in Europe in 2013 (Hodi et al., 2010). PD1-inhibitors intervene at another site of T-cell regulation. This site is more specific for the environment of the tumor. These antibodies (e.g. nivolumab or pembrolizumab) have also been investigated as treatment option of metastasized melanoma. Nivolumab was approved for the treatment of metastasized melanoma in 2015. In parallel, other tumor entities were also investigated in regard of treatment with nivolumab or pembrolizumab. Phase III data for nivolumab from predominantly heavily pretreated mRCC patients showed a PFS of 4.6 months and an OS of 25 months (Motzer et al., 2015c). Nivolumab was approved by the EMA (European Medicines Agency) for use in pretreated mRCC patients in April 2016. Nowadays, depending on the patients’ risk-profile, sunitinib, pazopanib, tivozantinib, and cabozantinib, but also CPIs such as nivolumab combined with ipilimumab or cabozantinib, avelumab combined with axitinib or pembrolizumab combined with axitinib are recommended as standard therapeutics in the first-line treatment of aRCC (Amsberg, 2020; Escudier et al., 2012; Ljungberg et al., 2015; “S3-Leitlinie Nierenzellkarzinom,” 2020). The combination of nivolumab and cabozantinib was recently approved as first-line treatment (Choueiri et al., 2021). Resistance to TKIs may be driven by adoption of alternative signaling pathways to compensate for the inhibition of VEGFR signaling and provide pro-survival stimulation.

Application of cabozantinib, nivolumab or the combination of lenvatinib and everolimus as well as of TKIs axitinib, pazopanib, sorafenib, or sunitinib or the mTOR inhibitor everolimus could be used as second-line therapy in patients that progress on VEGFR TKIs in first line ("S3-Leitlinie Nierenzellkarzinom," 2020). New combination therapies, such as Lenvatinib plus pembrolizumab demonstrated statistically significant and clinically meaningful improvements in PFS, OS, and objective response rate (ORR) versus sunitinib and are currently under review for EMA's approval (Motzer et al., 2021).

6.2 Rationale for the PAZOREAL Study

Real-life data are limited for pazopanib in 1st-line mRCC patients, and are even more limited for sequential treatment with pazopanib in 1st-line and everolimus or another targeted agent in 2nd-line. The therapy algorithm in mRCC has been evolving by the introduction of CPI (such as nivolumab or pembrolizumab), as well as new TKI (cabozantinib and lenvatinib + everolimus, respectively) as new treatment options for the 2nd-line following TKI in 1st-line.

At the time when this study was designed, nivolumab had not been approved in the EU, but based on published study results, the timely approval of nivolumab was assumed. Nivolumab, cabozantinib and lenvatinib have been approved for mRCC treatment during this non-interventional study (NIS), and their use in 2nd-line (and later lines) commenced immediately after approval in Germany. With the approval of nivolumab, the treatment algorithm for patients with mRCC has changed.

While the safety and efficacy of both, pazopanib in 1st-line mRCC, as well as Everolimus in 2nd-line mRCC have been evaluated in the pivotal randomized, double-blind, placebo-controlled, multinational trials and other clinical studies, real-world data are needed to further evaluate the safety, tolerability, effectiveness, and quality of life (QoL) of Pazopanib as 1st-line treatment of mRCC followed by nivolumab in 2nd-line. Real-world data from patients treated with Everolimus in 3rd-line after 2nd-line treatment with nivolumab are also of interest. There is an unmet need of such data in the real-world setting of the evolving treatment landscape in mRCC. Both pazopanib and everolimus differ substantially in tolerability profile from other drugs currently used in first- and 2nd-line therapy of mRCC, respectively, with advantages in major adverse events (AEs). Also in this respect, a characterization of the application in different sequences is of essential interest.

7 Research question and objectives

This non-interventional study was designed to observe how mRCC patients are treated with pazopanib in 1st-line, and what therapies are subsequently used in second and 3rd-line in a real-world setting with an evolving treatment landscape. The focus in 2nd-line was on everolimus, which was the current 2nd-line standard at the start of the study, and the evolving treatment landscape was observed in real-time: Since the checkpoint-inhibitor (CPI) nivolumab had been approved for use in the second (or later) lines, this treatment could also be documented. This evolution was also affecting the use of everolimus. After regulatory approval of nivolumab for the 2nd-line, this study thus also allowed documentation of patients being treated with everolimus in 3rd-line after 2nd-line treatment with nivolumab.

Any decisions on treatment was made by the treating physician, independently of the study. From 1st-line treatment with pazopanib onwards, the following treatment lines were documented in this study, as long as the treatment was in accordance with the German SmPC.

Objectives:

- To evaluate effectiveness of pazopanib in 1st-line and everolimus (also in the approved combination with lenvatinib) in 2nd- and 3rd-line therapy as well as nivolumab in 2nd-line therapy of mRCC patients in real life setting, by measuring the duration of treatment of the respective therapies.
- To test further parameters of effectiveness, safety and QoL in patients with mRCC who were treated with pazopanib in 1st-line therapy, everolimus (also in the approved combination with lenvatinib) in second or 3rd-line therapy, and nivolumab in 2nd-line therapy of mRCC patients in real life setting

8 Amendments and updates to the protocol

In Table 8-1 all amendments and updates as well as the reasons of it are depicted.

Table 8-1 Amendments and updates to the protocol

Number	Date	Section of study protocol	Amendment or update	Reason
1	13 March 2017	Section 3 Section 5 Section 7.1 Section 7.2 Section 7.3 Section 7.4 Section 7.5 Section 7.8 Section 9.2.2	Amendment to version 00	• Consideration of regulatory approvals of Nivolumab (Opdivo®), Cabozantinib (Cabometyx®) and combination of Everolimus (Afinitor®) and Lenvatinib (Kisplyx®) • Capturing the reality in the healthcare field as a function of regional differences respectively geographical proximity to the Treatment Center and depending on participation in structured Patient Education Program

				• Update on timelines regarding fast enrollment of 1st-line patients
2	07 November 2018	Section 3 Section 4 Section 9.3	Amendment to version 01	- Reporting of pregnancies: update concerning registration of pregnancies of female partners of male study participants

9 Research methods

9.1 Study design

PAZOREAL was a prospective, multi-center, non-interventional observational study to evaluate effectiveness, tolerability, safety, and QoL in patients with mRCC treated with pazopanib in the 1st-line, nivolumab or everolimus in 2nd-line, or everolimus (also in the approved combination with lenvatinib) in 3rd-line after nivolumab (Figure 9.1). Data on QoL were collected and analyzed using the EQ-5D-5L questionnaire for patients having consented in the data collection via questionnaire and having obtained their 1st questionnaire before the respecitive treatment started (i.e., QoL data was available for a subset of patients). The documentation of therapy sequences of nivolumab in the 2nd-line setting was initiated on 14 April 2016 after its approval in Europe on 06 April 2016.

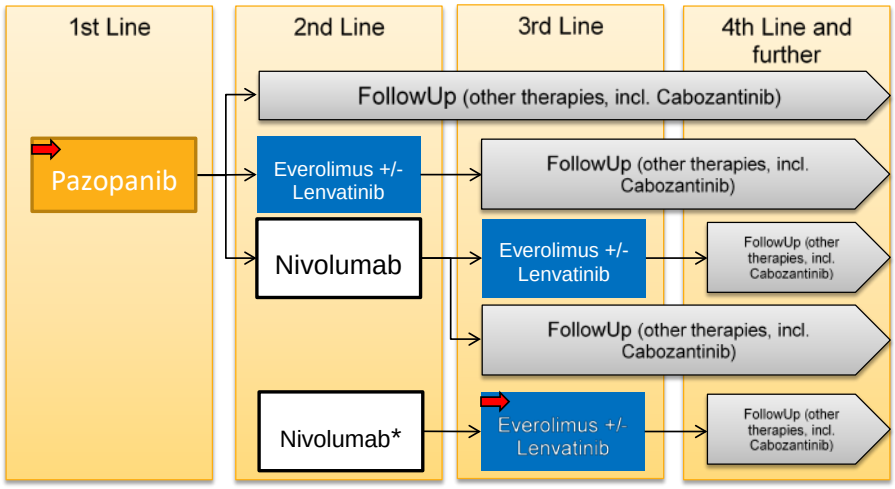


Figure 9.1 Study design

Red arrow: documentation in eCRF was allowed to start here: 1st-line pazopanib or 3rd-line everolimus after nivolumab in 2nd-line (treatment with nivolumab must have been carried out according to the approval).

* retrospective documentation of nivolumab in the 2nd-line. (This figure was provided in German within the observational plan by the sponsor.)

It was planned to include 450 eligible patients in about 150 sites: 400 patients with 1st-line treatment with pazopanib (cohort I) and 50 patients with 3rd-line treatment with everolimus after treatment with nivolumab in 2nd-line (cohort II) as depicted in Figure 9.1. The recruitment of eligible patients was competitive among the centers participating in PAZOREAL, i.e. there was no limit of patients to be recruited by an individual center.

The diagnostic and patient monitoring procedures were only those applied in clinical routine. Prescription of the medication was independent from the decision to include the patient into the study. The medical decisions and course of treatment, including diagnosis and follow-up, reflect exclusively the decision of the treating physician in routine clinical practice. The appointments for interaction between patient and treating physician were determined according to clinical necessity.
The choice of this methodical approach reflects the character of a NIS. There were no specified dose regimens or medical procedures defined within the NIS protocol. Every medical decision and course of treatment with pazopanib and further-line therapies reflect exclusively the decision of the treating physician in routine clinical practice. The concept of this NIS and its documentation procedure did not affect routine clinical practice in any aspect.
In the NIS protocol of PAZOREAL v2.0 dated 07 November 2018 (Annex 1 – List of Stand-Alone Documents), a suggestion for data collection was provided as described in Table 9-1.

Table 9-1 Data collection

	Baseline	Observation periods (every 12 weeks)	End of treatment	Medication switch	Follow-Up (every 6 months)
Demographic data	X				
Vital signs	X	X	X	X	
ECOG-Score	X	X		X	
Concomitant medication[F]	X	X	X	X	
Exposure data	X	X	X	X	
QoL[A]	X	X		X	
Prior therapies[B]	X				
Adverse events	X[C]	X	X	X	X
Laboratory[D]	X	X	X	X	
Disease assessment	X	X	X		X[E]
Reason treatment discontinuation			X		X
Subsequent therapies[G]					X
Survival status					X

ECOG = Eastern Cooperative Oncology Group

[A]: QoL data was available from a subset of patients. According to the agreement on the DGHO (Basel, 2015) there were no patient reported outcomes (PROs) at the end of treatment.

[B]: Only available for patients from cohort II.

[C]: Retrospective documentation for patientst from cohort II.

[D]: For laboratory tests in range of the normal values only the date of the test was documented. For values outside normal ranges, the differing values were documented.

[E]: Progression yes/no

[F]: Including Lenvatinib in the approved combination with Everolimus

[G]: Including Cabozantinib in the approved indication

(*This table was adapted from the observational plan provided by the sponsor.)*

Overall, this study was descriptive in nature and did not attempt to test any specific a priori hypotheses.

PAZOREAL was performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GCPs, GPP and the applicable legislation on NIS. PAZOREAL was examined by the Ethic Committee (EC) at the General Medical Council of the State of Baden-Wuerttemberg (*Landesärztekammer Baden-Württemberg*).

The sponsor of the study was Novartis Pharma GmbH, Nürnberg, Germany. The responsible parties and administrative structure of the study are detailed in Table 4-1 (cf.Chapter 4: Other responsible parties).

9.2 Setting

PAZOREAL was conducted in 167 sites all over Germany including oncologists in hospitals and outpatient clinics, and independent oncology practices. Patients meeting the study inclusion/exclusion criteria were selected between 10 December 2015 (first-patient-in; FPI) and 22 December 2017 (last-patient-in; LPI). Patients were followed from enrollment in the study until death, loss to follow-up, withdrawal of consent or study end date (whichever occured earlier). The follow-up period comprised follow-up visits every 6 months and lasted until End of study (EOS; last-patient-last-visit; 28 February 2021). Database lock (DBL) was performed on 11 June 2021.

9.3 Subjects

Eligible patients were adults with advanced/mRCC and a life expectancy of ≥ 6 months who started treatment with 1st-line pazopanib or 3rd-line everolimus maximum 8 weeks prior to informed consent.

All enrolled patients were assigned to either Cohort I (documentation started with 1st-line treatment with pazopanib) or Cohort II (documentation started with 3rd-line treatment with everolimus after 2nd-line nivolumab).

9.3.1 Inclusion Criteria

Patients were eligible, if all of the following criteria were met.

- Patients with a histological diagnosis of advanced / mRCC of any histology
- The treating physician has made the decision to treat the patient
    - with pazopanib in the 1st line, or
    - with everolimus (also in the approved combination with lenvatinib) in the 3rd-line after nivolumab in 2nd line (nivolumab treatment must have been in label)
- Written informed consent of the patient

- The treating physician assumes a life expectancy of at least 6 months
- Planned treatment is in line with the respective current German SmPC

9.3.2 Exclusion Criteria

Patients were not eligible, if any of the following criteria was met:
- Patients <18 years of age
- Patients unable to provide written informed consent
- Contra-indication according to the respective current German SmPC
- The patient is currently under active treatment in an interventional research study ("klinische Prüfung" according to German drug law)

9.4 Variables

Since PAZOREAL was a NIS, the following variables were captured from medical records as per documentation procedure in routine clinical practice. These data were transmitted pseudonymously into the eCRF. No diagnostic measures, nor treatment concepts, nor visit schedule were specified. No study specific data was collected.

Recommendations were made regarding the examination intervals (refer to Table 9-1)

All data were collected prospectively, with the following exceptions:

- Retrospective documentation of 1st-line treatment with pazopanib (cohort I) was allowed for up to 8 weeks after first intake of pazopanib, but only after informed consent of the respective patient. In this case, data were collected retrospectively from the 1st-line treatment period that had already elapsed.
- For patients in cohort II, 2nd-line treatment with nivolumab was documented retrospectively in all cases. Data collection of treatment with nivolumab was only allowed after informed consent of the respective patient and if treatment with nivolumab had been carried out in the approved indication , i.e. outside of clinical trials. Retrospective documentation of 3rd-line treatment with everolimus was allowed for up to 8 weeks after first intake of everolimus after 2nd-line treatment with nivolumab. In this case, data for everolimus were collected retrospectively from the 3rd-line treatment period that had already elapsed.

For patients who filled in QoL questionnaires (EQ-5D-5L), these questionnaires were also used as a data source.

Toxicities were classified and documented according to CTCAE criteria.

9.4.1 Demographic Data

Age (year of birth), gender, height (cm) and body weight (kg) at start of treatment (baseline). Further weight measurements could be documented at each visit according to the routine clinical practice and at the discretion of the investigator.

9.4.2 Vital Signs

Routine vital signs measurements included systolic and diastolic blood pressure and pulse measurements. Assessment of vital signs followed routine clinical practice and was documented accordingly at baseline visit, at each subsequent visit, at visits for change in therapy and at termination visit.

9.4.3 Concomitant Disease

Presence [yes; no] and any kind of relevant comorbidities including pre-existing abnormal laboratory values, could be documented at baseline as free-text capturing the start and end date (if applicable).

9.4.4 Disease History

Primary diagnosis of RCC (date) including type of histology, staging (classification according to tumor, lymph nodes, metastasis, grade; TNMG-classification) at enrollment and data for risk assessment according to Memorial Sloan-Kettering Cancer Center (MSKCC) score (Robert J. Motzer et al., 2002) and Heng Score (Escudier et al., 2012) were to be captured as available at baseline.

For calculation of the Heng Score the parameters of interest were: Karnofsky performance status (KPS) (< 80 %), Hemoglobin (< lower limit of normal), time from diagnosis to treatment (< 1 year), corrected calcium (> upper limit of normal), platelets (> upper limit of normal), neutrophils (> upper limit of normal).
For calculation of the MSKCC score the parameter of interest were: Karnofsky performance status (< 80%), hemoglobin (< lower limit of normal), time from diagnosis to treatment (< 1 year), corrected calcium (> 10 mg/dl), lactate dehydrogenase (> 1.5 × upper limit of normal).

Data concerning nephrectomy ([yes; no], if applicable: R-staging, nephrectomy status [radical; partial]) and metastasis (date of first metastasis, localization of metastases) could be documented at baseline.

9.4.5 ECOG/Karnofsky Performance Status

Study subjects' performance status as assessed by the local investigator according to the Eastern Cooperative Oncology Group (ECOG) or KPS scoring system. The ECOG or KPS could be documented at baseline, at each subsequent visit and at visits for change in therapy. The ECOG as well as the KPS rates a patient's ability to perform daily activities. The ECOG scores range from 0 to 5 with a lower score indicating a better performance. The KPS scores range from 0 to 100 with a higher score indicating a better performance. In case the Karnofsky Index was recorded, the Karnofsky Index value was transformed into the ECOG status according to Table 9-2 (Oken et al., 1982).

Table 9-2 Transformation of Karnofsky Index into ECOG Performance Status

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	**100**	**0**	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	**90**	**0**	Fully active, able to carry on all pre-disease performance without restriction
Normal activity with effort	**80**	**1**	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Care for self. Unable to carry on normal activity or to do active work	**70**	**1**	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Requires occasional assistance, but able to care for most of his needs	**60**	**2**	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	**50**	**2**	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Disabled. Requires special care and assistance	**40**	**3**	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Severely disabled. Hospitalization indicated though death nonimminent	**30**	**3**	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Very sick. Hospitalization necessary. Active supportive treatment necessary	**20**	**4**	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Moribund	**10**	**4**	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Dead	**0**	**5**	Dead

adapted from (Oken et al., 1982)

9.4.6 Concomitant Medication

Intake of concomitant medication [yes; no], including lenvatinib for patients treated with the approved combination of everolimus and lenvatinib in 3rd-line, was documented until the end of treatment with study medication capturing start and end date. The concomitant medication was coded using WHO Drug Dictionary.

9.4.7 Exposure data

9.4.7.1 1st-line therapy - pazopanib

Administration of pazopanib at baseline visit and at each subsequent visit.

- Treatment start date
- Daily dose

- Dose modifications
- Treatment interruption
- Reason for modification or interruption
- Treatment end date
- Reason for treatment end

9.4.7.2 2nd-line therapy – nivolumab

Administration of nivolumab at baseline visit for 2nd-line and at each subsequent visit.

- Treatment start date
- Daily dose
- Dose modifications
- Treatment interruption
- Reason for modification or interruption
- Treatment end date
- Reason for treatment end

9.4.7.3 2nd- or 3rd-line therapy – everolimus

Administration of everolimus at baseline visit for 2nd- or 3rd-line and at each subsequent visit.

- Treatment start date
- Daily dose
- Dose modifications
- Treatment interruption
- Reason for modification or interruption
- Treatment end date
- Reason for treatment end

9.4.7.4 2nd-line therapy - nivolumab (retrospective) for patients enrolled in 3rd-line with everolimus

Retrospective documentation of nivolumab in 2nd- line and prior 1st- line therapy at baseline visit for patients enrolled for 3rd- line treatment with everolimus.

- Substance class of 1st-line therapy
- Nivolumab data:
  - Treatment start date
  - Treatment interruption

- Reason for interruption
- Treatment end date
- Reason for treatment end

9.4.8 Patient-Reported Outcome (PRO)

PRO including QoL was collected via the standarized EQ-5D-5L questionnaire (as attachment of Study Protocol, Annex 1 – List of Stand-Alone Documents). EQ-5D-5L questionnaire was used only for the patients who had given their written consent for this and who were enrolled prospectively.

The first questionnaire in each therapy line was handed out to the study subject at the study site prior to first intake of the respective study medication. The centers had to provide a quiet place where the subject had sufficient time and space to concentrate on the questions and to complete the questionnaire. No checks for completeness had to be done. The subject was allowed to refuse to complete all or any part of a questionnaire Subsequent questionnaires were send quarterly by the iOMEDICO site management organization (iOMEDICO SMO GmbH, Freiburg, Germany) till patients either reached follow-up period or end of study, whatever came first.

9.4.9 Local factors

The distance between the patient's residence and the practice/hospital as well as the information about the patients' participation in a "Patient Education Program" and type of education program could be documented at baseline.

9.4.10 Reporting of Adverse Events, Serious Adverse Events, Adverse Drug Reactions and Seriuos Adverse Drug Reactions

For safety analysis, all AEs including serious AEs (SAEs), adverse drug reactions (ADRs) and serious ADRs (SADRs) had to be documented in the eCRF from start of therapy of the investigated drug in this NIS (Pazopanib, Everolimus, Nivolumab) until 30 days after completion of the treatment phase. SAEs which occurred more than 30 days after completion of the treatment phase had to be documentet in the eCRF if a causal in case a relationship to investigated drug existed or was suspected.

For patients who had already started therapy before inclusion in the NIS, the documentation start was moved back (retrospective documentation, postponement of the start of documentation by a maximum of 8 weeks was possible, but only with the written consent of the patient). All AEs, SAEs, ADRs, and SADRs were retrospectively included from the day of first pazopanib intake, which was maximal 8 weeks before inclusion.

If the patient was enrolled in 3rd line while receiving everolimus as after 2nd-line therapy with nivolumab, all AEs and ADRs (non-serious as well as serious) were documented retrospectively from the first timepoint of nivolumab administration.

An AE was defined as any untoward medical occurrence in a patient administered a drug investigated in this NIS, and which not necessarily had a causal relationship to that treatment. This included the following untoward events:

- Abnormal laboratory values if:

- deteriorating compared to respective baseline value (this condition did not apply if there was no respective baseline value) and if one of the following criteria applied:
  - considered as clinically relevant by the treating physician
  - associated with clinical signs or symptoms
  - required medical intervention
  - resulting in dose reduction
  - resulting in treatment interruption
  - resulting in discontinuation of treatment

Abnormal laboratory values were considered as SAE if the changes correspond to a CTCAE grade 3 or greater.

- Drug interactions with other drugs or food
- Drug exposure during pregnancy (maternal or paternal exposure)
- Drug exposure during lactation
- Inadequate or lack of efficacy
- Overdose (accidental or intended)
- Abuse
- Misuse
- Medication and administration error, including intake of medication from another person, output/delivery error or name confusion
- Accidental exposure to drug in an accident
- Drug addiction
- Withrawal / drop-off phenomen / rebound phenomen
- Father application (in temporal context) before or at conception of a child, regardless of the outcome of the pregnancy
- Unexpected positive effect
- Non-Compliance, i.e. patient non-compliance with application recommendations (e.g. dosage and mode of application) with clinical symptoms

An AE was classified as Treatment Emergent AE (TEAE) if it was temporally related to any study medication excluding retrospective nivolumab documentation. For the purpose of the statistical analyses, all AEs which occurred or worsened during the on-treatment period were classified as TEAE.

9.4.10.1 Documentation of Adverse Events

Any SAE (regardless of causality) had to be documented in the eCRF within 24 hours of awareness. Recurrent episodes, complications, or progression of the initial SAE had to be documented within 24 hours of awareness as a follow-up information to the original episode, regardless of when the event occurred. AEs which occurred 30 days after completion of treatment phase were only to be documented in the eCRF in case of suspected causal relationship of any investigated drug in this NIS.

Any non-serious AE (regardless of causality) had to be documented in the eCRF within 10 days of awareness.

Documentation of an AE had to include at least the following details:

- Description of the event (diagnosis)
- Start and end date of event
- Severity grading of the event according to CTCAE v4.03 (Per definition, AEs with CTC grade 4 were considered serious. Documentation of seriousness had to be done with the most applicable serious criterion.)
- Seriousness of event
- Causal relationship with the treatment
- Management and outcome of event

For all documented non-serious AEs iOMEDICO AG checked whether the AE classified as non-serious by the reporter is, by definition, a SAE. To verify whether the documented non-serious AE was a SAE, the EMA-IME[3] list was used as a basis in addition to the SAE definition in Table 9-3, even if the event was classified as non-serious by the physician.

[3] https://www.ema.europa.eu/documents/other/important-medical-event-terms-list-version-meddra-version-240_en.xlsx

Table 9-3 Definiton SAE

A SAE is defined as AE, for which at least one of the following criteria applies:
Fatal or life-threatening
Results in a permanent or significant disability or incapacity
Represents a congenital anomaly or birth defect
Necessitates inpatient treatment or prolongation of inpatient treatment, unless the treatment is for the following reasons: a) Hospitalizations that are part of the normal treatment or monitoring of the condition studied in the NIS and are not due to a worsening of the condition b) Elective hospital admissions or hospital admissions planned before inclusion in the NIS for treatment of existing conditions that have not worsened since use of the drugs studied in this NIS c) Hospital admission for social reasons and for short-term care without the presence of a deterioration in the patient's general condition
Medically important, i.e. an AE that puts the patient at risk

The Medical Dictionary for Regulatory Activities (MedDRA) v20.0 was used for classification of reported terms within respective System Organ Class (SOC) and Preferred Term (PT), which was performed by iOMEDICO AG.

9.4.10.2 Evaluation of (Serious) Adverse Events and (Serious) Adverse Drug Reactions

A medical causality assessment was mandatory and had to be documented in the eCRF:

- No causal relationship
- Causal relationship suspected

9.4.10.3 Protocol-exempt Events

Medical conditions or diseases that existed before the initial application of the investigated drugs (Pazopanib, Everolimus, Nivolumab) in this NIS were considered AEs only if they had worsened after treatment start with these drugs.

All fatal AEs had to be documented as SAE except for fatal AEs which occurred more than 30 days after completion of treatment with Pazopanib or Everolimus and if no causal relationship was suspected.

Progressive Disease (PD) had to be recorded in the eCRF, but not to be documented as an AE except for progression with fatal outcome.

9.4.11 Reporting and Documentation of Pregnancies

Any pregnancy of a patient receiving one of the Novartis-drugs investigated in this NIS, had to be reported to Novartis within 24 hours of awareness by using a designated pregnancy reporting form. Pregnancies were to be documented and reported separately from potential, simultaneous AEs/ADRs. Pregnancies had to be followed up accordingly.

Information on pregnancies that occurred during treatment in the study had also to be collected for female partners of male study participants treated with the drugs investigated in this NIS.

A corresponding ICF for the collection of data on the pregnancy and birth of the child had to be obtained for this purpose from the mother by the participating physician prior to documentation.

9.4.12 Laboratory

Laboratory values could be documented at each visit. In case of laboratory values outside the standard range, date of respective laboratory test result, and the respective values were collected.

9.4.13 Disease Assessment

Responses were determined and categorized (progressive disease (PD), Complete Remission (CR), Stable Disease (SD, i.e. non-CR, non-PD) or not evaluable) radiologically or clinically by the local investigator according to local routine clinical practice during treatment with study medication and captured every 12 weeks as per medical records.

9.4.14 Subsequent therapies

After end of treatment subsequent therapies including Cabozatinib according to the approved indication could be documented during follow up.

9.4.15 Survival status

Current survival status was documented every 6 months during follow up.

9.5 Data sources and measurement

9.5.1 Data source

The electronic data capture (EDC) system (iostudy office edc) used in this study was provided to the study sites by iOMEDICO AG. The data was derived from eCRF-entries made by the study sites. Data were transferred from source documents (i.e., patient's medical records) to the eCRF. Data were fully pseudonymized and all information collected in this study was treated strictly confidentially.

Captured data were validated by source data verification. The database quality was reviewed by onsite and remote monitoring of data entered in the eCRF. Completed eCRF data-entries were checked for compliance with the observational plan and for completeness, consistency, and accuracy. All steps of central quality checks were performed and recorded according to iOMEDICO-specific SOPs. Monitoring activities with direct site contact were conducted according the respective Novartis SOP.

The handling of questionnaires for PRO was organized with the support of iOMEDICO SMO GmbH. The iOMEDICO SMO GmbH handled the questionnaires with a pseudonymized subject identification process and had no access to subject data in the eCRF to ensure data protection requirements. Subject contact details received by iOMEDICO SMO GmbH were strictly separated from the data received and handled by iOMEDICO AG.

A statistical analysis plan (SAP) was developed and approved both by Novartis Pharma GmbH and iOMEDICO AG prior to first data evaluation. Final data analysis was based on the recent SAP v4.1, dated 14 November 2019 (Annex 1 - List of Stand-Alone Documents).

9.5.2 Patient-Reported Outcomes

PRO were collected only for the patients who had given their written consent for this and who were enrolled prospectively.

For cohort I, the initial PRO questionnaires (baseline questionnaire) were handed out by the responsible study site before patient started their treatment with 1st line pazopanib as well as before the start of 2nd line nivolumab and 3rd line everolimus treatment. Questionnaires were quarterly distributed to the study subjects by iOMEDICO SMO GmbH untill follow-up or end of study was reached, whatever comes first.

For cohort II, baseline questionnaire) were handed out by the responsible study site, only when enrollment was prospective before the start of 3rd line everolimus treatment. After this, iOMEDICO SMO GmbH send quarterly questionnaires to the patients till follow-up or end of study was reached, whatever comes first.

Subject contact details and date of consent were sent by the site to iOMEDICO SMO GmbH via a link in the EDC system. The iOMEDICO SMO GmbH organized the distribution of subsequent questionnaires according to the scheduled assessments via standard post mail. Study subjects returned completed questionnaires in a pre-paid neutral envelop with no sender information to iOMEDICO AG. At the iOMEDICO AG, the questionnaire data were collected and evaluated. Paper-based patient questionnaires served as source documents. Scanned data from questionnaires were saved on a separate database.

9.5.3 Safety related measurements

Safety-related data was recorded as part of the routine clinical practice (i.e., physical examination, vital signs, laboratory evaluations, and other safety-related assessments).

9.6 Bias

Patients were included in the study according to respective treating physician’s discretion. The medical decision and course of treatment with pazopanib, everolimus, or nivolumbab reflect exclusively the decision of the respective treating physician in routine clinical practice according to the respective current SmPC. Therefore, during data collection, much attention and efforts were made to ensure inclusion criteria and exclusion criteria were met and data quality was high. Regular remote data checks were performed. No randomization or stratification took place. Therefore, a comparison of different therapies in the same line was not possible. The data were analyzed using epidemological methods, and therefore the validity is limited.

9.7 Study size

In this study, it was planned to enroll 450 patients (400 patients in 1st-line (pazopanib) and 50 patients in 3rd-line (everolimus)) in about 150 study sites in Germany. Due to the non-

interventional character of this study no formal sample size calculation was conducted. No hypothesis testing was conducted. The sample size of 400 1st-line patients was chosen to guarantee representativeness for the investigated population. Recruitment of patients in a specific line was stopped when the respective number was reached. This did, however, not stop recruitment in the other line. Recruitment of patients in 1st-line was stopped on 31 August 2017 when 420 patients were enrolled. Due to end of recruitment period, recruitment of patients in 3rd-line was stopped on 01 March 2018 when 7 patients[4] were enrolled.

9.8 Data transformation

Data as available from routine clinical practice were collected via eCRFs and transmitted to a database. The eCRF contained a data dictionary providing a detailed description of each variable used in this study.

Computerized and manual consistency checks were performed, i.e. logical checks on data entries to check for inconsistencies.

A data management plan (DMP) defined how to deal with missing data and invalid entries, how data had to be cleaned, and which level of error was acceptable. The DMP described how data had to be tracked and coded, how query reports were to be generated and resolved, and how data was to be stored and secured. Finally, the DMP described a quality assurance system for data entry.

9.8.1 Main summary measures

The statistical methods and plans according to the final SAP v4.1 dated 14 November 2019 (Annex 1 – List of Stand-Alone Documents) are summarized in the following (sub-) sections. The statistical analysis of study results was performed using SAS™ Version 9.4.

9.8.1.1 Anaylysis Populations

The following analysis populations were used in the final analysis:

- **The full analysis set (FAS):** The primary analysis population included all patients for whom the documentation was started in the 1st-line (pazopanib treatment) or in the 3rd-line (everolimus treatment following 2nd-line nivolumab) and who received at least one dose of study drug in the respective therapy line (pazopanib / everolimus). In addition, the informed consent had to be signed by the patient not later than 8 weeks after start of treatment with 1st-line pazopanib or 3rd-line everolimus, respectively. Moreover the patient may not took part in any interventional research study (“klinische Prüfung” according to German drug law) at any time during the participation in the NIS PAZOREAL.
  All patients included in the primary analysis population were distributed to two different analysis sets. Patients who entered the study in the 1st-line setting (1st-line treatment: pazopanib) were included in the full analysis set I (FAS-I, cohort I). Patients who entered the study in the 3rd-line setting (study medication: everolimus after 2nd-line

[4] After enrollment, one patient was excluded due to the exclusion criteria ‘participation in another clinical trial’. Thus 6 patients were assigned to FAS-II, cohort II, i.e. treated with everolimus in 3rd-line setting.

nivolumab) were included in the full analysis set II (FAS-II, cohort II). The FAS-I and the FAS-II were the relevant populations for the effectiveness evaluation including exposure data.

- **Sensitivity analysis population: extended Full Analysis Set (FAS^{ext}):** For predefined analyses an FAS^{ext} was used, including all patients from the FAS as well as patients who fulfilled all criteria of the FAS except the criterion of participation in any interventional research study ("klinische Prüfung" according to German drug law) at any time during the participation in the NIS PAZOREAL (i.e. patients participating in any interventional study during participation in the PAZOREAL NIS were analyzed).
  Analyses of interest applied to:
  1. Time on Drug (ToD)
  2. Overall Survival (OS)
  3. Quality of Life (QoL)
- **Safety Set (SAF):** The secondary analysis population - the SAF - included all patients from the FAS who received at least one dose of study drug (pazopanib, everolimus or nivolumab) and for whom at least one further post-baseline information (e.g. laboratory) was available. This population was relevant for laboratory parameters and adverse events (AEs).
- **Sensitivity analysis population: SAF^{ext}:** This population comprised all patients from the SAF plus further patients that were excluded due to inspection findings, as described in 9.8.1.1.1. The SAF^{ext} served as the sensitivity analysis population for the presentation of AEs.

9.8.1.1.1 Exclusions from Analysis Populations

Patients identified as non-analyzable due to data (in)validity / GCP and data protection issues (no valid ICF, thus data must not be used; as documented in the "*Maßnahmenausschuss*") were fully excluded from the FAS and SAF.

Another set of patients was excluded from the FAS due to inspection findings resulting in withdrawal of IRB (ethics) approval for the respective site (as documented in the "*Maßnahmenausschuss*").

9.8.1.2 Pre-defined subgroups

Subgroup analyses were conducted for ToD, OS, best response, QoL and safety analyses, if each specification of any subgroup consisted of at least 5 patients.

Subgroup(s) of interest were:

- Gender: male / female
- Age at start of therapy line: <65 years / ≥65 years
- BMI at enrollment: <25 kg/m^2 / ≥25 kg/m^2 (only for 1st-line pazopanib and 3rd-line Everolimus)

- MSKCC Score at enrollment: favorable, intermediate, poor (only for 1st-line pazopanib and 3rd-line Everolimus)
- Histology: clear cell carcinoma / non-clear cell carcinoma
- Nephrectomy: yes / no

9.8.1.3 Descriptive and confirmatory statistics

Descriptive and confirmatory statistical methods were used in the statistical analysis of the data. Subject disposition, background and demographic characteristics were presented solely descriptively.

Summary statistics included the following parameters:

- nominal and ordinal variables: frequencies and percentages.
- continuous variables: number (N) of observations, mean, standard deviation, 25th percentile, median, 75th percentile, minimum and maximum.
- time-to-event variables: number (N) of observations, frequency and percentage of events and censored patients, quartiles (including median) with 95% CI, time-rates with 95%-CI

9.8.2 Main statistical methods

Time-to-event data (including OS and ToD) were estimated using the Kaplan-Meier method (Kaplan and Meier, 1958) to present median and quartiles of the time-to-event data together with the corresponding 95% confidence intervals (CI) according to Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) and the frequency and percentage of events and censored cases. The Kaplan-Meier estimates are displayed in table format and graphically in Kaplan-Meier survival plots.

9.8.3 Missing values

If not otherwise specified, missing values were generally not imputed. The analysis was conducted with available data.

Missing data in questionnaires were treated according to the manual.

For the calculation of age, the incomplete date of birth was handled as follows: The day was set to the 1st and month was set to July.

In case of time-to-event analyses, patients with an incomplete date were censored.

For all other analyses which were based on a date variable, a missing day was set to the 1st.

9.8.4 Sensitivity analyses

The following sensitivity analyses were performed:

- The MSKCC Score (Robert J Motzer et al., 2002) was calculated automatically by the EDC system on the basis of complete information for the minimal required data. The number of patients for whom no risk status was available was displayed.
- Regarding ToD and OS, a sensitivity analysis with trial-eligible patients - definition on the basis of (Marschner et al., 2017), (Motzer et al., 2013) and (Cora N Sternberg et al., 2010) – was performed. Therefore patients had to fulfill none of the following three "trial-ineligibility criteria":
    - Karnofsky Performance Status < 70%
    - Hemoglobin < Lower Limit of Normal
    - Non-clear Cell Carcinoma
- An FAS^{ext} was used for the sensitivity analysis of ToD, OS, QoL (see section 9.8.1.1).
- An SAF^{ext} was used for the sensitivity analysis of AEs (see section 9.8.1.1)

9.8.5 Amendments to the statistical analysis plan

The major changes made to SAP v1.0 (10 March 2017), SAP v2.0 (30 January 2018), and SAP v3.0 (15 October 2018) reflected in final SAP v4.1 (14 November 2019) are summarized in Table 9-4.

Table 9-4 Amendments to the statistical analysis plan

Amendment Number	Date	Sections of SAP	Reason / Comments
1	30 January 2018	Primary source of data. Primary analysis population; Primary source of data. Secondary analysis population; Subject disposition, background and demographic characteristics; Medications; Concomitant medication/s; Effectiveness Analyses; Safety analyses; Analysis of Quality of Life; List ouf output; References	SAP v2.0. Differentiation between timepoint of analyses for the definition of the analysis population; 6-month rate has been included in the SAP; two sensitivity analysis with trial eligible patients were included for TD and OS; addition of analyses regarding the distance between the patient's residence and the practice/hospital as well as the information about the patients' participation in a "Patient Education Program" according to current study protocol version; addition of table showing the first administered dose of Pazopanib, Everolimus, and Nivolumab respectively; addition of table showing patients (treated with Everolimus) receiving a combined therapy with Lenvatinib; addition of TD analysis for histology subgroup (clear vs. non-clear cell); addition of impact of local factors on TD and OS; addition of Kaplan-Meier plot of OS for all subgroup analyses; addition of summary table displaying TEAEs (related and non-related as well as serious and non-serious) by trial-elgible vs. trial-ineligible patients for 1st line Pazopanib; addition of source of reason for death (as recorded on the eCRF form

Amendment Number	Date	Sections of SAP	Reason / Comments
			"Überlebensstatus"); addition of the lowest on treatment result to table of the ECOG performance status; addition of table showing the impact of local factors on QoL; addition of differentiation between Pazopanib (1st line) and Nivolumab (2nd line) for figure showing reported problems by dimension and age group; addition of patient's participation in a Patient Education Program and distance between patient's residence and practice/hospital to table grouped by age displaying the EQ Visual Analogue scale.
2	15 October 2018	Primary source of data. Primary analysis population; Subgroup definitions; Subject disposition, background and demographic characteristics; Medications; Effectiveness Analyses; Safety Analyses; Analysis of Quality of Life; List of output; References	SAP v3.0. Addition of FAS^{ext} for predefined analyses; specification of age subgroup to age at start of therapy line; revision of BMI subgroup from BMI at baseline to BMI at enrollment; limitation of BMI subgroup to 1st line Pazopanib and 3rd line Everolimus; specification and revision of MSCKK Score subgroup; limitation of concomitant medication subgroup to 1st line Pazopanib and 3rd line Everolimus; deletion of reversed Kaplan-Meier plot for the observation time in each therapy line for FAS-I and FAS-II; addition of table displaying some parameters by nephrectomy status; addition of type of education program to table regarding the distance between the patient's residence and the practice/hospital as well as the information about the patients' participation in a "Patient Education Program; addition of an overview of patients with non-metastatic disease to summary tables of data measuring stage and severity of disease; addition of definition of the MSKCC Score; deletion of measures taking into account if the MSKCC Score cannot be calculated automatically; addition of calculation for relative dose intensity of Nivolumab; Specification of TD to TD for cohort I; addition of differention of calculation for TD for Nivolumab depending on the cycle length; addition of nephrectomy subgroup analyses for 1st line TD (Pazopanib); addition of sensitivity analysis for 1st line Pazopanib TD with the FAS^{ext}; addition of nephrectomy subgroup for analyses of OS for cohort I; revision of blood pressure category for safety analyses; addition of crosstable for patients receiving a antihypersensitive therapy showing the blood pressure categories from baseline compared to worst on treatment; addition of time-to-event analysis according to Kaplan-Meier for patients receiving 1st line Pazopanib treatment for ECOG/Karnofsky; specication of subgroup analysis for 1st line

Amendment Number	Date	Sections of SAP	Reason / Comments
			Pazopanib subgroup for the frequency of liver-related AEs and for treatment discontinuation due to liver toxisities; addition of histology subgroup to analysis of QoL; specification of table showing the impact of local factors on QoL for 1st line Pazopanib; addition of a boxplot showing the results for each period of QoL.
3	14 November 2019	Primary source of data. Primary analysis population; Primary source of data. Secondary analysis population; Active treatment (or exposed) group/Manin cohort; Endpoints; Subgroup definitions; Statistical methods; Assessment windows, baseline and post baseline definitions, missing data handling; Subject disposition, background and demographic characteristics; Medications; Effectiveness Analyses; Safety Analyses; Analysis of Quality of Life; List of output	SAP v4.1. Revision of definition of FAS; addition of SAF^{ext} as sensitivity analysis population; addition of Nivolumab in 2nd-line therapy as focus for primary analysis; deletion of reversed Kaplan-Meier method for calculation of overall TD; revision of minimum number of patients for subgroup analyses to at least 5 patients for all subgroups; deletion of concomitant medication subgroup; specification of on-treatment period for safety analyses; addition of categorial age at start of treatment to summary tables of patient characteristics; differentiation of calculation of age into age at informed consent and age at start of therapy; addition of number of patients with data records in the Follow-Up period for mediciation analyses; deletion of table displaying the number of reported concomitant medications in each specification of the ATC level 2; deletion of table displaying the specification of the ATC level 2 of concomitant medication per substance in case any AE is related to concomitant medication; revision of ORR to DCR; revision of 6-months survival rate to 12-months survival rate; revision of calculation of OS by reversed Kaplan-Meier method to Kaplan-Meier method; addition of sensitivity analyses for SAF^{ext}; revision of definition for TEAE; addition of table listing AEs experienced by most of the patients; deletion of differentiation by severity, grades 1/2 vs. 3/4 vs. 5 for displaying PT of TEAEs; addition of overview fo test results to table showing laboratory tests; deletion of subbroup analyses concerning laboratory tests; addition of table giving an overview of patients with liver monitoring according to SmPC (1st line Pazopanib); addition of number of patients with questionnaires sent to respective table; revision of table numbers for table showing the impact of local factors on QoL for 1st line Pazopanib as well as for summary table, grouped by age; deletion of age subgroup for table 14.3.8c;

9.9 Quality control

For data capturing and data management a Java-based validated software (i.e., iostudy office edc) was deployed. The eCRFs for data capturing included online validation of eCRFs during data capturing, e.g. check on range, plausibility, and typing errors. In addition to the system-based plausibility checks, computerized and manual consistency checks were undertaken, i.e. logical checks on data entries to check for inconsistencies. A formal query process was implemented to solve inconsistencies in documented data.

In the time period between the first COVID-19 case in Germany (27 January 2020) and date of last-subject-last-visit (28 February 2021), 130 study subjects were observed. No subject visits were delayed or cancelled due to the COVID-19 pandemic. For one subject a COVID-19 infection (CTCAE 2) during treatment with pazopanib has been reported. Validation of the database quality was carried out by onsite monitoring. All planned onsite monitoring visits took place. All study objectives were addressed and evaluated as planned and defined in the study protocol. No protocol amendment was required due to the COVID-19 pandemic. Taken together, the COVID-19 pandemic had no impact on the conduct of the study.

10 Results

10.1 Participants

Between 10-Dec-2015 and 22-Dec-2017, 427 patients were enrolled in PAZOREAL and 398 patients were treated. Patient disposition is depicted in Figure 10.1.

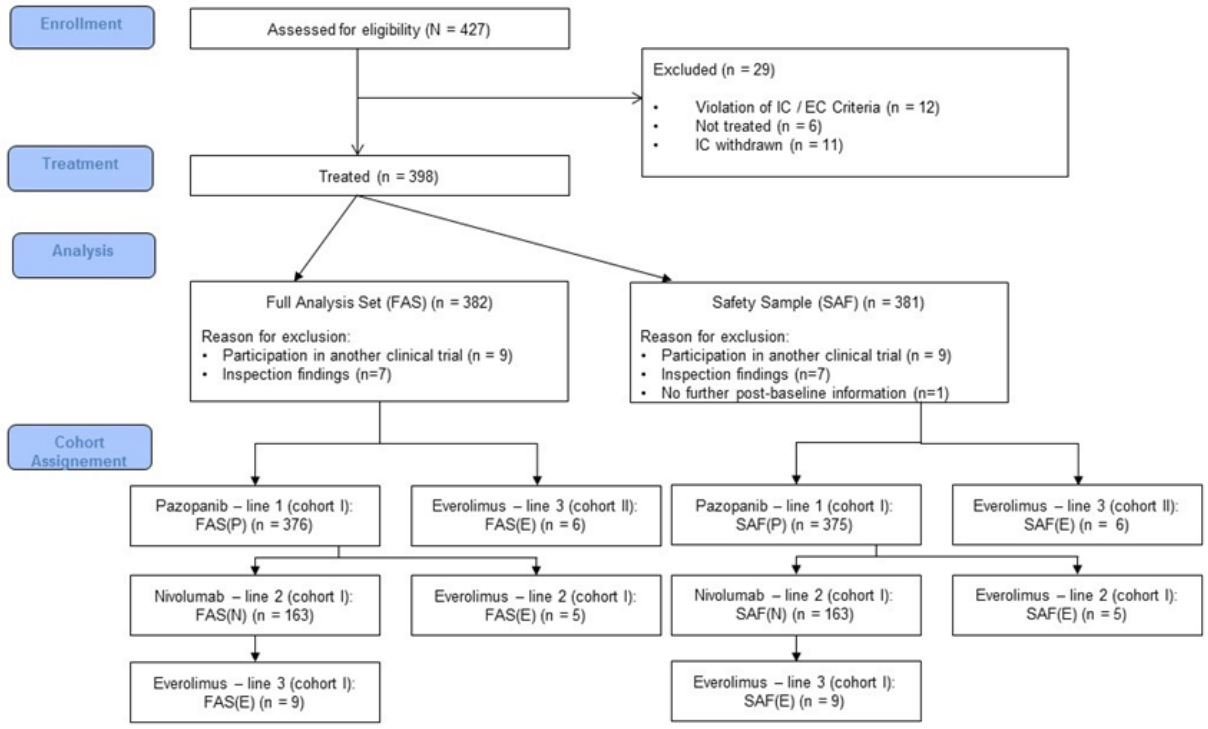


Figure 10.1 CONSORT flow chart

Source: PAZOREAL TFL: Figure 14.1a-1. Consort flow chart FAS

After enrollment, 29 patients were excluded due to following reasons i) violation of IC/EC criteria (12 patients), ii) not treated (6 patients), and iii) IC withdrawn (11 patients).

The number of patients included in the full analysis set (FAS) and in the safety set (SAF)) are displayed. Respective reasons for exclusion are provided. (Figure 10.1)

In the FAS, 376 patients were assigned to cohort I and were treated with pazopanib in 1st-line setting (FAS(P)), while 6 patients were assigned to cohort II (i.e. were treated with everolimus in 3rd-line setting; FAS(E)). After 1st-line pazopanib, 163 patients were treated with nivolumab in 2nd-line (FAS(N)) and of these 9 patients received the 3rd-line treatment everolimus (FAS(E)). (c.f. Figure 10.2)

In the SAF, 375 patients were assigned to cohort I and were treated with pazopanib in 1st-line setting (SAF(P)), while 6 patients were assigned to cohort II (i.e. were treated with everolimus in 3rd-line setting; SAF(E)). After 1st-line pazopanib, 163 patients were treated with nivolumab in 2nd-line (SAF(N)) and of these 9 patients received the 3rd-line treatment everolimus (SAF(E)). (cf. Figure 10.3)

In addition, after 1st-line pazopanib, 5 patients were treated with 2nd-line everolimus. However, due to the small number of patients treated with either everolimus in 2nd-line (cohort I) or everolimus in 3rd-line (after nivolumab 2nd-line application documented retrospectively, cohort II) the results and analyses presented in this section are focused on cohort I and respective FAS and SAF cohorts with patients receiving 1st-line pazopanib and/or 2nd-line nivolumab.

10.1.1 Course of therapy

The FAS was composed of 382 patients, thereof 376 patients of cohort I and 6 patients of cohort II (Figure 10.2). The SAF composed of 381 patients (Figure 10.3), of these 179 (41.9%) patients died, thereof 174 (40.7%) patients of cohort I and 5 (1.2%) patients of cohort II. (cf. appendix: *PAZOREAL TFL: Table 14.1.1a-1 Overview of patients*)

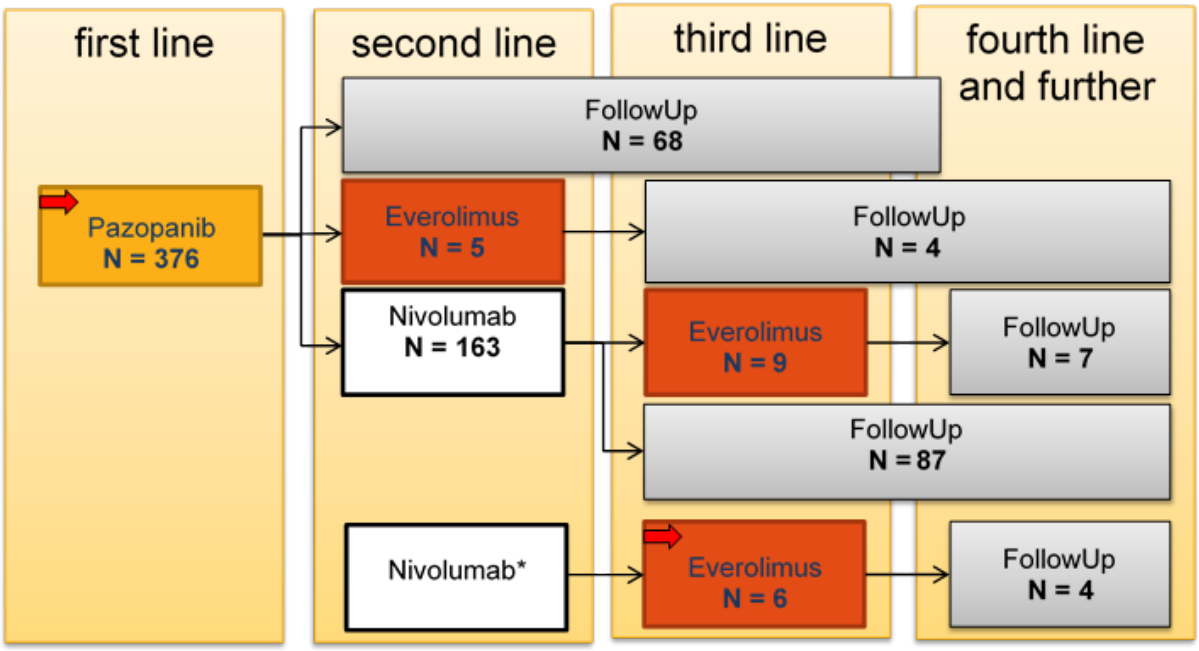


Figure 10.2 Course of therapy of patients FAS

Red arrows: study documentation started here.

* Retrospective documentation of nivolumab in 2nd line.

All patients not going to a further therapy line or to FollowUp had a documented End of Study. Substances administered in the FollowUp phase as subsequent antineoplastic therapy are displayed in *PAZOREAL TFL:* Table 14.2.1h-2-1.1.

Source: PAZOREAL TFL: Figure 14.1b-1. Course of therapy of patients FAS

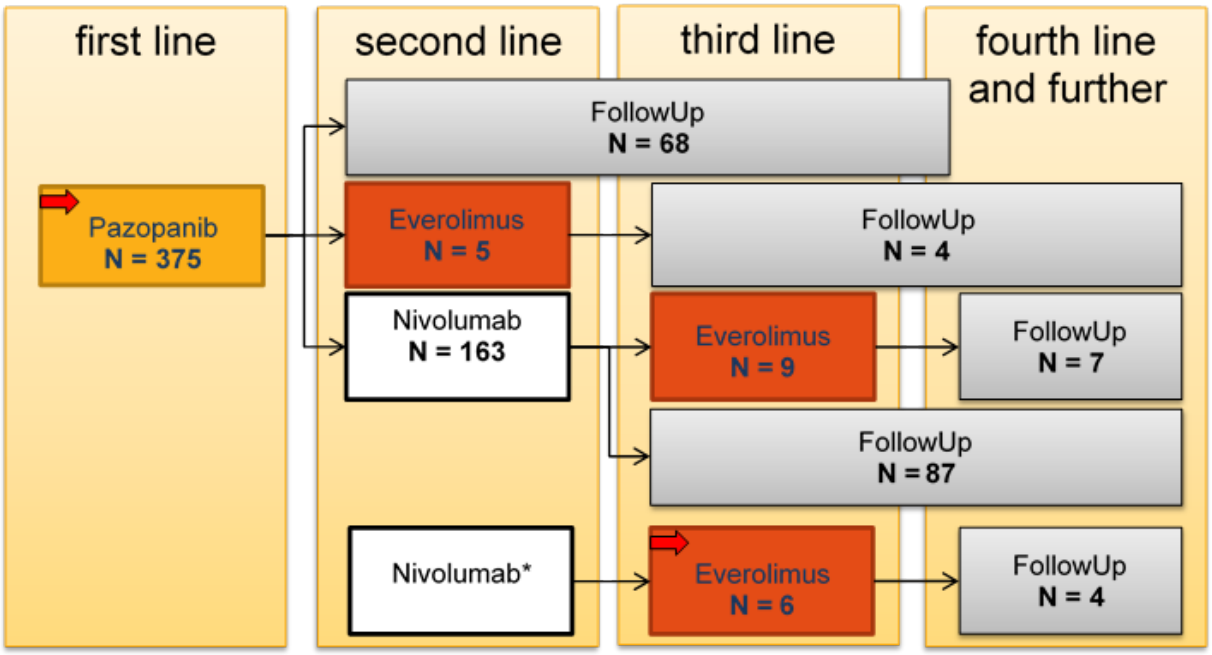


Figure 10.3 Course of therapy of patients SAF

Red arrows: study documentation started here.

* Retrospective documentation of nivolumab in 2nd line.

All patients not going to a further therapy line or to FollowUp had a documented End of Study. Substances administered in the FollowUp phase as subsequent antineoplastic therapy are displayed in appendix *PAZOREAL TFL: Table 14.2.1h-2-1.1.*

Source: PAZOREAL TFL: Figure 14.1b-2. Course of therapy of patients SAF

10.1.2 Observation time

Cohort I

The median observation time for cohort I (first prescription of pazopanib until last contact or death) was 44.6 months (95% CI 43.2 – 47.1 months), while 180 patients (47.9%) were censored (due to death or missing EOS documentation). Figure 10.4 shows the observation time according to the Kaplan-Meier method.

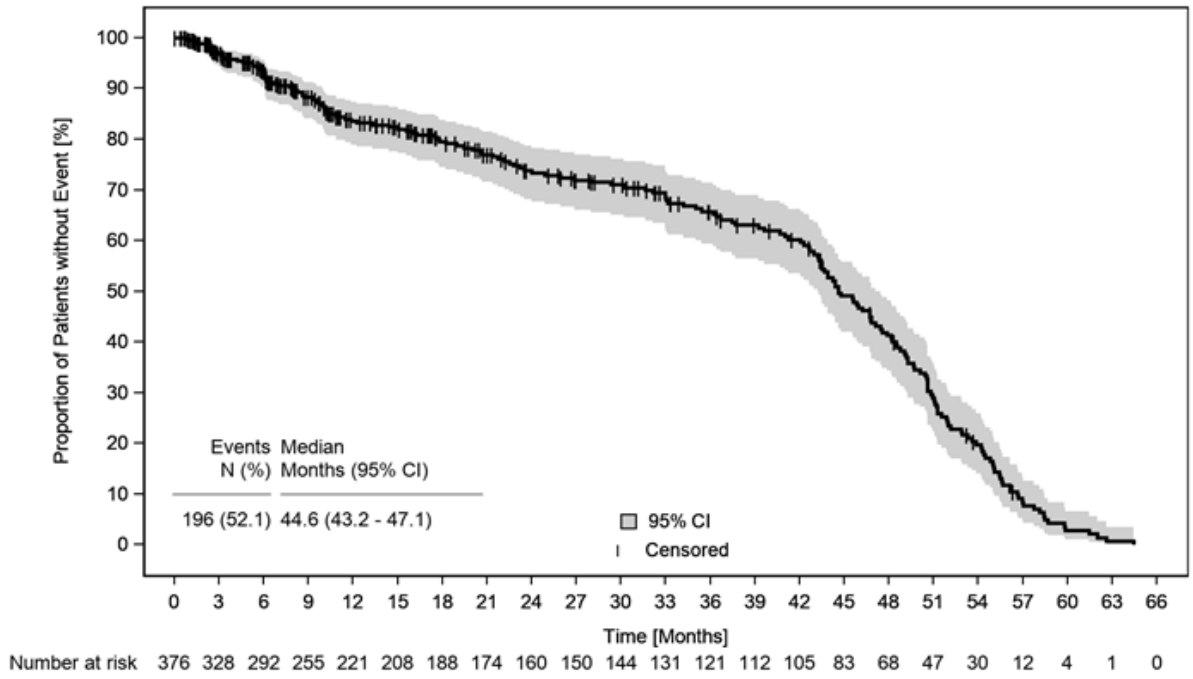


Figure 10.4 Observation time cohort I

Observation time for cohort I estimated by the reversed Kaplan-Meier method using the date of first documented study drug administration (for cohort I: start of pazopanib treatment) as start date and the date of last contact as end date. Patients who died during the study were censored with the date of death. 'Patient without Event' refer to deceased patients as well as to patients without documented end of study.
Source PAZOREAL TFL: Table 14.2.2a-1 Observation period

Cohort II

Details on analysis of observation period for cohort II are provided in the appendix *(PAZOREAL TFL: Table 14.2.2a-2 Observation period)*

10.2 Descriptive data

All key baseline charactersitics of the FAS cohort I population are depicted in Table 10-1 with a focus on patients with 1st-line pazopanib treatment (FAS(P)). Also respective patients with subsequent 2nd-line nivolumab treatment are considered (FAS(N)), while respective patients with 2nd- and 3rd-line everolimus treatment are unconsidered due to the small number of patients. Accordingly, in FAS cohort II (N=6, c.f. Figure 10.1, Figure 10.2, Figure 10.3) respective data were provided in tables in the appendix.

10.2.1 Baseline Characteristics

Cohort I

In the FAS, cohort I, the median age at baseline was 69.7 years and most of the patients receiving 1st-line pazopanib, FAS(P) were older than 65 years (n=244, 64.9%, Table 10-1). Also, patients receiving subsequent 2nd-line nivolumab (FAS(N)) were mostly older than 65 years (n=114, 69.9%). *(PAZOREAL TFL: Table 14.1.1c-2-1.3 Categorial age at start of treatment [years] - 2nd line nivolumab).* For patients treated 2nd- and 3rd-line everolimus, respective details to categorial age are provided in appendix (*PAZOREAL TFL: Table 14.1.1c-2-1.2 Categorial age at start of treatment [years] - 2nd line everolimus, Table 14.1.1c-2-1.5 Categorial age at start of treatment [years] – 3rd line everolimus).*

At enrollment, the majority of patients were male (n=257, 68.4%) and had a median body mass index (BMI) of 26.4 kg/m² (range 16.8-58.4 kg/m²). Most of the patients had an ECOG performance status of 0 or 1 (n=301, 80.1%), indicating a good baseline performance status (Table 10-1).

Median time from primary diagnosis of RCC to the first administration of pazopanib was 11.0 months with a broad range of 0.2 to 339.3 months.

A small fraction of the patients had locally advanced disease without metastases at enrollment (n=23, 6.1%), while the vast majorityof the patients presented with metastatic disease (n=353, 93.9%). The main sites for metastases were lung, bone, liver and lymph nodes (58.0%, 25.5%, 16.2%, 26.1%).

Location of the tumor at initial diagnosis was mainly in the left (n=186, 49.5%) or right kidney (n=174, 46.3%) and in 16 patients (4.3%) in both kindeys.

The primary tumor was predominantly composed of clear cells in all patients (n=304, 80.9%). Detailed information of histology in cohort I is provided in the appendix *PAZOREAL TFL: Table 14.1.1d-3a-1.1 Histology*. Patients with 1st-line pazopanib (FAS(P) n=376) presented with clear cell histology in 80.9% and with non-clear cell histology in 10.1% of cases, while 9.0% had an unknown histology (*PAZOREAL TFL: Table 14.1.1d-3b-1.1 Histology – 1st line pazopanib.*) Patients with 2nd-line nivolumab (FAS(N) n=163) presented with clear cell histology in 83.4% (n=136) and with non-clear cell histology in 11.0% (n=18) of cases, while 5.5% had an unknown histology (*PAZOREAL TFL: Table 14.1.1d-3b-1.3 Histology - 2nd line nivolumab.*)

In FAS (P) study population (n=376) 146 patients (38.8%) were identified as “trial-eligible” patients who fulfilled none of the three “trial-ineligibility criteria”, i.e. Karnofsky Performance Status <70%, hemoglobin < lower limit of normal range, Non-clear Cell Carcinoma Histology. 184 patients (48.9%) were identified as not trial-eligible. 46 patients (12.2%) were not assigned to one of the groups due to the missing of at least one of the three “trial-ineligibility criteria”. (*PAZOREAL TFL: Table 14.1.1c-7-1.1 Overview of trial-eligible* patients - 1st line pazopanib*).

In the FAS (N) study population (n=163) 64 patients (39.3%) were identified as “trial-eligible” patients, 81 (49.7%) patients as not trial-eligible and 18 patients (11.0%) could not be assigned due to the missing of at least one of the three “trial-ineligibility criteria”. (*PAZOREAL TFL: Table 14.1.1c-7-1.3 Overview of trial-eligible* patients - 2nd line nivolumab*)

For patients treated 2nd- and 3rd-line everolimus respective details to trial eligibility are provided in the appendix (*PAZOREAL TFL: Table 14.1.1c-7-1.2 Overview of trial-eligible* patients - 2nd line everolimus, Table 14.1.1c-7-1.5 Overview of trial-eligible* patients - 3rd line everolimus)*

Table 10-1 Patient characteristics – FAS (all) / FAS (P) cohort I

Characteristic	Cohort I, FAS (all), N =376
Gender, n (%)	
Female	119 (31.6%)
Male	257 (68.4%)
Median age (range), in years	69.7 (38.5-89.2)
Categorial age at start of treatment (FAS(P))	< 65 years: 132 (35.1%) ≥ 65 years: 244 (64.9%)
Median weight at baseline (range), in kg	79.0 (42.0-160.0)
Median BMI at baseline (range), in kg/m²	26.4 (16.8-58.4)
Number of "trial-eligible" patients, n (%)*	146 (38.8%)
Median time interval from primary diagnosis to first administration of pazopanib (range), in months	11.0 (0.2-339.3)
ECOG performance status, n (%)	
0	197 (52.4%)
1 (good)	104 (27.7%)
2 (moderate)	40 (10.6%)
3 (poor)	1 (0.3%)
4 (completely disabled)	1 (0.3%)
Not done/Missing	32 (8.5%)/1 (0.3%)
Histology, n (%)	
Clear cell	304 (80.9%)
Non-clear cell	38 (10.1%)
Unknown	34 (9.0%)
Patients with tumor in both kidneys at primary diagnosis, n (%)	16 (4.3%)
Locally advanced disease at enrollment, n (%)	23 (6.1%)
Metastatic or non-metastatic disease at enrollment, n (%)	

Characteristic	Cohort I, FAS (all), N =376
Metastatic disease	353 (93.9%)
Non-metastatic disease	23 (6.1%)
Number of metastatic sites, n (%)	
0	23 (6.1%)
1-3	322 (85.6%)
4-6	31 (8.2%)
5 most frequent localization of metastases, n (%)	
Lung	218 (58.0%)
Bone	96 (25.5%)
Liver	61 (16.2%)
Lymph nodes, regional	53 (14.1%)
Lymph nodes, distal	45 (12.0%)

Source: PAZOREAL TFL: TFL: Table 14.1.1c-1-1 Age at date of informed consent; Table 14.1.1c-2-1.1 Categorial age at start of treatment, Table 14.1.1c-3-1 Gender, Table 14.1.1c-4-1 Weight, Table 14.1.1c-5-1 BMI, Table 14.1.1c-6-1 ECOG performance status, Table 14.1.1c-7-1.1 Overview of trial-eligible patients, Table 14.1.1d-1-1.1 Time interval from primary diagnosis to first administration of pazopanib, Table 14.1.1d-15a-1 Locally advanced disease (at enrollment) by nephrectomy, Table 14.1.1d-10-1.1 Metastatic or non-metastatic disease (at enrollment), Table 14.1.1d-11-1.1 Locally advanced disease (at enrollment), Table 14.1.1d-2-1.1 Tumor localization at primary diagnosis, Table 14.1.1d-5-1.1 Number of patients with nephrectomy (at enrollment), Table 14.1.1d-9-1.1 Nephrectomy status (at enrollment, Table 14.1.1d-13-1.1 Localization of metastases (at enrollment), Table 14.1.1d-12-1.1 Overview of patients with non-metastatic disease: locally advanced disease (at enrollment), Table 14.1.1d-14-1.1 Number of metastatic sites per patient (at enrollment).*

*Defined as patients fulfilling none of the three 'trial-ineligibility criteria': 1) Karnofsky Performance Status <70%; 2) Haemoglobin < Lower Limit of Normal, 3) Non-clear Cell Carcinoma Histology.

Cohort I: Nephrectomy status

At enrollment, most of the patients had undergone radical (n=248, 66.0%) or partial nephrectomy (n=55, 14.6%) before entering the study. No residual tumor (R0) was documented for 225 patients (59.8%), RX was reported for 47 patients (12.5%). For patients without metastasic disease at enrollment, no residual tumor (R0) was documented for 12 patients (52.2%), RX was reported for 2 patients (8.7%). (cf. Table 10-2)

Table 10-2 Baseline characteristics by nephrectomy (FAS (all) cohort 1)

Nephrectomy status at enrollment, n (%)	
Yes	303 (80.6%)

No nephrectomy	73 (19.4%)
Median age at date of informed consent, in years (range)	no nephrectomy: 68.3 (44.4, 86.0) / nephrectomy: 70 (38.5, 89.2)
Type of nephrectomy	55 partial (14.6%) / 248 radical (66.0%)
Locally advanced disease (at enrollment) by nephrectomy	no nephrectomy (n=73) / nephrectomy (n=303)
yes	4 (5.5%) / 19 (6.3%)
Patients with non-metastatic disease at enrollment (n=23)	
Nephrectomy / no nephrectomy, n (% of 23 patients)	19 (82.6%) / 4 (17.4%)
R-Staging: R0 / R1 / Rx / no nephrectomy, n (% of 23 patients)	12 (52.2%) / 5 (21.7%) / 2 (8.7%) / 4 (17.4%)
R-Staging (at enrollment), n (% of 376 patients)	
R0	225 (59.8%)
R1	25 (6.6%)
R2	5 (1.3%)
RX	47 (12.5%)
Missing	1 (0.3%)
No nephrectomy	73 (19.4%)

Source: PAZOREAL TFL: TFL: Table 14.1.1d-15a-1 Locally advanced disease (at enrollment) by nephrectomy, Table 14.1.1d-5-1.1 Number of patients with nephrectomy (at enrollment), Table 14.1.1d-15c-1 Age at date of informed consent [years] by nephrectomy, Table 14.1.1d-9-1.1 Nephrectomy status (at enrollment, Table 14.1.1d-6-1.1 Overview of patients with non-metastatic disease: nephrectomy (at enrollment), Table 14.1.1d-7-1.1 R-Staging (at enrollment, Table 14.1.1d-8-1.1 Overview of patients with non-metastatic disease: R-Staging (at enrollment).

In the FAS(P) (n=376) out of the patients with nephrectomy at enrollment (n=303) 127 patients (41.9%) were identified as “trial-eligible” patients, while 140 patients (46.2%) were identified as “not trial-eligible”. Out of 73 patiens without nephrectomy 19 patients (26.0%) were identiefied as “trial-eligible” and 44 patients (60.3%) as “not trial-eligible”. Respectively, 36 patients (11.9%) and 10 patients (13.7%) with and without nephrectomy could not be assigned due to the missing of at least one of the three “trial-ineligibility criteria”. (*PAZOREAL TFL: Table 14.1.1d-15b-1 Overview of trial-eligible* patients by nephrectomy - 1st line pazopanib*).

Cohort II

Baseline characteristics of cohort II are provided in the appendix (*PAZOREAL TFLs: Table 14.1.1c-1-2 Age at date of informed consent; Table 14.1.1c-2-2.2 Categorial age at start of treatment – 3rd line everolimus, Table 14.1.1c-3-2 Gender, Table 14.1.1c-4-2 Weight, Table 14.1.1c-5-2 BMI, Table 14.1.1c-6-2 ECOG performance status, Table 14.1.1c-7-2.2 Overview of trial-eligible* patients, Table 14.1.1d-1-2.2 Time interval from primary diagnosis to first administration of pazopanib, Table 14.1.1d-10-2.2 Metastatic or non-metastatic disease (at enrollment), Table 14.1.1d-11-2.2 Locally advanced disease (at enrollment), Table 14.1.1d-2-2.2 Tumor localization at primary diagnosis, Table 14.1.1d-3a-2.2 Histology, Table 14.1.1d-5-2.2 Number of patients with nephrectomy (at enrollment), Table 14.1.1d-9-2.2 Nephrectomy status (at enrollment, Table 14.1.1d-14-1.1 Number of metastatic sites per patient (at enrollment), Table 14.1.1d-13-2.2 Localization of metastases (at enrollment), Table 14.1.1d-7-2.2 R-Staging (at enrollment))*

10.2.2 Local Factors

Cohort I

Distance between the patient's residence and the practice/hospital was documented for 160 patients (42.6 %). 56 patients (35 %) of them had a documented distance of <10km and 104 patients (65 %) of ≥10km. (*PAZOREAL TFL: Table 14.1.1c-8-1 Distance between the patients' residence and the practice/hospital*)

Data about participation in a Patient Education Program were available for 192 patients (51.1% of FAS - cohort I). 4 patients (2.1 %) of them were documented as participating and 188 patients (97.9 %) as not participating in a Patient Education Program. (*PAZOREAL TFL: Table 14.1.1c-9-1 Number of patients participating in a Patient Education Program*). Data on type of Patient Education Programm were available for 4 patients and are provided in the appendix (*PAZOREAL TFL: Table 14.1.1c-10-1 Type of the Patient Education Program*).

Cohort II

Details on local factors in cohort II are provided in the appendix (*PAZOREAL TFL: Table 14.1.1c-8-2 Distance between the patients' residence and the practice/hospital, Table 14.1.1c-9-2 Number of patients participating in a Patient Education Program, Table 14.1.1c-10-2 Type of the Patient Education Program*).

10.2.3 Risk scores: MSKCC and Heng score

Cohort I

In cohort I, the MSKCC risk score was available in 85 (22.6%) out of 376 patients and was unambiguously categorized according to the MSKCC criteria. Of those, 20 patients (23.5%) had favorable risk, 52 patients (61.2%) were assigned to the intermediate-risk group, and 13 patients (15.3%) were categorized as poor risk. (Table 10-3)

Table 10-3 Risk scores MSKCC and IMDC Heng Score

MSKCC risk score, n (%) **N=376**	
Favorable (0 risk factors)	20 (5.3%)
Intermediate (1-2 risk factors)	52 (13.8%)
Poor (3-4 risk factors)	13 (3.5%)
Missing	291 (77.4%)
Heng Score, (complete data at enrollment) n (%)	
Favorable (0 risk factors)	16 (4.3%)
Intermediate (1-2 risk factors)	43 (11.4%)
Poor (≥3 risk factors)	21 (5.6%)
Missing	296 (78.7%)

MSKCC (Memorial Sloan-Kettering Cancer Center), IMDC (International Metastatic RCC Database Consortium)

Source: PAZOREAL TFLs: Table 14.1.1e-1a-1.1 MSKCC risk factors (complete data) at enrollment, Table 14.1.1e-1b-1.1 MSKCC risk factors (complete data) at enrollment - only patients with available score, Table 14.1.1e-5-1.1 Heng Score (complete data) at enrollment

For 291 patients (77.4%) in FAS – cohort I, the MSKCC risk score was not calculated due to missing values and parameters which were required for calculation (Table 10-4). In most cases (67.3%) the albumin value was missing, followed by missing values for calcium (22.9%) or LDH (24.5%) and the Karnofsky performance status (22.3%). A detailed overview of missing parameter and values were provided in the appendix (*PAZOREAL TFL: Table 14.1.1e-3-1.1 Overview of missing/unknown values* (MSKCC Score)*).

Table 10-4 Missing/unknown values* (MSKCC Score) FAS - cohort I

		FAS – cohort 1 (N=376)
Number of patients with missing/unknown values* (MSKCC Score)	Patients with missing MSKCC Score	291 (77.4%)
Number of patients with missing/unknown values* (MSKCC Score)	Patients with missing/unknown albumin value	253 (67.3%)
Number of patients with missing/unknown values* (MSKCC Score)	Patients with missing/unknown calcium value	86 (22.9%)
Number of patients with missing/unknown values* (MSKCC Score)	Patients with missing/unknown hemoglobin value	23 (6.1%)

		FAS – cohort 1 (N=376)
Number of patients with missing/unknown values* (MSKCC Score)	Patients with missing/unknown Karnofsky performance status	84 (22.3%)
Number of patients with missing/unknown values* (MSKCC Score)	Patients with missing/unknown LDH value	92 (24.5%)
Number of patients with missing/unknown values* (MSKCC Score)	Patients with missing/unknown time data**	18 (4.8%)

*Values/parameters which are required for the calculation of the MSKCC Score (albumin, calcium, hemoglobin, KPS, LDH, time data).
**Missing/unknown data on time interval from diagnosis to start of 1st-line therapy.
All percentages refer to the total number of patients included in the Full Analysis Set. Multiple answers possible.
Source: Table 14.1.1e-3-1.1 Overview of missing/unknown values (MSKCC Score)*

The Heng Score was available in 80 (21.3%) out of 376 patients and could be unambiguously calculated according to the Heng risk criteria. Of those, 16 patients (20%) qualified for the favorable, 43 patients (53.8%) for the intermediate, and 21 patients (26.3%) for the poor risk category (Table 10-3).

Cohort II

Details on Risk scores of patients in cohort II are provided in the appendix (MSKCC risk score: *PAZOREAL TFL: Table 14.1.1e-4a-2.2 MSKCC risk groups (complete data) at enrollment, Table 14.1.1e-4b-2.2 MSKCC risk groups (complete data) at enrollment - only patients with available score, Table 14.1.1e-2-2.2 Number of patients with missing/unknown values* (MSKCC Score), Table 14.1.1e-3-2.2 Overview of missing/unknown values* (MSKCC Score),* Heng Score: *PAZOREAL TFL: Table 14.1.1e-5-2.2 Heng Score (complete data) at enrollment)*)

10.2.4 Comorbidity and concomitant medication

Cohort I

In cohort I, at least one comorbidity was present in 344 patients (91.5%). Data on medical history are listed in the appendix (*PAZOREAL TFL: Table 14.1.1f-2-1 Medical history: Preferred Term by System Organ Class* and *Table 14.1.1f-3-1 Medical history: Preferred Term by ongoing status*).

Concomitant medications were administered to 261 patients (69.4%) of patients receiving 1st-line pazopanib. Respective data related to concomitant medication are provided in the appendix (*PAZOREAL TFL: Table 14.4.1a-1-1.1 Concomitant medication - 1st line pazopanib*). In 153 (93.9%) of the patients with 2nd-line nivolumab concomitant medication was administered. Respective data related to concomitant medication are provided in the appendix (*PAZOREAL TFL: Table 14.4.1a-1-1.3 Concomitant medication – 2nd line nivolumab*).

Respective details for patients with 2nd-line and 3rd-line everolimus are provided in the appendix (*PAZOREAL TFL: Table 14.4.1a-1-1.2 Concomitant medication - 2nd line everolimus, Table 14.4.1a-1-1.5 Concomitant medication - 3rd line everolimus*). For documented combined therapy with lenvatinib see *PAZOREAL TFL: Table 14.4.1b-1.2 Combined therapy with lenvatinib - 2nd line everolimus and Table 14.4.1b-1.5 Combined therapy with lenvatinib - 3rd line everolimus*.

Cohort II

Respective details on comorbidity of patients in cohort II are provided in the appendix (*PAZOREAL TFL: Table 14.1.1f-1-2 Number of patients with previous/concomitant disease, Table 14.1.1f-2-2 Medical history: Preferred Term by System Organ Class* and *Table 14.1.1f-3-2 Medical history: Preferred Term by ongoing status*). For concomitant medication and documented combined therapy with lenvatinib see *PAZOREAL TFL: Table 14.4.1a-1-2.2 Concomitant medication - 3rd line everolimus and Table 14.4.1b-2.2 Combined therapy with lenvatinib - 3rd line everolimus* in the appendix.

10.2.5 TNM classification and grading

Cohort I

TNM classification, grading, and resection status were assessed for the tumor at enrollment into the study. At enrollment, 5 patients (1.3%) presented with T0, 75 patients (19.9%) with T1, 36 patients (9.6%) with T2, 133 patients presented with T3 (35.4%) and 19 patients (5.1%) with T4. TX was documented for 31 patients (8.2%), and 77 patients (20.5%) had an unknown T-stage (appendix *PAZOREAL TFL: Table 14.1.1d-4a-1.1 T-Stage (at enrollment)*).

N0 was documented for most of the patients in the analysis population (n=119, 31.6%), N1 was documented for 49 patients (13.0%), N2 for 22 patients (5.9%), and NX was reported for 108 patients (28.7%). Out of 376 patients, 77 patients (20.5%) had an unknown N-stage and data were missing for 1 patient (0.3%) (cf. appendix *PAZOREAL TFL: Table 14.1.1d-4b-1.1 N-Stage (at enrollment)*).

M1-stage was documented in 248 patients (66.0%), while M0 was documented for 12 patients (3.2%) and MX for 39 patients (10.4%). The M-stage was unknown for 77 patients (20.5%). (see appendix *PAZOREAL TFL: Table 14.1.1d-4c-1.1 M-Stage (at enrollment)*)

G-stage was documented in 375 patients (99.7%). At enrollment, most patients had a G2-tumor (123 patients, 32.7%) or a G3-tumor (90 patients, 23.9%). G1 was documented for 18 patients (4.8%), G4 for 23 patients (6.1%), and GX for 44 patients (11.7%). An unknown G-stage was documented for 77 patients (20.5%) and data were missing for 1 patient (0.3%). (see appendix *PAZOREAL TFL: Table 14.1.1d-4d-1.1 G-Stage (at enrollment)*)

Cohort II

Details on TNM classification and grading of cohort II are provided in the appendix: T-Stage: *PAZOREAL TFL: Table 14.1.1d-4a-2.2 T-Stage (at enrollment)*, N-Stage: *PAZOREAL TFL: Table 14.1.1d-4b-2.2 N-Stage (at enrollment)*, M-Stage*: PAZOREAL TFL: Table 14.1.1d-4c-*

2.2 M-Stage (at enrollment) , G-Stage*: PAZOREAL TFL: Table 14.1.1d-4d-2.2 G-Stage (at enrollment).*

10.3 Effectiveness data

Results and analyses presented in this section are focused on cohort I and respective FAS cohorts with patients receiving 1st-line pazopanib and/or 2nd-line nivolumab, i.e. i) 'FAS - cohort I' including all patients from the FAS entering the study in the 1st-line pazopanib, which is relevant for all analyses not focussing on one line of treatment; ii) 'FAS (P)' including the total number of patients included in the FAS for 1st-line treatment with pazopanib, iii) 'FAS (P, t.e.)' including the total number of trial-eligible patients included in the FAS for 1st-line treatment with pazopanib, iv) 'FAS (N)' including the total number of patients included in the FAS for 2nd-line treatment with nivolumab after enrollment in 1st line pazopanib, and v) 'FAS (N, t.e.)' including the total number of trial-eligible patients included in the FAS for 2nd-line treatment with nivolumab after enrollment in 1st line pazopanib.

10.3.1 Cohort I: Treatment with pazopanib 1st-line

In PAZOREAL study, 376 patients received as 1st-line study medication pazopanib *(PAZOREAL TFL: Table 14.2.1a-1-1.1 Overview of received medication (1st line))*. Details on treatment dose, dose modifications and treatment interruptions are provided in the appendix *PAZOREAL TFL: Table 14.2.1b-1.1 Overview of first administered dose [mg] - pazopanib - 1st line pazopanib.*

In 248 patients (66%) the first administered dose of pazopanib was 800 mg, for 100 patients (26.6%) the first administered dose of pazopanib was 400 mg. (Table 10-5)

Table 10-5 First administered dose [mg] - pazopanib - 1st line pazopanib

		FAS (P) (N=376)
Overview of first administered dose [mg] - pazopanib	200	14 (3.7%)
Overview of first administered dose [mg] - pazopanib	400	100 (26.6%)
Overview of first administered dose [mg] - pazopanib	500	1 (0.3%)
Overview of first administered dose [mg] - pazopanib	600	13 (3.5%)
Overview of first administered dose [mg] - pazopanib	800	248 (66.0%)

The table shows the first documented administered dose.
Source: *PAZOREAL TFL: Table 14.2.1b-1.1 Overview of first administered dose [mg] - pazopanib - 1st line pazopanib*

The relative dose intensity of pazopanib was available for 374 patients with a median relative dose intensity of 87.6% (range 16.4 – 100%, see appendix *PAZOREAL TFL: Table 14.2.1c-1.1 Relative dose intensity of pazopanib [%] - 1st line pazopanib*). In 164 patients (43.6%) the lowest administered dose was 400 mg pazopanib, in 149 patients (39.6%) the lowest dose was 800 mg. (Table 10-6)

Table 10-6 Lowest administered dose [mg] – pazopanib – 1st line pazopanib

		FAS (P) (N=376)
Overview of lowest administered dose [mg] – pazopanib	200	36 (9.6%)
Overview of lowest administered dose [mg] – pazopanib	300	1 (0.3%)
Overview of lowest administered dose [mg] – pazopanib	400	164 (43.6%)
Overview of lowest administered dose [mg] – pazopanib	600	26 (6.9%)
Overview of lowest administered dose [mg] – pazopanib	800	149 (39.6%)

Source: PAZOREAL TFL: Table 14.2.1d-1.1 Overview of lowest administered dose [mg] - pazopanib - 1st line pazopanib

10.3.1 Cohort I: Treatment modification – 1st-line pazopanib

In 250 patients (66.5%) the initially administered dose was modified. Thereof, 1 case (0.4%) had a documented dose increase, while in 227 cases (90.8%) a dose reduction and in 114 cases (45.6%) an interruption of treatment were documented. (Appendix *PAZOREAL TFL: Table 14.2.1e-1-1.1 Number of patients with treatment modifications - 1st line pazopanib*).

Dose reduction

While 149 patients (39.6%) had no documented dose reduction, 227 patients (60.4%) experienced at least one dose reduction during their treatment with pazopanib. Dose reductions without (suspected) drug relation were reasoned by physician's decision (n=158, 42%), patients wish (n=31, 8.2%) and (S)AE (n=23, 6.1%). Non-complience and return to prior dose was documented for 2 (0.5%) and 21 patients (5.6%), respectively. In 109 cases (29.0%) the dose reductions were reasoned by toxicity with suspected drug relation (see appendix *PAZOREAL TFL: Table 14.2.1f-1-1.1 Reason for dose reduction(s) - 1st line pazopanib*). The extend of the dose reduction was specified in 252 cases: In 75 cases the dose reduction was made according to SmPC, in 177 cases the dose reduction was made according to clinical assessment (see appendix *PAZOREAL TFL: 14.2.1f-2-1.1 Specification for dose reduction(s) - 1st line pazopanib*).

Dose interruption

Treatment with pazopanib was temporarily interrupted in 114 patients (30.3%), while 262 patients (69.7%) had no documented dose interruption (see appendix *PAZOREAL TFL: Table 14.2.1g-1-1.1 Reason for dose interruption(s) - 1st line pazopanib*). In case a patient had more than one interruption multiple answers were possible. Reasons were (S)AE (n=50, 13.3%), patient wish (n=15, 4.0%), and physician decision (n=22, 5.9%). Toxicity as suspected adverse drug-reaction was documented as reason for 56 patients (14.9%). In 104 patients (27.7%) the duration of all reported temporary interruptions was equal to or more than 7 days and for 10 patients (2.7%) less than 7 days (see appendix *PAZOREAL TFL: Table 14.2.1g-2-1.1 Duration of therapy interruption(s) (cat.) - 1st line pazopanib*). The median duration of temporary interruptions was 26 days with a minimum duration of 1 day and a maximum of 710 days, while the duration refers

to the sum of all reported interruptions per patient (during one therapy line). (see appendix *PAZOREAL TFL: Table 14.2.1g-3-1.1 Duration of therapy interruption(s) [days] - 1st line pazopanib*)

10.3.1 Cohort I: Main reason for end of treatment – 1st line pazopanib

For 349 patients (92.8%) of the analysis population end of treatment was documented. Reasons for end of therapy documentation were as follows: Progressive disease (n=197, 52.4%), Toxicity (therapy-related) (n=51, 13.6%), (Serious) Adverse event (not therapy-related) (n=22, 5.9%), death (n=22, 5.9%), Investigator's decision (not toxicity, not therapy-related) (n=15, 4.0%), patient's wish (not toxicity, not therapy-related) (n=21, 5.6%), lost to follow-up (n=9, 2.4%), non-compliance (n=1, 0.3 %) and other reasons (n=11, 2.9%), see also *PAZOREAL TFL: Table 14.1.1b-1-1.1 Main reason for end of treatment - 1st line pazopanib* in appendix. For 23 patients (6.1%) treatment was ongoing after end of study observation and for 4 patient no reason for end of treatment was documented.

10.3.2 Cohort I: Treatment with nivolumab 2nd line

Details on treatment dose, dose modifications and treatment interruptions for cohort I patients treated in 2nd-line with nivolumab are provided in the appendix *PAZOREAL TFL: Table 14.2.1b-1.3 Overview of first administered dose [mg] - nivolumab – 2nd line nivolumab.*

For 123 patients (75.5%) the first administered dose per weight of nivolumab was 3 mg/kg, for 25 patients (15.3%) the first administered dose of nivolumab was 240 mg (Table 10-7Table 10-5).

Table 10-7 First administered dose - nivolumab - 2nd line nivolumab

		FAS (N) (N=163)
Overview of first administered dose - nivolumab	3 mg/kg	123 (75.5%)
Overview of first administered dose - nivolumab	213 mg	1 (0.6%)
Overview of first administered dose - nivolumab	240 mg	25 (15.3%)
Overview of first administered dose - nivolumab	480 mg	14 (8.6%)

Source: PAZOREAL TFL: Table 14.2.1b-1.3 Overview of first administered dose [mg] - nivolumab – 2nd line nivolumab

The relative dose intensity of nivolumab was available for 100 patients (based on the dose recorded in mg/kg) with a median relative dose intensity of 100% (range 36.2 – 101.0%). (Appendix *PAZOREAL TFL: Table 14.2.1c-1-1.3 Relative dose intensity of nivolumab [%] - 2nd line nivolumab*). Furthermore, the relative dose intensity of nivolumab was available in 39 patients (based on the dose recorded in mg) with a median relative dose intensity of 95.3% (range 28.3 – 103.7%). (Appendix *PAZOREAL TFL: Table 14.2.1c-2-1.3 Relative dose intensity of nivolumab [%] - 2nd line nivolumab*). For 124 patients (76.1%) the lowest administered dose was 3 mg/kg nivolumab, for 41 patients (25.2%) the lowest dose was 240 mg. Note that patients for whom the dose of nivolumab was provided in [mg] as well as in [mg/kg] were counted twice (Table 10-8).

Table 10-8 Lowest administered dose - nivolumab - 2nd line nivolumab

		FAS (N) (N=163)
Overview of lowest administered dose - nivolumab	3 mg/kg	124 (76.1%)
Overview of lowest administered dose - nivolumab	195 mg	1 (0.6%)
Overview of lowest administered dose - nivolumab	240 mg	41 (25.2%)
Overview of lowest administered dose - nivolumab	480 mg	21 (12.9%)

Patients for whom the dose of nivolumab was specified in mg as well as in mg/kg were counted twice.

(Source: PAZOREAL TFL: Table 14.2.1d-1.3 Overview of lowest administered dose - nivolumab - 2nd line nivolumab)

10.3.3 Cohort I: Treatment modification – 2nd-line nivolumab

The initially administered dose of nivolumab was modified for 90 patients (55.2%). Thereof, 18 cases (11%) had a documented dose increase, while in 26 cases (16%) a dose reduction and in 71 cases (43.6%) an interruption of treatment had been documented. (Appendix *PAZOREAL TFL: Table 4.2.1e-1-1.3 Number of patients with treatment modifications - 2nd line nivolumab*).

Dose reduction

Of 163 patients, 137 patients (84%) were without dose reductions and 26 (16%) had a documented dose reduction. For one patient the reason for dose reduction was physician decision, while in 25 patients the respective reason was missing. (Appendix *PAZOREAL TFL: Table 14.2.1f-1-1.3 Reason for dose reduction(s) - 2nd line nivolumab*) In all cases no further details were documented. (Appendix *PAZOREAL TFL: Table 14.2.1f-2-1.3 Specification for dose reduction(s) - 2nd line nivolumab*)

Treatment interruption

2nd-line treatment with nivolumab was temporarly interrupted in 71 patients (43.6%), while 92 patients (56.4%) had no documented dose interruption (Appendix *PAZOREAL TFL: Table 14.2.1g-1-1.3 Reason for dose interruption(s) - 2nd line nivolumab*). Reasons were (S)AE (n=24, 14.7%), patient wish (n=14, 8.6%), and physician decision (n=13, 8.0%). Toxicity as suspected drug related reason was documented in 16 patients (9.8%). Multiple answers were possible. In 66 patients (40.5%) the duration of temporarly interruptions was equal or more than 7 days and in 5 patients (3.1%) less than 7 days. (Appendix *14.2.1g-2-1.3 Duration of therapy interruption(s) (cat.) - 2nd line nivolumab*). The median duration of temporary interruptions was 29 days with a minimum duration of 1 day and a maximum of 496 days, while the duration refers to the sum of all reported interruptions per patient (during one therapy line, appendix *Table 14.2.1g-3-1.3 Duration of therapy interruption(s) [days] - 2nd line nivolumab*).

10.3.4 Cohort I: Main reason for end of treatment – 2nd-line nivolumab

For 143 patients (87.7%) of the FAS (N) analysis population end of treatment was documented. Reasons for end of therapy documentation were as follows: progressive disease (n=87, 53.4%),

toxicity (therapy-related) (n=14, 8.6%), death (n=11, 6.7%),lost to follow-up (n=2, 1.2%) and non-compliance (n=1, 0.6%). The reasons (Serious) Adverse event (not therapy-related), Investigator's decision (not toxicity, not therapy-related) and patient's wish (not toxicity, not therapy-related) as well as other reasons were documented for 7 patients (4.3%), each, see also *PAZOREAL TFL: Table 14.1.1b-1-1.3 Main reason for end of treatment - 2nd line nivolumab* in appendix. For 19 patients (11.7%) treatment was ongoing after end of study observation and for 1 patient no reason for end of treatment was documented.

10.3.5 Cohort I: Treatment with 2nd-line everolimus and 3rd-line everolimus

In the FAS – cohort I, 5 patients (1.3%) received 2nd-line therapy everolimus and 9 patients (2.4%) received 3rd-line therapy everolimus, cf. Figure 10.2. (see also appendix *PAZOREAL TFL: Table 14.2.1a-2-1.1 Overview of received medication (2nd line) and Table 14.2.1a-3-1.1 Overview of received medication (3rd line))*. Due to the small number of patients effectiveness data are provided in the appendix.

2nd -line everolimus:

For treatment details see *PAZOREAL TFL: Table 14.2.1b-1.2 Overview of first administered dose [mg] - everolimus – 2nd line everolimus, Table 14.2.1c-1-1.2 Relative dose intensity of everolimus [%] - 2nd line everolimus, Table 14.2.1d-1.2 Overview of lowest administered dose - everolimus - 2nd line everolimus* in the appendix.

For treatment modification see *PAZOREAL TFL: Table 4.2.1e-1-1.2 Number of patients with treatment modifications - 2nd line everolimus, Table 14.2.1f-1-1.2 Reason for dose reduction(s) - 2nd line everolimus, Table 14.2.1f-2-1.2 Specification for dose reduction(s) - 2nd line everolimus* in appendix.

For details on Dose interruption see *PAZOREAL TFL: Table 14.2.1g-1-1.2 Reason for dose interruption(s) - 2nd line everolimus, Table 14.2.1g-2-1.2 Duration of therapy interruption(s) (cat.) - 2nd line everolimus, Table 14.2.1g-3-1.2 Duration of therapy interruption(s) [days] - 2nd line everolimus* in appendix.

For details on main reasons for end of treatment see *PAZOREAL TFL: Table 14.1.1b-1-1.2 Main reason for end of treatment – 2nd line everolimus* in appendix.

3rd-line everolimus:

For treatment details see *PAZOREAL TFL: Table 14.2.1b-1.5 Overview of first administered dose [mg] - everolimus – 3rd line everolimus, Table 14.2.1c-1-1.5 Relative dose intensity of everolimus [%] – 3rd line everolimus, Table 14.2.1d-1.5 Overview of lowest administered dose - everolimus – 3rd line everolimus* in appendix.

For treatment modification see *PAZOREAL TFL: Table 4.2.1e-1-1.5 Number of patients with treatment modifications – 3rd line everolimus, Table 14.2.1f-1-1.5 Reason for dose reduction(s) – 3rd line everolimus, Table 14.2.1f-2-1.5 Specification for dose reduction(s) – 3rd line everolimus* in appendix.

For details on dose interruption see *PAZOREAL TFL: Table 14.2.1g-1-1.5 Reason for dose interruption(s) – 3rd line everolimus, Table 14.2.1g-2-1.5 Duration of therapy interruption(s) (cat.) – 3rd line everolimus, Table 14.2.1g-3-1.5 Duration of therapy interruption(s) [days] – 3rd line everolimus* in appendix.

For details on main reasons for end of treatment see *PAZOREAL TFL: Table 14.1.1b-1-1.5 Main reason for end of treatment – 3rd line everolimus* in appendix.

10.3.6 Cohort II: Treatment with 2nd-line nivolumab and 3rd-line everolimus

In FAS – cohort II, 6 patients (100%) received 3rd -line therapy everolimus, after previous 2nd-line nivolumab and previous 1st-line TKI-therapy, cf. Figure 10.2 (*PAZOREAL TFL: Table 14.2.1a-3-2.2 Overview of received medication (3rd line), Table 14.2.1a-2-2.2 Overview of received medication (2nd line, retrospective), Table 14.2.1a-1-2.2 Overview of received medication (1st line, retrospective)).* Due to the small number of patients in cohort II outcome data are provided in appendix, only.

For treatment details see *PAZOREAL TFL: Table 14.2.1b-2.2 Overview of first administered dose [mg] - everolimus – 3rd line everolimus, Table 14.2.1c-1-2.2 Relative dose intensity of everolimus [%] – 3rd line everolimus, Table 14.2.1d-2.2 Overview of lowest administered dose - everolimus – 3rd line everolimus* in appendix.
For treatment modification see *PAZOREAL TFL: Table 4.2.1e-1-2.2 Number of patients with treatment modifications – 3rd line everolimus, Table 14.2.1f-1-2.2 Reason for dose reduction(s) – 3rd line everolimus, Table 14.2.1f-2-2.2 Specification for dose reduction(s) – 3rd line everolimus* in appendix.
For details on dose interruption see *PAZOREAL TFL: Table 14.2.1g-1-2.2 Reason for dose interruption(s) – 3rd line everolimus, Table 14.2.1g-2-2.2 Duration of therapy interruption(s) (cat.) – 3rd line everolimus, Table 14.2.1g-3-2.2 Duration of therapy interruption(s) [days] – 3rd line everolimus* in appendix.
For details on main reasons for end of treatment see *PAZOREAL TFL: Table 14.1.1b-1-2.2 Main reason for end of treatment – 3rd line everolimus, Table 14.1.1b-1-2.1 Main reason for end of treatment – 2nd line nivolumab* in appendix.

10.3.7 Therapy sequences

Cohort I

In the FAS – cohort I, patients who entered the follow-up phase are depicted in Table 10-9.

Table 10-9 Number of patients in Follow-Up – cohort I
(see also Figure 10.2)

			FAS - cohort I (N=376)
	Prior therapy		
Number of patients in Follow-Up	1st line pazopanib	Patients in Follow-Up	68 (18.1%)
Number of patients in Follow-Up	2nd line everolimus	Patients in Follow-Up	4 (1.1%)
Number of patients in Follow-Up	2nd line nivolumab	Patients in Follow-Up	87 (23.1%)
Number of patients in Follow-Up	3rd line everolimus	Patients in Follow-Up	7 (1.9%)

Source: PAZOREAL TFL: Table 14.2.1i-1-1.1 Number of patients in Follow-Up

Patients receiving a subsequent antineoplastic therapy after prior therapy with either 1st-line pazopanib, 2nd line nivolumab or 2nd line or 3rd line everolimus are depicted in Table 10-10. After 1st-line pazopanib treatment 42 patients (11.2%) and after 2nd line Nivolumab 62 patients (16.5%) received a subsequent antineoplastic therapy. The substances applied for these patients included substances belonging to either TKI, PD-L1-inhibitors, VEGF/FGF-inhibitors or mTOR-inhibitors. While after 1st-line pazopanib subsequent therapy mostly was a combination therapy including the PD-L1- inhibitor Nivolumab and TKI Cabozantinib, after 2nd line nivolumab subsequent therapy mostly was solely the TKI Cabozantinib or another TKI, while combination therapies were less frequent. Details on substances of subsequent antineoplastic therapies are provided in the appendix *PAZOREAL TFL: Table 14.2.1h-2-1.1 Substances of subsequent antineoplastic therapy.*

Table 10-10 Patients with subsequent antineoplastic therapy – cohort I

			FAS – cohort I (N=376)
	Prior therapy		
Patients with subsequent antineoplastic therapy	1st line Pazopanib	Yes	42 (11.2%)
Patients with subsequent antineoplastic therapy	2nd line Everolimus	Yes	3 (0.8%)
Patients with subsequent antineoplastic therapy	2nd line Nivolumab	Yes	62 (16.5%)
Patients with subsequent antineoplastic therapy	3rd line Everolimus	Yes	6 (1.6%)

This table displays the number of patients who entered the follow-up period and received a subsequent antineoplastic therapy other than predefined in the protocol.

The last documented therapy line = 'Prior therapy'.

Source: PAZOREAL TFL: Table 14.2.1h-1-1.1 Patients with subsequent antineoplastic therapy

Cohort II

Number of patient in Follow-up and details on therapy sequences for patients in cohort II are provided in the appendix *PAZOREAL TFL: Table 14.2.1i-1-2.2 Number of patients in Follow-Up, Table 14.2.1h-1-2.2 Patients with subsequent antineoplastic therapy and Table 14.2.1h-2-2.2 Substances of subsequent antineoplastic therapy.*

10.3.8 Main reason for end of study

Cohort I

For 369 patients (98.1%) of cohort I end of study was documented. Reasons for end of study documentation were as follows: death (n=172, 45.7%), lost to follow-up (n=57, 15.2%), observation period of the NIS has been completed (n=93, 24.7%), patient's wish (n=33, 8.8%) and other reasons (n=14, 3.7%), see also in the appendix *PAZOREAL TFL: Table 14.1.1b-2-1 Main reason for end of study FAS cohort I and also PAZOREAL TFL: Table 14.1.1b-2-3 Main reason for end of study SAF - cohort I.*

Cohort II

Main reasons for end of study for patients in cohort II are provided in appendix *PAZOREAL TFL: Table 14.1.1b-2-2 Main reason for end of study FAS cohort II and also PAZOREAL TFL: Table 14.1.1b-2-4 Main reason for end of study SAF - cohort II*.

10.4 Main results

10.4.1 Primary Endpoint: Time on drug

Cohort I: Treatment period (overall ToD)

The median ToD for for patients started with 1st-line pazopanib, i.e. start date of first pazopanib administration until end date of last administration of study medication (i.e. either 1st-line pazopanib, 2nd-line everolimus or nivolumab or 3rd-line everolimus), was 10.0 months (95% CI 8.5-11.7, Figure 10.5) The 6-month time on drug rate was 66.7% (61.6%-71.2%).

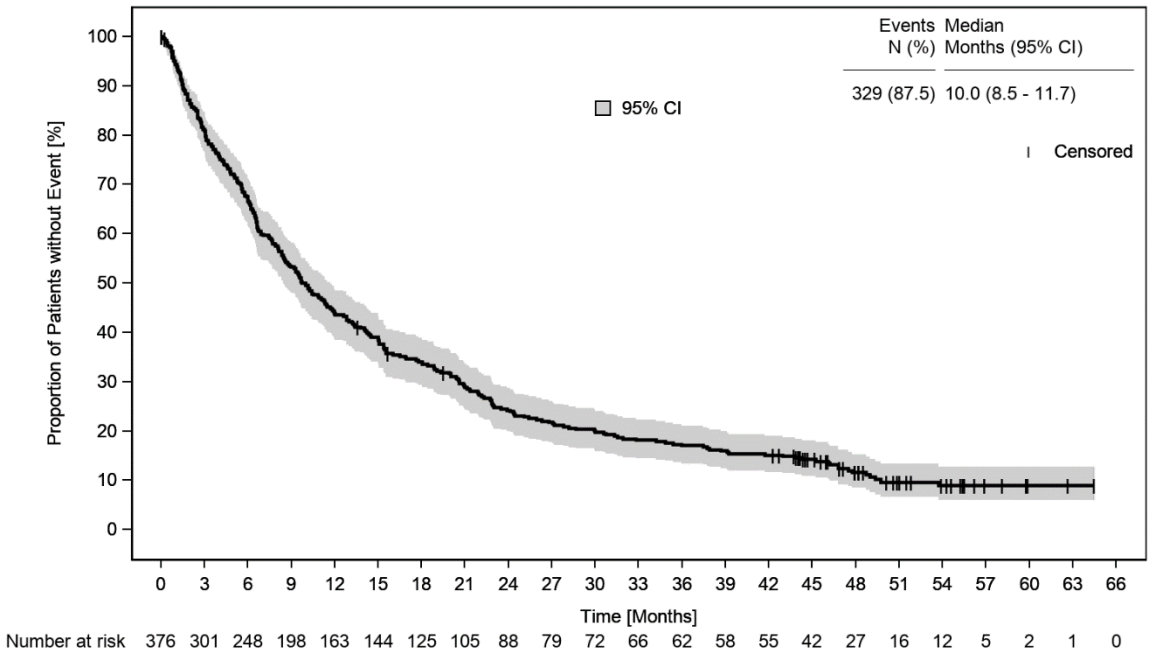


Figure 10.5 Overall time on drug [months] 1st-line pazopanib – cohort I

The overall time on drug for cohort I is defined as date of last recorded application of any study drug within the PAZOREAL study minus date of first recorded application of pazopanib. 'Patients without events' refer to living patients as well to patients without documented end of treatment of any study drug.

Source PAZOREAL TFL: Figure 14.2.3a-1-1.1 Overall time on drug [months]

Cohort I: Sensitivity analysis: Overall time on drug trial-eligible patients

In FAS (P, t.e.) 124 patients (84.9%) had an event and 22 patients (15.1%) were censored due to missing end date of last study medication administration (Figure 10.6). The median time on

drug was 11.3 months (95% CI 9.2-14.3) and the 6-month time on drug rate was 70.5% (95% CI 62.4%-77.2%) see also in the appendix *PAZOREAL TFL: Table 14.2.3e-2-1 Sensitivity analysis: Overall time on drug [months] (trial-eligible patients) - 1st line pazopanib FAS cohort 1 and also PAZOREAL TFL: Figure 14.2.3d-1-1.1 Sensitivity analysis: Overall time on drug [months] (trial-eligible* patients).*

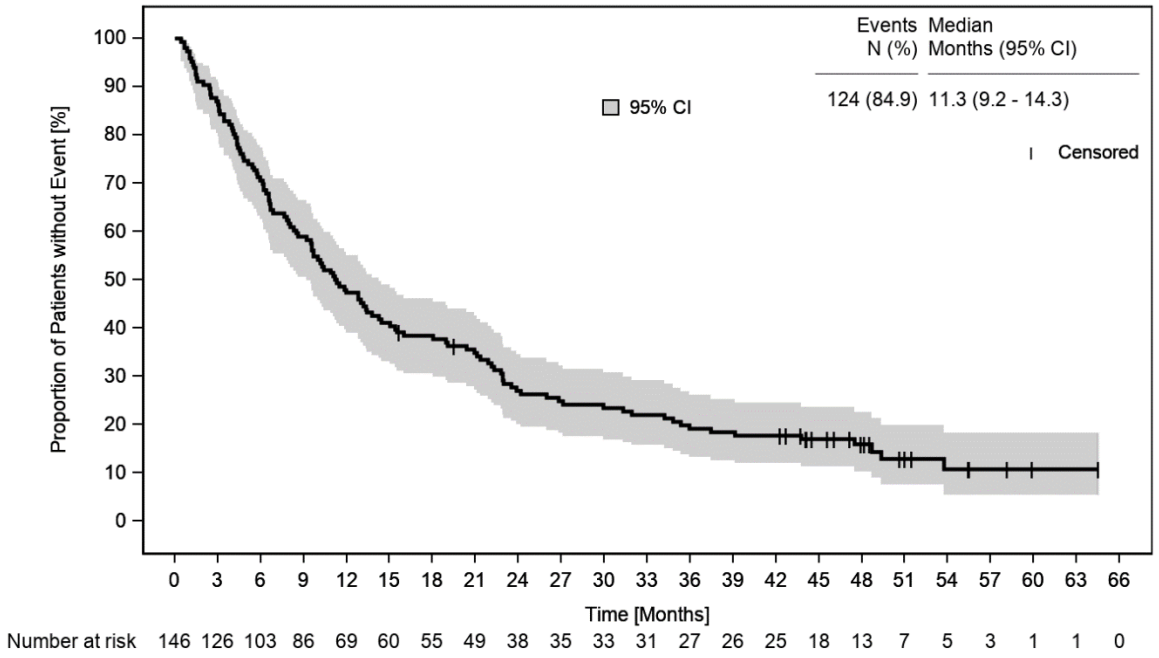


Figure 10.6 Sensitivity analysis: Overall ToD [months] (trial-eligible* patients)

ToD: Time on Drug, 'Patients without events' refer to living patients as well to patients without documented end of treatment of any study drug.; *Source: PAZOREAL TFL: Table 14.2.3e-2-1 Sensitivity analysis: Overall time on drug [months] (trial-eligible patients) - 1st line pazopanib FAS cohort 1 and also PAZOREAL TFL: Figure 14.2.3d-1-1.1 Sensitivity analysis: Overall time on drug [months] (trial-eligible* patients).* *Defined as patients fulfilling none of the three 'trial-ineligibility criteria': Karnofsky Perfor-mance Status <70%, Haemoglobin < Lower Limit of Normal, Non-clear Cell Carcinoma Histology.

10.4.1.1 Cohort I: 1st-line pazopanib

In FAS – cohort I, 376 patients received 1st-line therapy pazopanib and were assigned to FAS (P).

Time on drug

Median time on drug of pazopanib was 6.3 months (95% CI 5.6 – 7.4); 27 patients (7.2%) were censored (due to missing documentation of date of therapy end) and data from 349 patients (92.8%) were not censored (Figure 10.7).

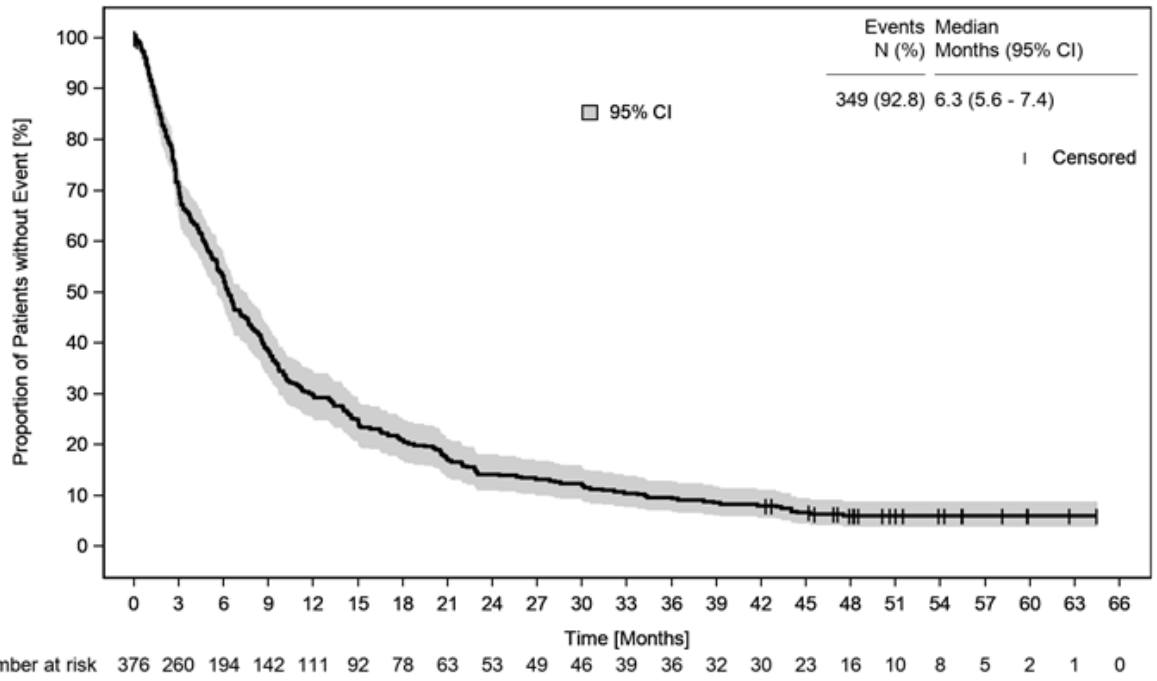


Figure 10.7 Time on drug [months] - 1st line pazopanib – cohort I

The time on drug was estimated by the reversed Kaplan-Meier method using the date of first documented study drug administration as start date and the date of last documented study drug administration as end date (within one line of treatment). Patients without documented end of treatment were censored. 'Patients without events' refer to living patients as well to patients without documented end of treatment.

Source: PAZOREAL TFL: Table 14.2.3a-1-1.1 Time on drug [months] - 1st line pazopanib, PAZOREAL TFL: Figure 14.2.3a-1-1.1 Time on drug [months] - 1st line pazopanib

Details for Time on drug analysis of patients included in the FAS^{ext} are provided in the appendix *PAZOREAL TFL: Table 14.2.3f-1-1.1 Time on drug [months] - 1st line pazopanib FAS (extended) - cohort I))*

Time on drug by Gender

In FAS(P) male patients (n=257) had a median time on drug of 6.6 months (95% CI 5.6-8.3), while female patients (n=119) had a median time on drug of 5.8 months (95% CI 4.3 - 7.3). The respective 6-month time on drug rate by gender was 53.9% (95% CI 47.6%- 59.8%) and 48.3% (95% CI 39.1%- 57.0%) (*PAZOREAL TFL: Table 14.2.3b-1-1.1 Time on drug [months] by gender - 1st line pazopanib).*

Time on drug by Age

In FAS(P) patients aged <65years (n=132) had a median time on drug of 6.0 months (95% CI 4.9-7.4), while patients aged ≥65years (n=244) had a median time on drug of 6.6 months (95% CI 5.5 - 8.1). The respective 6 month time on drug rate by Age category was 49.2% (95% CI 40.5% - 57.4%) and 53.8% (95% CI 47.2%- 59.8%, *PAZOREAL TFL: Table 14.2.3b-2-1.1 Time on drug [months] by age at start of therapy line - 1st line pazopanib).*

Time on drug by BMI at enrollment

In FAS(P) patients with a BMI of <25kg/m^2 (n=122) had a median time on drug of 6.3 months (95% CI 4.5-7.9), while patients with a BMI ≥25 kg/m² (n=208) had a median time on drug of 6.3 months (95% CI 5.2 - 8.3). The 6-month time on drug rate in both BMI groups was 51.7% with respective 95% CI of 42.4%- 60.2% and 44.7%- 58.2% (*PAZOREAL TFL: Table 14.2.3b-3-1.1 Time on drug [months] by BMI at enrollment - 1st line pazopanib).*

Time on drug by MSKCC Score at enrollment

In FAS(P) patients with favorable risk (n=20), with intermediate risk (n=52) and poor risk (n=13) had a median time on drug of 9.4 months (95% CI 1.3-16.5), of 4.5 months (95% CI 3.0-6.5) and of 2.8 months (95% CI 2.1-6.0). The 6-month time on drug rate by MSKCC score at enrollment was 55.0% (95% CI 31.3%- 73.5%), 42.3% (95% CI 28.8%- 55.2%) and 23.1% (95% CI 5.6%- 47.5%), respectively (*PAZOREAL TFL: Table 14.2.3b-4-1.1 Time on drug [months] by MSKCC Score at enrollment - 1st line pazopanib).*

Time on drug by histology

In FAS(P) patients with clear cell carcinoma (n=304) had a median time on drug of 6.3 months (95% CI 5.6-7.6, Figure 10.8). Patients with non-clear cell carcinoma had a median time on drug of 7.6 months (95% CI 3.3-13.9). The 6-month time on drug rate by histology was 52.8% (95% CI 47.0%- 58.3%) in patients with clear cell carcinoma and 54.1% (95% CI 36.9%- 68.4%) in patients with non-clear cell carcinoma (*PAZOREAL TFL: Table 14.2.3b-5-1.1 Time on drug [months] by histology - 1st line pazopanib).*

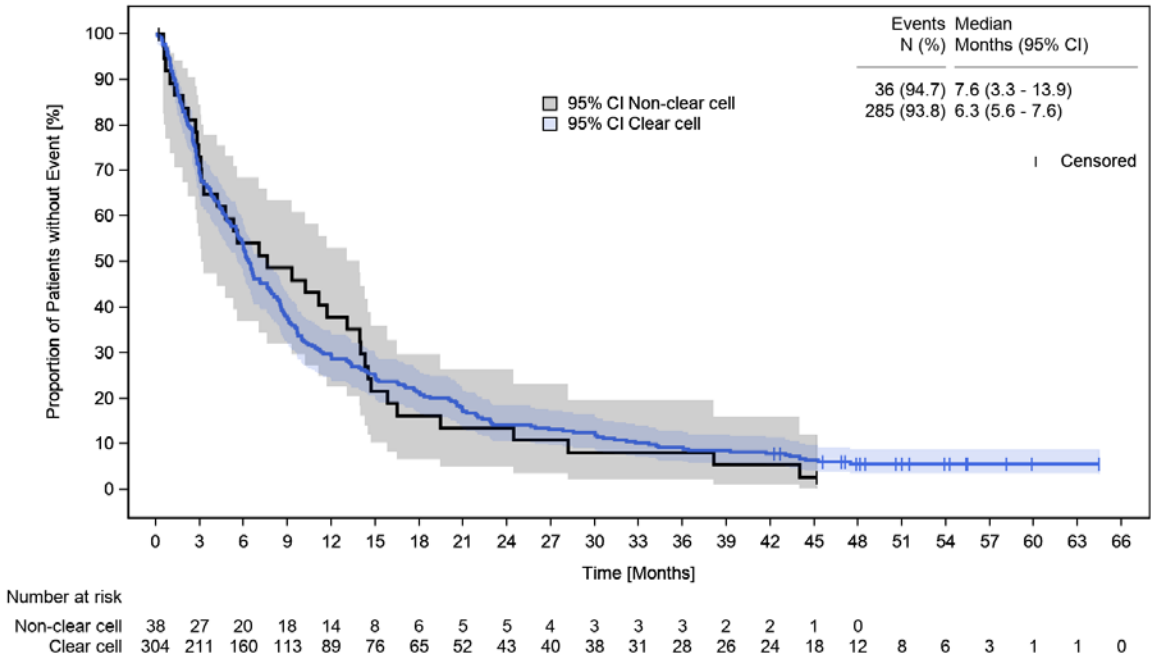


Figure 10.8 Time on drug [months] by histology – 1st-line pazopanib

'Patients without events' refer to living patients as well to patients without documented end of treatment.
(Source: PAZOREAL TFL: Table 14.2.3b-5-1.1 Time on drug [months] by histology - 1st line pazopanib, PAZOREAL TFL: Figure 14.2.3e-1-1.1 Time on drug [months] by histology - 1st line pazopanib)

Time on drug by nephrectomy

In FAS(P) patients with documented nephrectomy (n=303) had a median time on drug of 7.1 months (95% CI 6.1-8.5). Patients without documented nepherectomy had a median time on drug of 4.2 months (95% CI 2.8-5.5). The 6-month time on drug rate by nephrectomy was 56.1% (95% CI 50.3%-61.5%) in patients with documented nephrectomy and 35.2% (95% CI 24.4%- 46.3%) in patients without documented nephrectomy (*PAZOREAL TFL: Table 14.2.3b-6-1.1 Time on drug [months] by nephrectomy - 1st line pazopanib).*

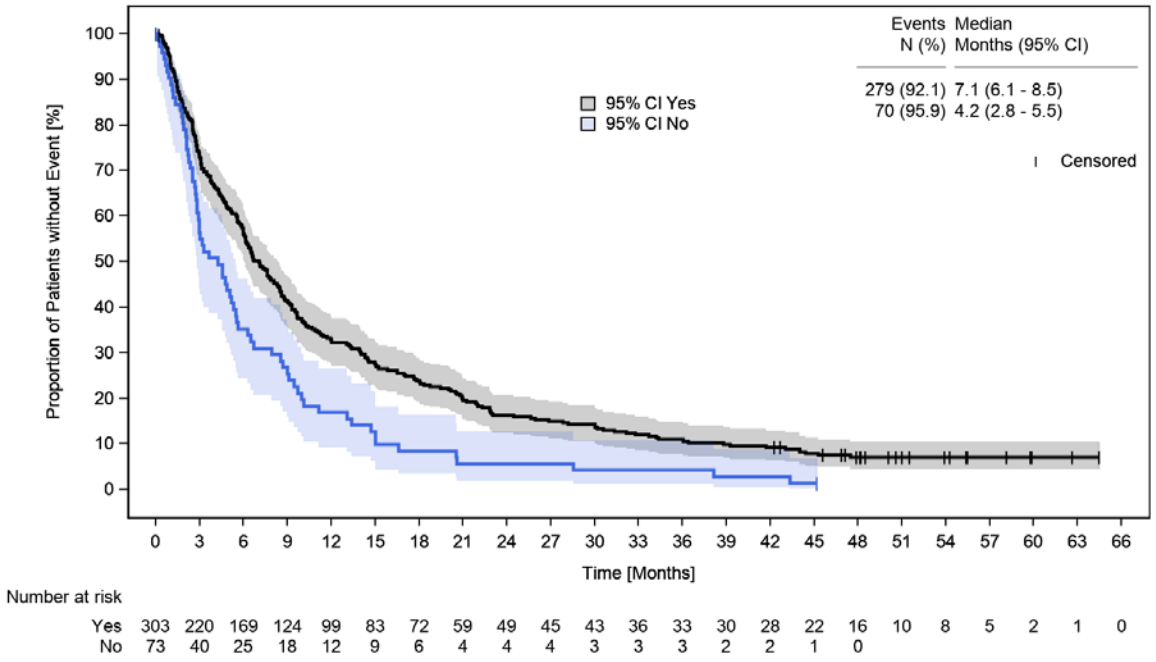


Figure 10.9 Time on drug [months] by nephrectomy – 1st-line pazopanib

'Patients without events' refer to living patients as well to patients without documented end of treatment.
(Source: PAZOREAL TFL: Table 14.2.3b-6-1.1 Time on drug [months] by nephrectomy - 1st line pazopanib, PAZOREAL TFL: Figure 14.2.3e-2-1.1 Time on drug [months] by nephrectomy - 1st line pazopanib)

Time on drug by participating in a Patient Education Program

In FAS(P) only 4 patients were documented as participating in a Patient Education Program and had a median time on drug of 8.1 months (95% CI 4.5-NA). Most patients were documented as not participating in a Patient Education Program (n=188) and had a median time on drug of 10.2 months (95% CI 8.6-13.4). The reseptive 6-month time on drug rate was 75.0% (95% CI 12.8%-96.1%) and 70.2% (95% CI 63.1%- 76.2%, *PAZOREAL TFL: Table 14.2.3c-1-1.1 Time on drug [months] by participating in a Patient Education Program - 1st line pazopanib).*

Time on drug by distance between the patients' residence and the practice/hospital

In FAS(P) patients with a distance of <10km (n=56, 48 patients (85.7%) with event) had a median time on drug of 8.1 months (95% CI 5.5-13.4), while patients with a distance of ≥10km (n=104) had a median time on drug of 14.8 months (95% CI 10.1-18.7). The respective 6-month time on drug rate by distance was 60.7% (95% CI 46.7%- 72.1%) and 78.8% (95% CI 69.7%- 85.5%, *PAZOREAL TFL: Table 14.2.3c-2-1.1 Time on drug [months] by distance- 1st line pazopanib).*

Sensitivity analysis: Time on drug trial-eligible patients

In FAS (P, t.e.) 131 patients (89.7%) had an event and 15 patients (10.3%) were censored due to missing documented end of treatment for this sensitivity analysis (Figure 10.10). The median time on drug was 7.7 months (95% CI 6.1-9.0) and the 6-month time on drug rate was 58.9% (95% CI 50.5% - 66.4%, *PAZOREAL TFL: Table 14.2.3e-1-1.1 Sensitivity analysis: Time on drug [months] (trial-eligible patients) - 1st line pazopanib).*

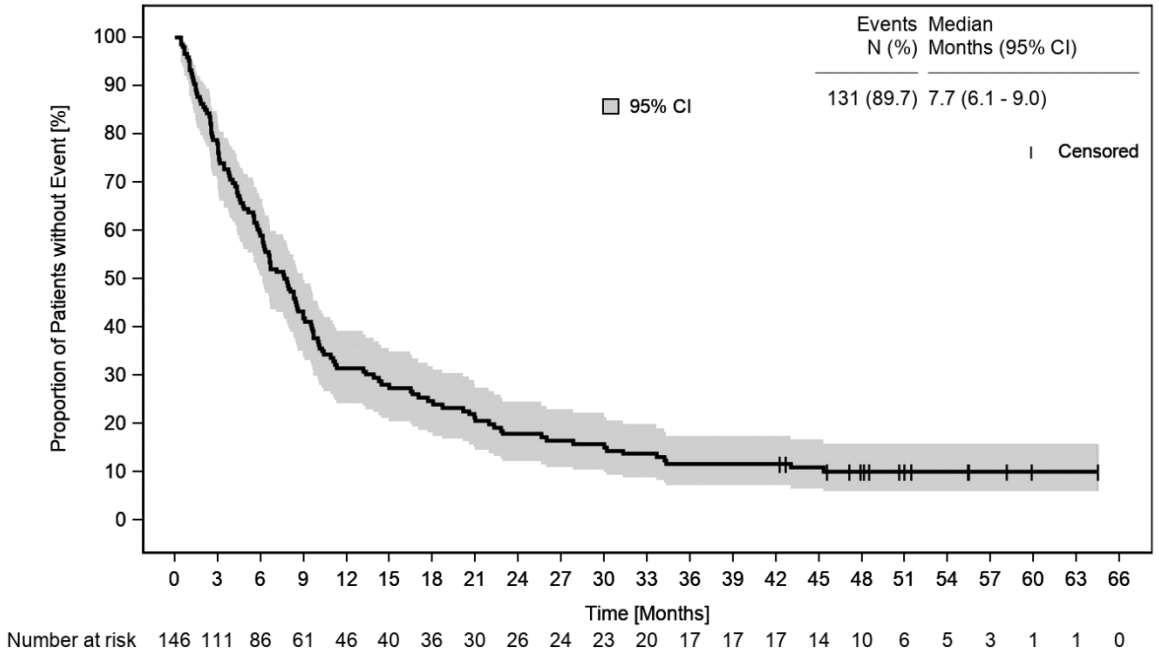


Figure 10.10 Sensitivity analysis: ToD trial-eligible* patients – 1st-line pazopanib

'Patients without events' refer to living patients as well to patients without documented end of treatment.
*ToD: Time on Drug, *Defined as patients fulfilling none of the three 'trial-ineligibility criteria': Karnofsky Performance Status <70%, Haemoglobin < Lower Limit of Normal, Non-clear Cell Carcinoma Histology. (Source: PAZOREAL TFL: Table 14.2.3e-1-1.1 Sensitivity analysis: Time on drug [months] (trial-eligible patients) - 1st line pazopanib, PAZOREAL TFL: Figure 14.2.3d-1-1.1 Sensitivity analysis: Time on drug [months] (trial-eligible* patients) - 1st line pazopanib)*

Best response and disease control rate (DCR)

In FAS (P) CR as best response was achieved in 36 patients (9.57%) and SD, definded as non-CR or non-PD, in 178 patients (47.34%). Thus the DCR, comprised by patients with CR and SD, was 56.91%. PD was the best response in 81 patients (21.54%). For 2 patients, no best response was evaluable and in 79 patients (21.01%) no assessment was done (cf.Table 10-11).

Best response was assessed in 259 patient (68.9%) by radiologic assessment, in 38 patients (10.1%) by clinical assessment *(PAZOREAL TFL: Table 14.2.3g-2-1.1 Kind of response assessment (best response) - 1st line pazopanib).*

Table 10-11 Best response and disease control rate* (DCR) – 1st-line pazopanib

		Total (N=376)	95%-CI
Best response / DCR	Complete response (CR)	36 (9.57%)	[6.97, 13.00]
Best response / DCR	Stable disease (non-CR, non-PD)	178 (47.34%)	[42.35, 52.39]
Best response / DCR	- - - - - - - - DCR* - - - - - - - -	214 (56.91%)	[51.86, 61.83]
Best response / DCR	Progressive disease (PD)	81 (21.54%)	[17.68, 25.98]
Best response / DCR	Not evaluable	2 (0.53%)	[0.02, 2.05]
Best response / DCR	Not done	79 (21.01%)	[17.19, 25.42]

Displayed are the 95%-CIs according to Agresti & Coull.
For the analysis, best response from the end of study screen will be only used if no other documentation of response is available.
* Defined as Complete response or Stable disease.

Source: PAZOREAL TFL: Table 14.2.3g-1-1.1 Best response and disease control rate (DCR) - 1st line pazopanib*

Details on subgroup analyses of best response are provided in Table 10-12 by gender, Table 10-13 by categorial age, Table 10-14 by metastatic disease, Table 10-15 by MSKCC risk group, Table 10-16 by nephrectomy, Table 10-17 by Heng Score, Table 10-18 by T-Stage, Table 10-19 by N-Stage, Table 10-20 by ECOG at baseline, Table 10-21 by localization of metastases.

Table 10-12 Best response by gender – 1st-line pazopanib

		Patients in FAS (N=376)	
Gender		**Female (N=119)**	**Male (N=257)**
Best response by gender	Complete response (CR)	8 (6.7%)	28 (10.9%)
Best response by gender	Stable disease (non-CR, non-PD)	58 (48.7%)	120 (46.7%)
Best response by gender	Progressive disease (PD)	27 (22.7%)	54 (21.0%)
Best response by gender	Not evaluable	0 (0.0%)	2 (0.8%)
Best response by gender	Not done	26 (21.8%)	53 (20.6%)

Source: PAZOREAL TFL: Table 14.1.0-1-1 Best response by gender - 1st line pazopanib

Table 10-13 Best response by categorial age – 1st-line pazopanib

		Patients in FAS (N=376)	
Categorial age		**<65 years (N=132)**	**≥65 years (N=244)**
Best response by categorial age	Complete response (CR)	14 (10.6%)	22 (9.0%)
Best response by categorial age	Stable disease (non-CR, non-PD)	61 (46.2%)	117 (48.0%)
Best response by categorial age	Progressive disease (PD)	32 (24.2%)	49 (20.1%)
Best response by categorial age	Not evaluable	2 (1.5%)	0 (0.0%)

		Patients in FAS (N=376)	
Categorial age		**<65 years (N=132)**	**≥65 years (N=244)**
Best response by categorial age	Not done	23 (17.4%)	56 (23.0%)

Source: PAZOREAL TFL: Table 14.1.0-2-1 Best response by categorial age - 1st line pazopanib

Table 10-14 Best response by metastatic disease – 1st-line pazopanib

		Patients in FAS (N=376)	
Metastatic disease		**Metastatic disease (N=353)**	**Non-metastatic disease (N=23)**
Best response by metastatic disease	Complete response (CR)	33 (9.3%)	3 (13.0%)
Best response by metastatic disease	Stable disease (non-CR, non-PD)	170 (48.2%)	8 (34.8%)
Best response by metastatic disease	Progressive disease (PD)	74 (21.0%)	7 (30.4%)
Best response by metastatic disease	Not evaluable	2 (0.6%)	0 (0.0%)
Best response by metastatic disease	Not done	74 (21.0%)	5 (21.7%)

Source: PAZOREAL TFL: Table 14.1.0-3-1 Best response by metastatic disease - 1st line pazopanib

Table 10-15 Best response by MSKCC – 1st-line pazopanib

		Patients in FAS (N=376)		
MSKCC risk group		**Intermediate (N=52)**	**Poor (N=13)**	**Favorable (N=20)**
Best response by MSKCC risk group	Complete response (CR)	4 (7.7%)	1 (7.7%)	0 (0.0%)
Best response by MSKCC risk group	Stable disease (non-CR, non-PD)	20 (38.5%)	2(15.4%)	12 60.0%)
Best response by MSKCC risk group	Progressive disease (PD)	15 (28.8%)	6 46.2%)	3 (15.0%)
Best response by MSKCC risk group	Not evaluable	1 (1.9%)	0 (0.0%)	0 (0.0%)
Best response by MSKCC risk group	Not done	12 (23.1%)	4 30.8%)	5 (25.0%)

Source: PAZOREAL TFL: Table 14.1.0-4-1 Best response by MSKCC - 1st line pazopanib

Table 10-16 Best response by nephrectomy – 1st-line pazopanib

		Patients in FAS (N=376)	
Nephrectomy		**No nephrectomy (N=73)**	**Nephrectomy (N=303)**
Best response by nephrectomy	Complete response (CR)	4 (5.5%)	32 (10.6%)
Best response by nephrectomy	Stable disease (non-CR, non-PD)	28 (38.4%)	150 (49.5%)

		Patients in FAS (N=376)	
Nephrectomy		**No nephrectomy (N=73)**	**Nephrectomy (N=303)**
Best response by nephrectomy	Progressive disease (PD)	22 (30.1%)	59 (19.5%)
Best response by nephrectomy	Not evaluable	1 (1.4%)	1 (0.3%)
Best response by nephrectomy	Not done	18 (24.7%)	61 (20.1%)

Source: PAZOREAL TFL: Table 14.1.0-5-1 Best response by nephrectomy - 1st line pazopanib

Table 10-17 Best response by Heng Score – 1st-line pazopanib

		Patients in FAS (N=376)		
Heng Score		**Intermediate (N=43)**	**Poor (N=21)**	**Favorable (N=16)**
Best response by Heng Score	Complete response (CR)	3 (7.0%)	2 (9.5%)	0 (0.0%)
Best response by Heng Score	Stable disease (non-CR, non-PD)	17 (39.5%)	5 (23.8%)	9 (56.3%)
Best response by Heng Score	Progressive disease (PD)	13 (30.2%)	8 (38.1%)	3 (18.8%)
Best response by Heng Score	Not evaluable	1 (2.3%)	0 (0.0%)	0 (0.0%)
Best response by Heng Score	Not done	9 (20.9%)	6 (28.6%)	4 (25.0%)

Source: PAZOREAL TFL: Table 14.1.0-6-1 Best response by heng score - 1st line pazopanib

Table 10-18 Best response by T-Stage – 1st-line pazopanib

		Patients in FAS (N=376)				
T-Stage		**T1 (N=75)**	**T2 (N=36)**	**T3 (N=133)**	**T4 (N=19)**	**T0 (N=5)**
Best response by T-Stage	Complete response (CR)	10(13.3%)	1 (2.8%)	17(12.8%)	2(10.5%)	0 (0.0%)
Best response by T-Stage	Stable disease (non-CR, non-PD)	3 (50.7%)	21(58.3%)	61(45.9%)	3(15.8%)	3(60.0%)
Best response by T-Stage	Progressive disease (PD)	18(24.0%)	9 (25.0%)	25(18.8%)	5(26.3%)	0 (0.0%)
Best response by T-Stage	Not evaluable	0 (0.0%)	0 (0.0%)	2 (1.5%)	0 (0.0%)	0 (0.0%)
Best response by T-Stage	Not done	9 (12.0%)	5 (13.9%)	28(21.1%)	9(47.4%)	2(40.0%)

Source: PAZOREAL TFL: Table 14.1.0-7-1 Best response by T-Stage - 1st line pazopanib

Table 10-19 Best response by N-Stage – 1st-line pazopanib

		Patients in FAS (N=376)		
N-Stage		**N0 (N=119)**	**N1 (N=49)**	**N2 (N=22)**
Best response by N-Stage	Complete response (CR)	9 (7.6%)	9 (18.4%)	4 (18.2%)
Best response by N-Stage	Stable disease (non-CR, non-PD)	71 (59.7%)	16 (32.7%)	10 (45.5%)
Best response by N-Stage	Progressive disease (PD)	19 (16.0%)	13 (26.5%)	3 (13.6%)
Best response by N-Stage	Not evaluable	1 (0.8%)	0 (0.0%)	0 (0.0%)
Best response by N-Stage	Not done	19 (16.0%)	11 (22.4%)	5 (22.7%)

Source: PAZOREAL TFL: Table 14.1.0-7-1 Best response by N-Stage - 1st line pazopanib

Table 10-20 Best response by ECOG at baseline – 1st-line pazopanib

		Patients in FAS (N=376)			
ECOG at baseline		**ECOG 0 (N=197)**	**ECOG 1 (N=104)**	**ECOG 2 (N=40)**	**ECOG ≥3 (N=2)**
Best response by ECOG at baseline	Complete response (CR)	30(15.2%)	2 (1.9%)	3 (7.5%)	0(0.0%)
Best response by ECOG at baseline	Stable disease (non-CR, non-PD)	100(50.8%)	50(48.1%)	13(32.5%)	0(0.0%)
Best response by ECOG at baseline	Progressive disease (PD)	31 (15.7%)	32(30.8%)	10(25.0%)	1(50.0%)
Best response by ECOG at baseline	Not evaluable	1(0.5%)	0(0.0%)	1(2.5%)	0 (0.0%)
Best response by ECOG at baseline	Not done	35 (17.8%)	20(19.2%)	13(32.5%)	1(50.0%)

Source: PAZOREAL TFL: Table 14.1.0-8-1 Best response by ECOG at baseline - 1st line pazopanib

Table 10-21 Best response by localisation of metastases – 1st-line pazopanib

		Patients in FAS (N=376)						
localisation of metastases		**Lung (N=218)**	**Bone (N=96)**	**Liver (N=61)**	**Lymph nodes (regional) (N=53)**	**Lymph nodes(distal) (N=45)**	**Other (N=144)**	**Non-metastatic disease (N=23)**
Best response by localisation of metastases	Complete response (CR)	25 (11.5%)	4 (4.2%)	7 (11.5%)	2 (3.8%)	3 (6.7%)	11 (7.6%)	3 (13.0%)
Best response by localisation of metastases	Stable disease (non-CR, non-PD)	96 (44.0%)	48 (50.0%)	28 (45.9%)	27 (50.9%)	22 (48.9%)	70 (48.6%)	8 (34.8%)
Best response by localisation of metastases	Progressive disease (PD)	48 (22.0%)	28 (29.2%)	16 (26.2%)	14 (26.4%)	11 (24.4%)	27 (18.8%)	7 (30.4%)

		Patients in FAS (N=376)						
localisation of metastases		**Lung (N=218)**	**Bone (N=96)**	**Liver (N=61)**	**Lymph nodes (regional) (N=53)**	**Lymph nodes(distal) (N=45)**	**Other (N=144)**	**Non-metastatic disease (N=23)**
Best response by localisation of metastases	Not evaluable	1 (0.5%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.4%)	0 (0.0%)
Best response by localisation of metastases	Not done	48 (22.0%)	15 (15.6%)	10 (16.4%)	10 (18.9%)	9 (20.0%)	34 (23.6%)	5 (21.7%)

Source: PAZOREAL TFL: Table 14.1.0-9-1 Best response by localization of metastases - 1st line pazopanib

10.4.1.2 Cohort I: 2nd-line nivolumab

In FAS cohort I, 163 patients received 2nd-line therapy nivolumab and were assigned to FAS (N).

Time on drug

Median therapy duration of nivolumab was 4.8 months (95% CI 3.7 – 6.5); 20 patients (12.3%) were censored (due to missing documentation of date of therapy end) and data from 143 patients (87.7%) were not censored (Figure 10.11).

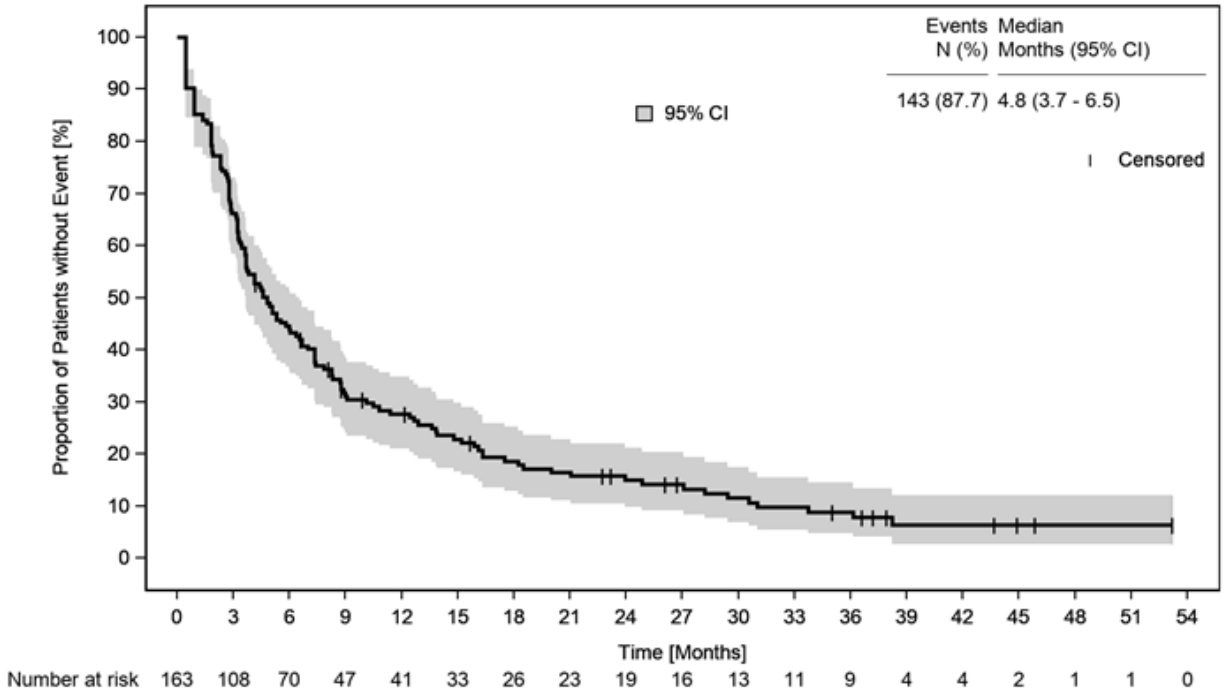


Figure 10.11 Time on drug [months] – 2nd-line nivolumab – cohort I

'Patients without events' refer to living patients as well to patients without documented end of treatment.

The time on drug was estimated by the reversed Kaplan-Meier method using the date of first documented nivolumab drug administration as start date and the date of last documented nivolumab administration as end date (within one line of treatment). Patients without documented end of treatment were censored.

Source: PAZOREAL TFL: Table 14.2.3a-1-1.3 Time on drug [months] - 2nd line nivolumab, PAZOREAL TFL: Figure 14.2.3a-1-1.3 Time on drug [months] - 2nd line nivolumab.

Time on drug by Gender

In FAS(N) male patients (n=112, 101 patients (90.2%) with event) had a median time on drug of 4.6 months (95% CI 3.7-6.3), while female patients (n=51, 42 patients (82.4%) with event) had a median time on drug of 4.8 months (95% CI 2.9 – 9.1). Respective 6-month time on drug rate by gender was 42.6% (95% CI 33.3%- 51.5%) and 46.7% (95% CI 32.6%- 59.6%). (*PAZOREAL TFL: Table 14.2.3b-1-1.3 Time on drug [months] by gender - 2nd line nivolumab)*

Time on drug by Age

In FAS(N) patients aged <65years (n=49, 45 patients (91.8%) with event) had a median time on drug of 4.1 months (95% CI 2.9-5.8), while patients aged ≥65years (n=114, 98 patients (86.0%) with event) had a median time on drug of 5.3 months (95% CI 3.7-7.4). Respective 6-month time on drug rate by age category was 36.7% (95% CI 23.6%- 50.0%) and 47.0% (95% CI 37.6%-55.9%, *PAZOREAL TFL: Table 14.2.3b-2-1.3 Time on drug [months] by age at start of therapy line - 2nd line nivolumab).*

Time on drug by histology

In FAS(N) patients with clear cell carcinoma (n=117 (86%) events, 19 patients were censored) had a median time on drug of 5.3 months (95% CI 3.7-7.4), while patients with non-clear cell carcinoma (n=18 events) had a median time on drug of 3.0 months (95% CI 1.8-6.1, Figure 10.12). The 6-month time on drug rate by histology was 46.7% (95% CI 38.1%- 54.9%) in patients with clear cell carcinoma and 33.3% (95% CI 13.7%- 54.5%) in patients with non-clear cell carcinoma (*PAZOREAL TFL: Table 14.2.3b-3-1.3 Time on drug [months] by histology - 2nd line nivolumab).*

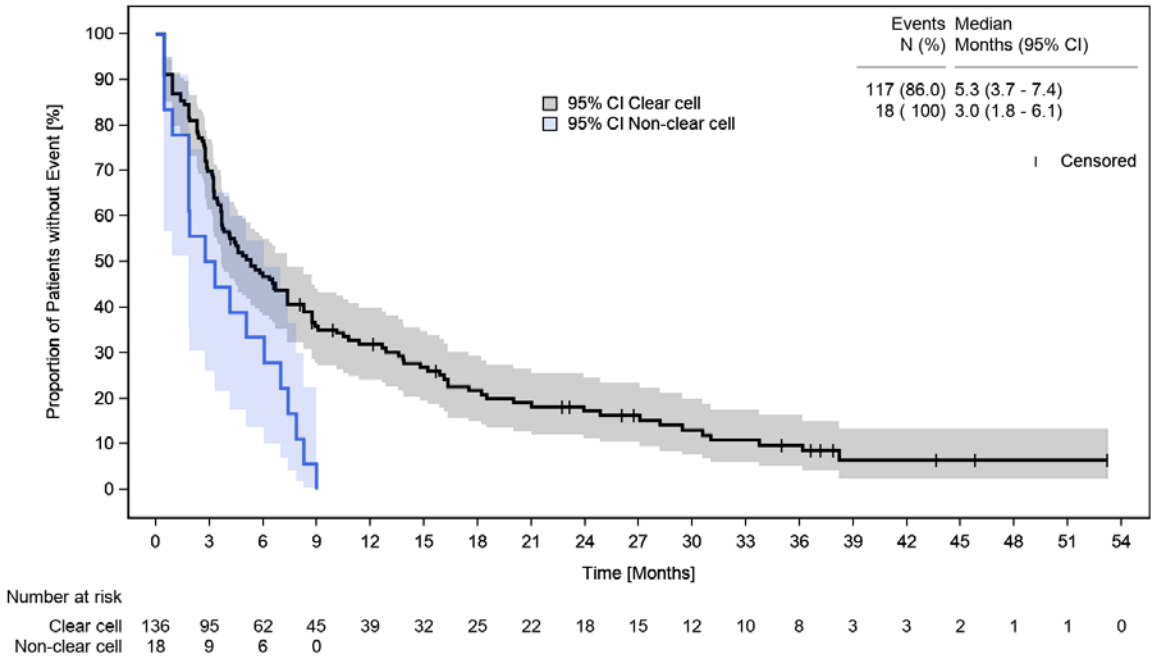


Figure 10.12 Time on drug [months] by histology – 2nd-line nivolumab

'Patients without events' refer to living patients as well to patients without documented end of treatment.

Source: PAZOREAL TFL: Table Table 14.2.3b-3-1.3 Time on drug [months] by histology - 2nd line nivolumab, PAZOREAL TFL: Figure 14.2.3e-1-1.3 Time on drug [months] by histology - 2nd line nivolumab.

Sensitivity analysis: Time on drug trial-eligible patients

In FAS (N, t.e.) 57 patients (89.1%) had an event and 7 patients (10.9%) were censored due to missing documented end of treatment for this sensitivity analysis (Figure 10.13). The median time on drug was 3.9 months (95% CI 3.1-6.7) and the 6-month time on drug rate was 42.2% (95% CI 30.0% - 53.8%, *PAZOREAL TFL: Table 14.2.3e-1-1.3 Sensitivity analysis: Time on drug [months] (trial-eligible patients) - 2nd line nivolumab).*

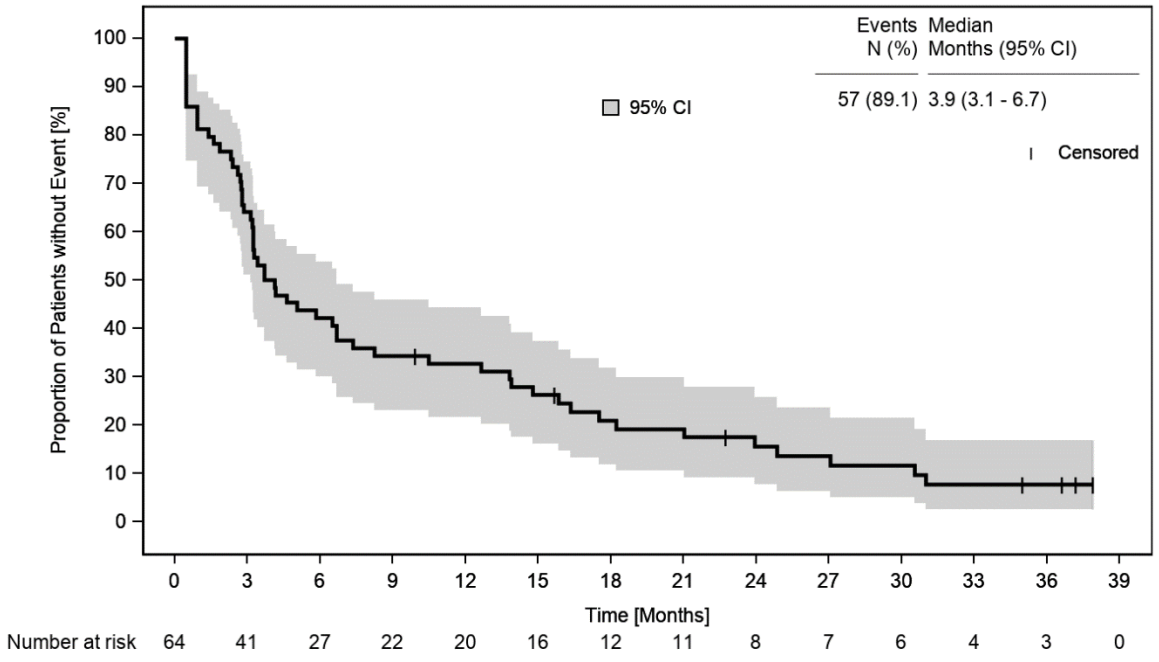


Figure 10.13 Sensitivity analysis: ToD trial-eligible* patients – 2nd-line nivolumab

'Patients without events' refer to living patients as well to patients without documented end of treatment.

*Defined as patients fulfilling none of the three 'trial-ineligibility criteria': Karnofsky Performance Status <70%, Haemoglobin < Lower Limit of Normal, Non-clear Cell Carcinoma Histology.

Source: PAZOREAL TFL: Table 14.2.3e-1-1.3 Sensitivity analysis: Time on drug [months] (trial-eligible patients) - 2nd line nivolumab , Figure 14.2.3d-1-1.3 Sensitivity analysis: Time on drug [months] (trial-eligible patients) - 2nd line nivolumab*

Best response and disease control rate (DCR)

In FAS (N) CR as best response was achieved in 10 patients (6.13%) and SD in 61 patients (37.42%). Thus the DRC was 43.56%. PD was the best response in 56 patients (34.36%). Best response was assessed in 110 patients (67.5%) by radiologic assessment, in 17 patients (10.4%) by clinical assessment *(PAZOREAL TFL: Table 14.2.3g-2-1.3 Kind of response assessment (best response) – 2nd line nivolumab).* For 36 patients (22.91%) no assessment was done (cf. Table 10-22).

Table 10-22 Best response and DCR* - 2nd-line nivolumab

		Total (N=163)	95%-CI
Best response / DCR	Complete response (CR)	10 (6.13%)	[3.24, 11.05]
Best response / DCR	Stable disease (non-CR, non-PD)	61 (37.42%)	[30.36, 45.07]
Best response / DCR	- - - - - - - - DCR* - - - - - - - -	71 (43.56%)	[36.18, 51.23]
Best response / DCR	Progressive disease (PD)	56 (34.36%)	[27.49, 41.94]

		Total (N=163)	95%-CI
Best response / DCR	Not done	36 (22.09%)	[16.37, 29.09]

Displayed are the 95%-CIs according to Agresti & Coull.
For the analysis, best response from the end of study screen will be only used if no other documentation of response is available.
* Defined as Complete response or Stable disease.

Source: PAZOREAL TFL: Table 14.2.3g-1-1.3 Best response and disease control rate (DCR) - 2nd line nivolumab*

10.4.1.3 Cohort I: 2nd-line everolimus and 3rd-line everolimus

Due to the small number of patients details on the different analyses of patients receiving 2nd-line or 3rd-line therapy with everolimus in cohort I are provided in the appendix as follows:

Time on drug

Details on Time on drug are provided in appendix: *PAZOREAL TFL: Table 14.2.3a-1-1.2 Time on drug [months] - 2nd line everolimus, Figure 14.2.3a-1-1.2 Time on drug [months] - 2nd line everolimus, Table 14.2.3a-1-1.5 Time on drug [months] - 3rd line everolimus, Figure 14.2.3a-1-1.5 Time on drug [months] - 3rd line everolimus*.

Details on Sensitivity analyses, i.e. time on drug in trial-eligible patients are provided in appendix: *PAZOREAL TFL: Table 14.2.3e-1-1.2 Sensitivity analysis: Time on drug [months] (trial-eligible patients) - 2nd line everolimus and Table 14.2.3e-1-1.5 Sensitivity analysis: Time on drug [months] (trial-eligible patients) - 3rd line everolimus*.

Best response and disease control rate DCR

Details on best responses, DCR and kind of response are provided in appendix: *PAZOREAL TFL: Table 14.2.3g-1-1.2 Best response and disease control rate* (DCR) - 2nd line everolimus, Table 14.2.3g-2-1.2 Kind of response assessment (best response) - 2nd line everolimus, and Table 14.2.3g-1-1.5 Best response and disease control rate* (DCR) - 3rd line everolimus, Table 14.2.3g-2-1.5 Kind of response assessment (best response) - 3rd line everolimus*.

10.4.1.4 Cohort II: 2nd-line nivolumab and 3rd-line everolimus

Due to the small number of patients details on the different analyses of patients of cohort II being enrolled in 3rd line everolimus after 2nd line nivolumab are provided in the appendix as follows:

Time on drug

For cohort II, respective details of Time on drug of patients receiving 2nd-line therapy nivolumab and for patients receiving 3rd-line therapy everolimus are provided in appendix: *PAZOREAL TFL: Table 14.2.3a-1-2.1 Time on drug [months] - 2nd line nivolumab, Table 14.2.3a-1-2.2 Time on drug [months] - 3rd line everolimus, Figure 14.2.3a-1-2.2 Time on drug [months] - 3rd line everolimus.*

Details on sensitivity analyses, i.e. time on drug in trial-eligible patients are provided in appendix: *PAZOREAL TFL: Table 14.2.3e-1-2.1 Sensitivity analysis: Time on drug [months] (trial-eligible patients) - 2nd line nivolumab and Table 14.2.3e-1-2.2 Sensitivity analysis: Time on drug [months] (trial-eligible patients) - 3rd line everolimus.*

Best response and disease control rate DCR

Details on best responses, DCR and kind of response are provided in appendix: *PAZOREAL TFL: Table 14.2.3g-1-2.2 Best response and disease control rate* (DCR) - 3rd line everolimus; Table 14.2.3g-2-2.2 Kind of response assessment (best response) - 3rd line everolimus.*

10.4.2 Secondary endpoint: Overall survival

Cohort I

For FAS(all) cohort I median OS was 35.9 months (95% CI: 28.2-48.3). Of 376 evaluable patients 174 patients died (46.3%) and 202 patients (53.7%) not known to have died were censored at the last date known alive (*PAZOREAL TFL: Table 14.2.4a-1-1.1 Overall Survival [months]*). The Kaplan-Meier plot of OS is shown in Figure 10.14.

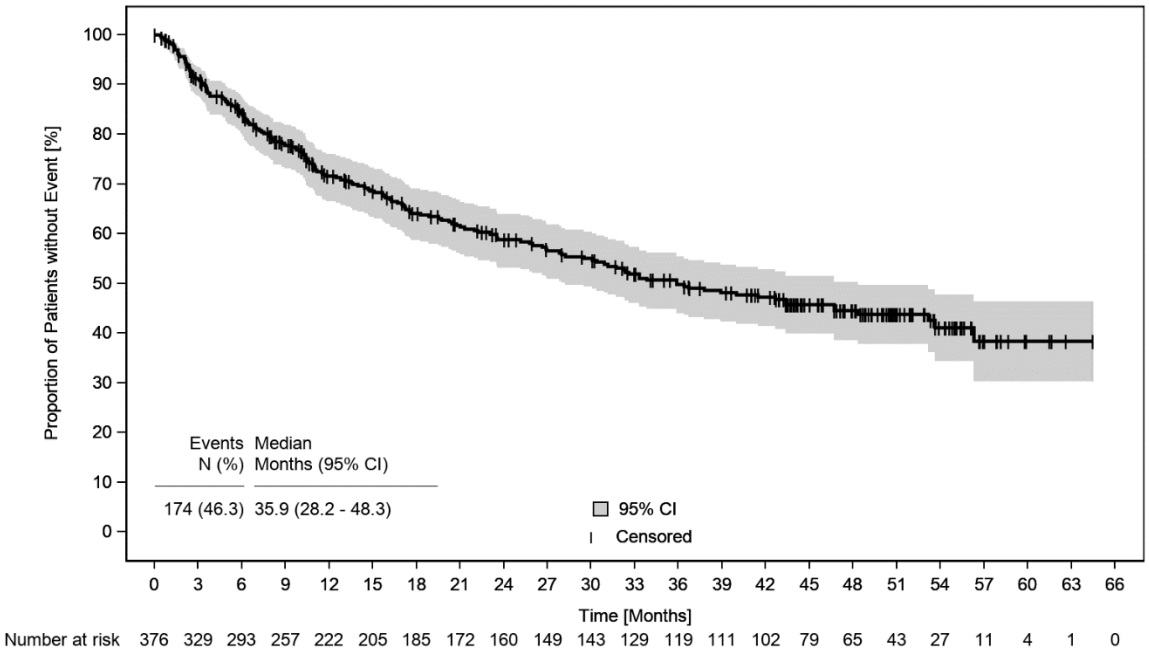


Figure 10.14 Overall Survival [months] FAS(all) cohort I

'Patients without events' refer to living patients.

Source: PAZOREAL TFL: Figure 14.2.4a-1-1.1 Overall Survival [months]

Trial eligible patients

Sensitivity analysis of trial-eligible patients revealed a median OS of 53.2 months (95% CI: 38.9-NA). Of 146 evaluable patients 59 patients died (40.4%) and 87 patients (59.6%) not known to have died were censored at the last date known alive (*PAZOREAL TFL: Table 14.2.4c-1-1.1 Sensitivity analysis: Overall Survival [months] (trial-eligible patients)*). The Kaplan-Meier plot of OS is shown in Figure 10.15.

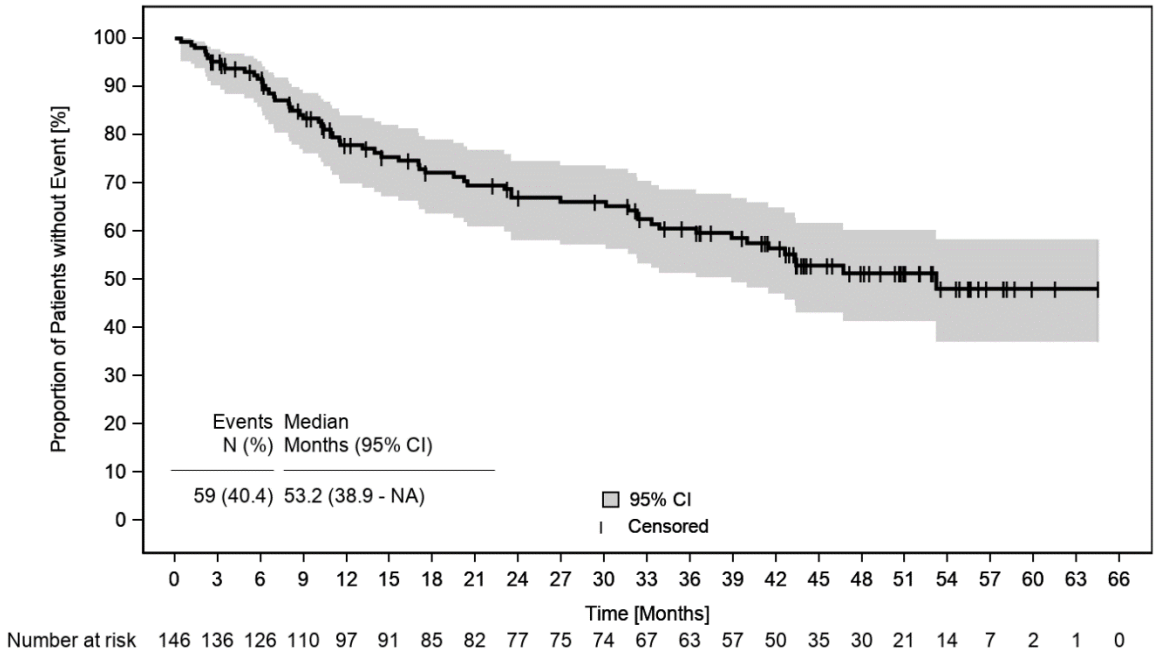


Figure 10.15 Sensitivity analysis: Overall Survival trial-eligible* patients

'Patients without events' refer to living patients.

Source: PAZOREAL TFL: Figure 14.2.4b-1-1.1 Sensitivity analysis: Overall Survival [months] (trial-eligible patients)*

**Defined as patients fulfilling none of the three 'trial-ineligibility criteria': Karnofsky Performance Status <70%, Haemoglobin < Lower Limit of Normal, Non-clear Cell Carcinoma Histology.*

2nd-line therapy nivolumab vs. other after 1st-line pazopanib

After start of 1st-line treatment (OS1) with pazopanib patients with 2nd-line nivolumab had a median OS of 53.2 months (95% CI: 36.7-NA), while patients with any other 2nd-line therapy had a median OS of 36.4 months (95% CI: 19.5-NA). For more details, f.e. number of events and censored cases refer to Table 10-23. Respective Kaplan-Meier plot of OS is shown in Figure 10.16.

Table 10-23 OS by 2nd-line therapy (nivolumab vs. other) – 1st-line pazopanib

		Patients with 2nd-line treatment (N=210)	
		Nivolumab (N=163)	**Other substance(s) (N=47)**
Overall Survival	Events (n[%])	68 (41.7%)	25 (53.2%)
Overall Survival	Censored (n[%])	95 (58.3%)	22 (46.8%)
Overall Survival	25%-Quantile [95% CI] (months)	20.2 (15.7 - 28.2)	16.3 (10.0 - 28.0)

		Patients with 2nd-line treatment (N=210)	
		Nivolumab (N=163)	**Other substance(s) (N=47)**
Overall Survival	50%-Quantile (Median) [95% CI] (months)	53.2 (36.7 - NA)	36.4 (19.5 - NA)
Overall Survival	75%-Quantile [95% CI] (months)	NA (NA - NA)	56.3 (56.3 - NA)
Overall Survival	12-month Overall Survival Rate [95%-CI]	86.9% (80.4% - 91.3%)	82.9% (68.7% - 91.1%)

Source: PAZOREAL TFL: Table 14.2.4b-6-1.1 Overall Survival [months] by 2nd-line therapy (nivolumab vs. other) - 1st line pazopanib

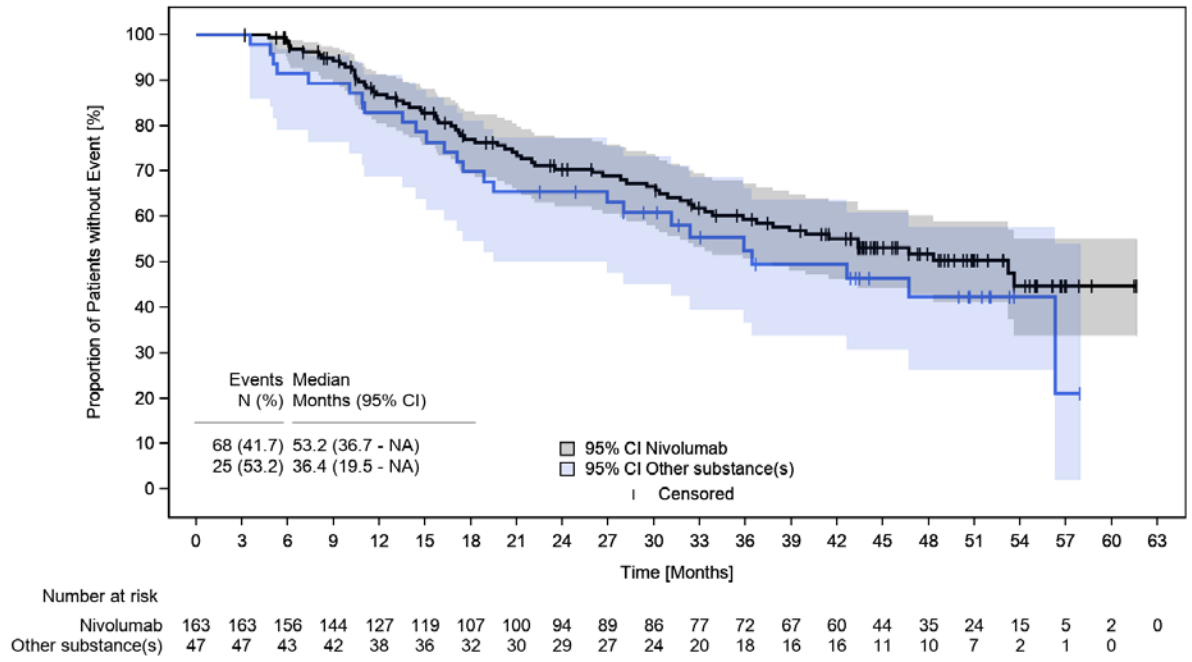


Figure 10.16 Overall Survival by 2nd-line therapy (nivolumab vs. other)

'Patients without events' refer to living patients.

Source: PAZOREAL TFL: Figure 14.2.4a-4-1.1 Overall Survival [months] by 2nd-line therapy (nivolumab vs. other)

Median overall survival after start of 2nd-line treatment (OS2) with either nivolumab or an other therapy was 30.4 months (95% CI: 22.6-NA) and 26.6 months (95% CI: 9.6-NA), respectively. Kaplan-Meier plot of OS is shown in Figure 10.17.

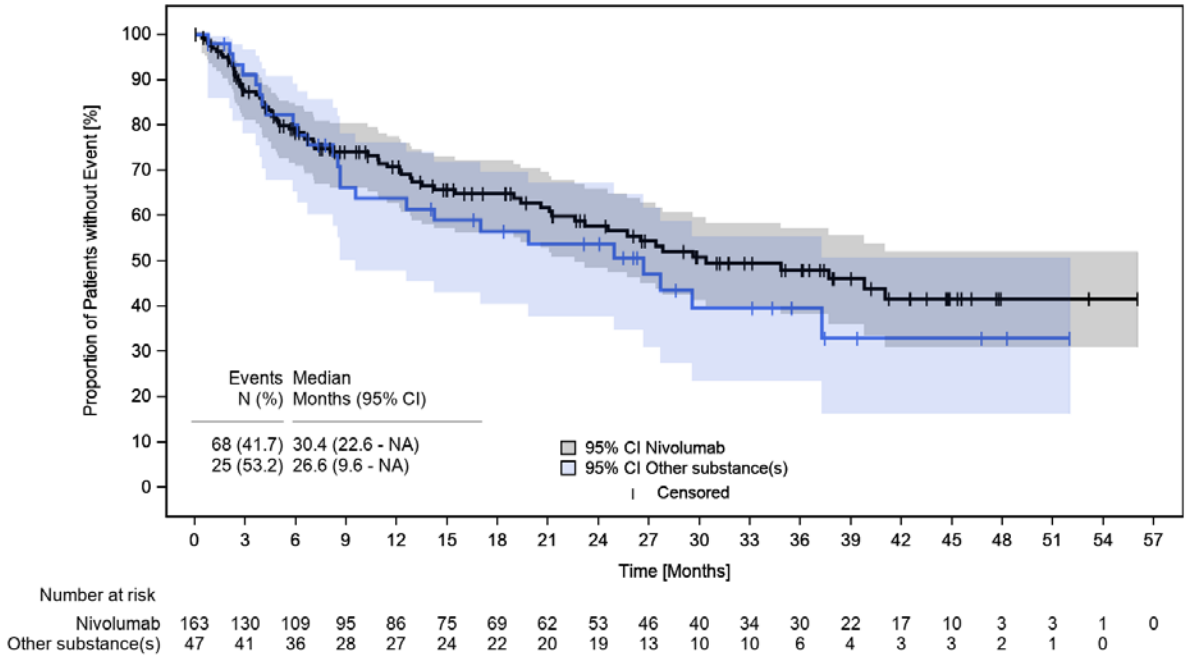


Figure 10.17 Overall Survival starting from 2nd-line by 2nd-line therapy

'Patients without events' refer to living patients.

Source: PAZOREAL TFL: Figure 14.2.4a-4-1.2 Overall Survival [months] starting from 2nd line by 2nd-line therapy (nivolumab vs. other)

Further subgroups

Further sensitivity analyses of OS were done with subgroups gender, age at start of therapy line and BMI at enrollment and with subgroups MSKCC score at enrollment, nephrectomy (cf. Figure 10.18), which results are provided Table 10-24 and Table 10-25, respectively. OS by local factors, i.e. patients' participation in a patient education program and distance between residence and hospital/practice are depicted in Table 10-26. Across analytic population in part high number of censored cases were observed, analyses were characterized by in part immature data, and by overlapping confidence intervals within subgroups.

Table 10-24 Sensitivity analysis: OS by gender, age and BMI

	Gender		Age at start of therapy line		BMI at enrollment	
FAS	**female**	**male**	**<65 years**	**≥65 years**	**<25 kg/m²**	**≥25 kg/m²**
Patients (N)	119	257	132	244	122	208
Events n (%)	64 (53.8%)	110 (42.8%)	69 (52.3%)	105 (43.0%)	66 (54.1%)	89 (42.8%)

Median [95% CI]	31.2 [19.7-35.9]	46.7 [26.9-56.3]	30.4 [23.0-43.4]	43.4 [29.5-NA]	26.9 [16.2-40.0]	43.4 [30.1-NA]
12-month OS-Rate [95%-CI] (%)	67.7% [58.1-75.5]	73.3% [67.1-78.5]	69.6% [60.7-76.9]	72.5% [66.1-77.9]	66.2% [56.5-74.1]	73.0% [66.1-78.8]

Source: PAZOREAL TFL: Table 14.2.4b-1-1.1 Overall Survival [months] by gender, Table 14.2.4b-2-1.1 Overall Survival [months] by age at start of therapy line, Table 14.2.4b-3-1.1 Overall Survival [months] by BMI at enrollment.

Table 10-25 Sensitivity analysis: OS by MSKCC score, nephrectomy

	MSKCC score			**Nephrectomy**	
FAS	favorable	intermediate	poor	yes	no
Patients (N)	20	52	13	303	73
Events n (%)	7 (35.0%)	26 (50.0%)	9 (69.2%)	131 (43.2%)	43 (58.9%)
Median [95% CI]	NA [8.9 – NA]	25.1 [13.5-37.8]	10.4 [2.5-NA]	43.4 [32.6- NA]	15.7 [7.8-23.5]
12-month OS-Rate [95%-CI] (%)	77.0% [49.0-90.9]	68.7% [53.5-79.9]	44.0% [16.8-68.4]	76.1% [70.7- 80.7]	51.8% [39.0- 63.1]

Source: PAZOREAL TFL: Table 14.2.4b-4-1.1 Overall Survival [months] by MSKCC Score at enrollment, Table 14.2.4b-5-1.1 Overall Survival [months] by nephrectomy

Table 10-26 Sensitivity analysis: OS by local factors.

	Participating in a patient education program		**Distance between the patients' residence and the practice/hospital**	
FAS	yes	no	<10km	≥10km
Patients (N)	4	188	56	104
Events n (%)	3 (75.0%)	66 (35.1%)	17 (30.4%)	33 (31.7%)
Median [95% CI]	22.9 [9.7- NA]	NA [53.2-NA]	NA [NA-NA]	56.3 [53.2-NA]
12-month OS-Rate [95%-CI] (%)	75.0% [12.8- 96.1]	91.3% [86.2- 94.6]	96.4% [86.2- 99.1]	99.0% [93.3- 99.9]

Source: PAZOREAL TFL: Table 14.2.4d-1-1.1 Overall Survival [months]by participating in a Patient Education Program, Table 14.2.4d-2-1.1 Overall Survival [months] by distance.

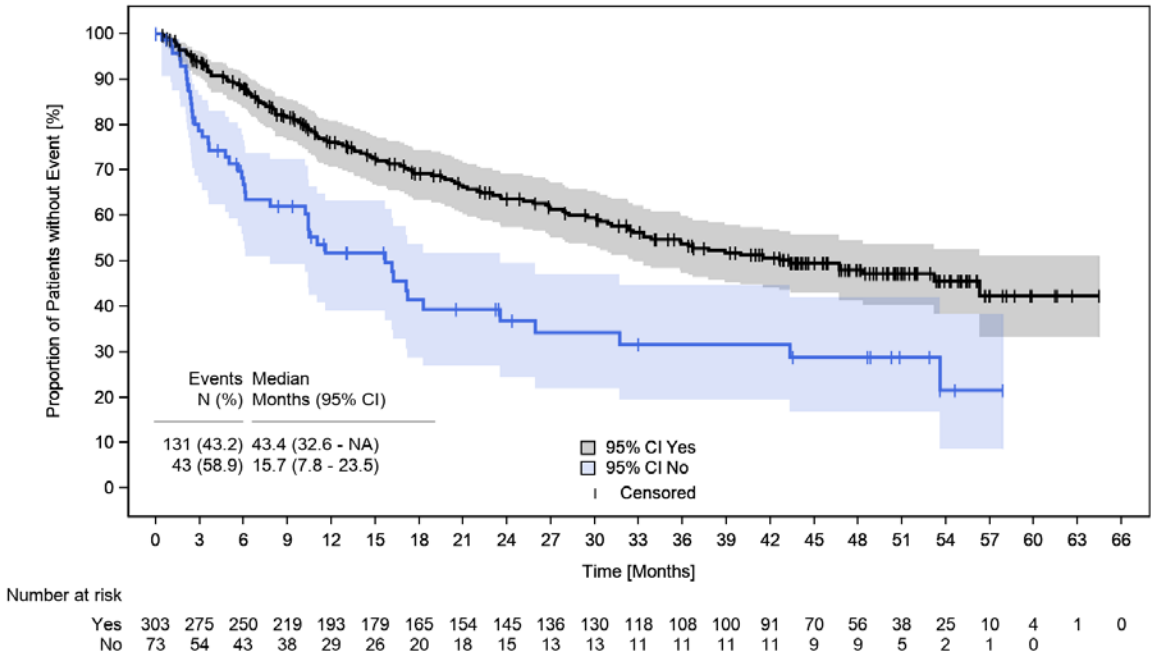


Figure 10.18 Sensitivity analysis: Overall Survival [months] by nephrectomy

'Patients without events' refer to living patients.

Source: PAZOREAL TFL: Figure 14.2.4a-3-1.1 Overall Survival [months] by nephrectomy

For FAS(extended) details on OS are provided in appendix: *PAZOREAL TFL: Table 14.2.4e-1-1.1 Overall Survival [months]*.

Cohort II

For cohort II, respective details of OS are provided in appendix: *PAZOREAL TFL: Table 14.2.4a-1-2.2 Overall Survival [months], Table 14.2.4a-2-2.2 Overall Survival [months] (retro.), Table 14.2.4c-1-2.2 Sensitivity analysis: Overall Survival [months] (trial-eligible patients), and Table 14.2.4c-2-2.2 Sensitivity analysis: Overall Survival [months] (trial-eligible patients, retro.).*

10.4.3 Secondary endpoint: Progression prior onset of a new therapy

Cohort I

Of patients with 1st-line pazopanib treatment 212 patients (56.4%) had a progressive disease and of these 127 patients (33.8%) received the subsequent 2nd-line treatment with either nivolumab or everolimus. For 41 patients out of 164 patients (25.0%) without documented progression a subsequent treatment with either nivolumab or everolimus and for 16 patients an other antineoplastic therapy was documented. Details are depicted in Table 10-27.

Table 10-27 Patients with PD prior new therapy line – 1st-line pazopanib

		FAS (P) (N=376)
Number of patients with progressive disease (PD) prior onset of a new therapy line	Progression (further therapy line)	127 (33.8%)
Number of patients with progressive disease prior onset of a new therapy line	Progression (subsequent antineoplastic therapy)	26 (6.9%)
Number of patients with progressive disease prior onset of a new therapy line	Progression (no further therapy line)	59 (15.7%)
Number of patients with progressive disease prior onset of a new therapy line	No progression documented (further therapy line)	41 (10.9%)
Number of patients with progressive disease prior onset of a new therapy line	No progression documented (subsequent antineoplastic therapy)	16 (4.3%)
Number of patients with progressive disease prior onset of a new therapy line	No progression documented (no further therapy line)	107 (28.5%)

Source: PAZOREAL TFL: Table 14.2.5-1.1 Number of patients with progressive disease prior onset of a new therapy line - 1st line pazopanib

Of patients with 2nd-line nivolumab treatment 96 patients (58.9%) had a progressive disease. and of these 9 patients (5.5%) received the subsequent 3rd-line treatment with everolimus and 54 patients (33.1%) received an other subsequent antineoplastic therapy. For 8 patients out of 67 patients (11.9%) without documented progression a subsequent antineoplastic therapy was documented. Details are depicted in Table 10-28.

Table 10-28 Patients with PD prior new therapy line – 2nd-line nivolumab

		FAS (N) (N=163)
Number of patients with progressive disease prior onset of a new therapy line	Progression (further therapy line)	9 (5.5%)
Number of patients with progressive disease prior onset of a new therapy line	Progression (subsequent antineoplastic therapy)	54 (33.1%)
Number of patients with progressive disease prior onset of a new therapy line	Progression (no further therapy line)	33 (20.2%)
Number of patients with progressive disease prior onset of a new therapy line	No progression documented (subsequent antineoplastic therapy)	8 (4.9%)
Number of patients with progressive disease prior onset of a new therapy line	No progression documented (no further therapy line)	59 (36.2%)

Source: PAZOREAL TFL: 14.2.5-1.3 Number of patients with progressive disease prior onset of a new therapy line - 2nd line nivolumab

For patients of cohort I with 2nd-line and 3rd-line everolimus, details of patients with progressive disease prior onset of a new therapy are provided in appendix: *PAZOREAL TFL: Table 14.2.5-1.2 Number of patients with progressive disease prior onset of a new therapy line - 2nd line everolimus and Table 14.2.5-1.5 Number of patients with progressive disease prior onset of a new therapy line - 3rd line everolimus.*

Cohort II

For cohort II, respective details of patients with progressive disease prior onset of a new therapy are provided in appendix: *PAZOREAL TFL: Table 14.2.5-2.2 Number of patients with progressive disease prior onset of a new therapy line - 3rd line everolimus*.

10.5 Quality of Life (QoL)

Cohort I

For FAS(extended) details on QoL data are provided in appendix: *PAZOREAL TFL: Table 14.3.8c-6 up to -10-5.1 EQ-5D-5L*.

10.5.1 Cohort I: 1st-line pazopanib

Evaluable questionnaires

Of patients with 1st-line pazopanib treatment (FAS(P)) 279 patients (74.2%) were identified as qualifying for the questionnaire project and were assigned to FAS (QS,P), 97 patients (25.8%) did not qualify for the questionnaire project (appendix: *PAZOREAL TFL: Table 14.3.8a-1-1.1 Overview of patients qualifying for the questionnaire project - 1st line pazopanib*). Out of the FAS(QS,P) population to 229 patients the baseline-questionnaire was handed out (see appendix *PAZOREAL TFL: Table 14.3.8a-2-1.1 Number of patients with questionnaires sent - 1st line pazopanib*) The detailed numbers of filled questionnaires (at least one evaluable question per questionnaire) that had been handed back at respective period (visit) are shown in appendix *PAZOREAL TFL: Table 14.3.8a-3-1.1 Number of filled questionnaires - 1st line pazopanib*. At baseline 219 questionnaires were available for analysis, after 3months the number deceased to 141 evaluable questionnaires, after 24 months the number was reduced to 31 questionnaires and after 24 months the QoL of only 11.1% of patients (FAS(QS,P)) could be analyzed.

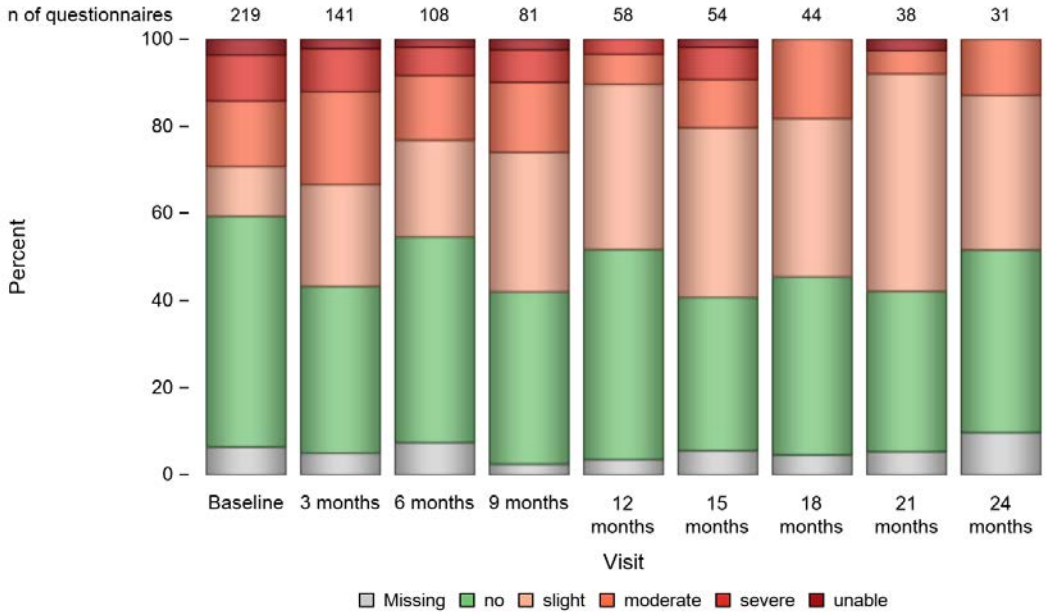
EQ-5D-5L items

All levels of each dimension, i.e. mobility, self-care, usual activity, pain/discomfort, anxiety/depression with frequencies in total, by age group (<65 years / ≥65 years), by histology (clear cell vs. non-clear cell) and by local factors are provided in appendix (*PAZOREAL TFL: Table 14.3.8b-1 to -25-1.1*).

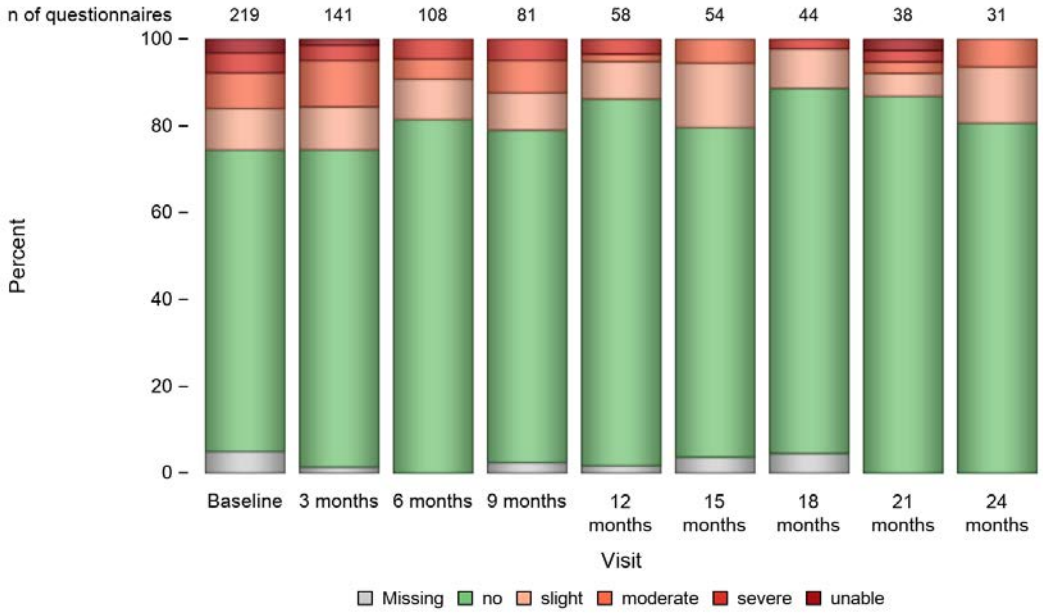
The reported response levels for each dimension at baseline and during 1st-line pazopanib treatment are depicted in Figure 10.19. The EQ-5D-5L- scores generally remained unchanged under treatment: most patients reported “no” problems with regard to self-care, while for dimensions “Usual activity” and “Pain/Discomfort” most proportion of patients reported “slight” up to “extremely” problems. For the dimensions “Mobility” and “Anxiety/Depression” about half of the patients reported “no” problems. Details on reported response levels for each dimension are depicted in appendix *PAZOREAL TFL: Table 14.3.8b-1 up to -5-1.1*. Details on transformed reported response levels into two categories “no problems” (i.e. response level

"no") and "problems" (i.e. response levels "slight/slightly" up to "unable/extreme/extremely") for each dimension are depicted in appendix *PAZOREAL TFL: Table 14.3.8c-1 up to -5-1.1.*

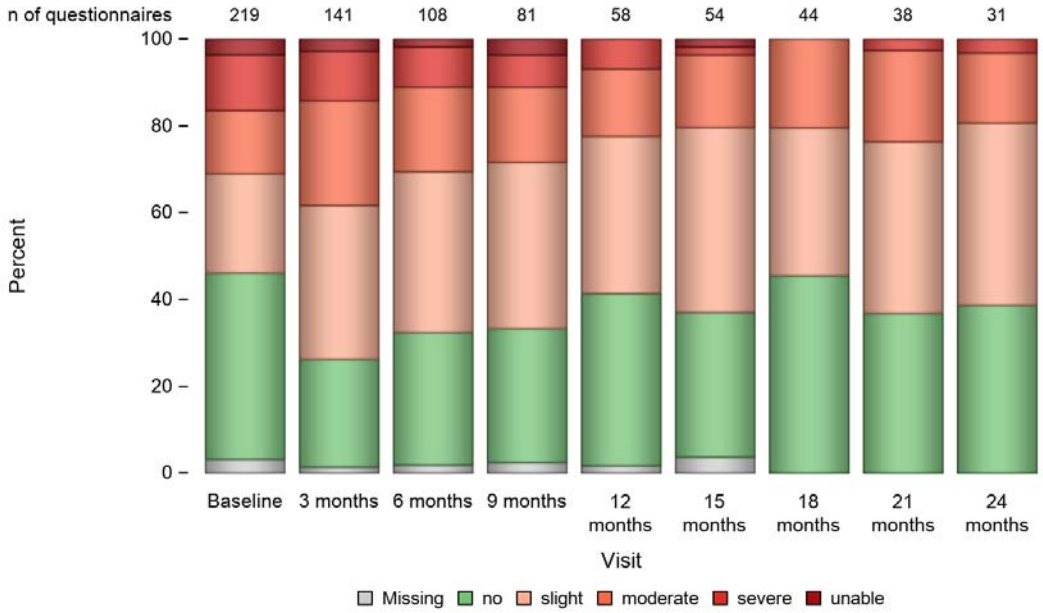
Mobility – I have ... problems walking / I am ... to walk



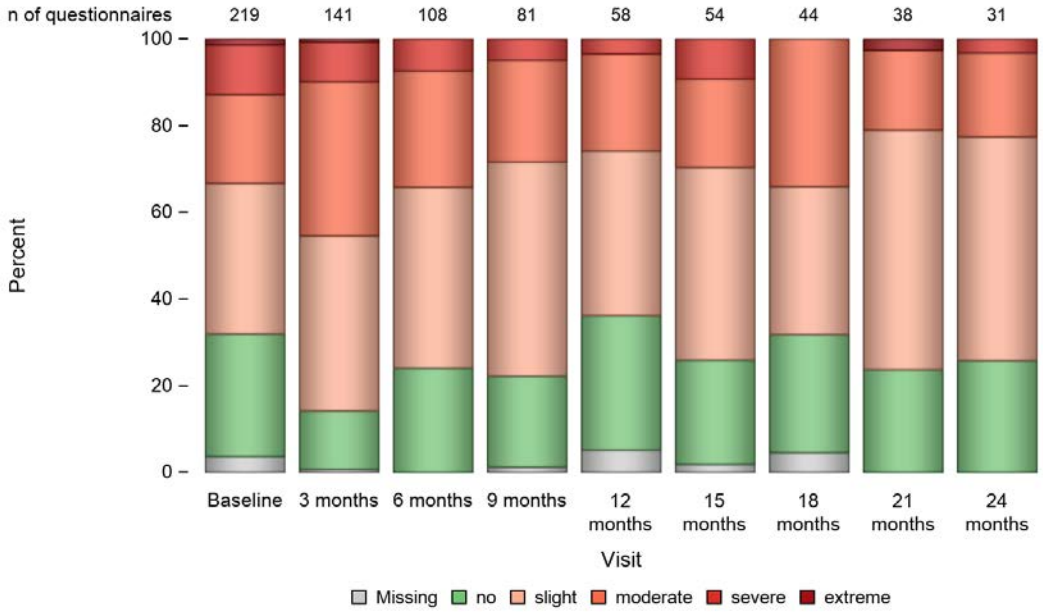
Self-Care – I have ... problems washing or dressing myself / I am ... to wash or dress myself



Usual activity – I have ... problems doing my usual activities / I am ... to do my usual activities



Pain/Discomfort – I have ... pain or discomfort



Anxiety/Depressiom – I am ... anxious or depressed

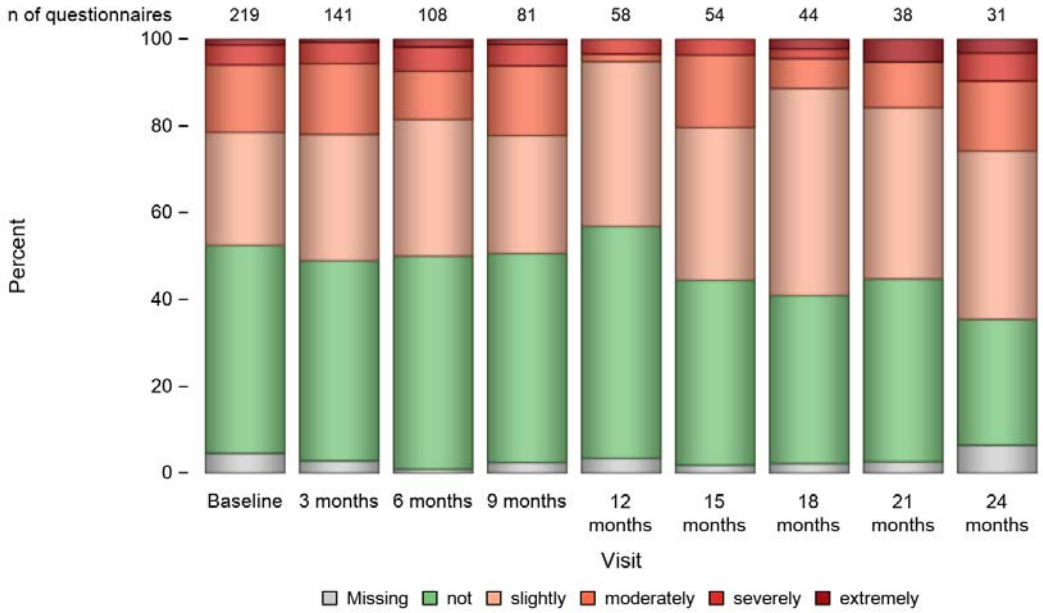


Figure 10.19 EQ-5D-5L 1st-line pazopanib

For each dimension the proportion of levels (not, slight/slightly, moderate/moderately, severe/severely, unable/extreme/extremely) at baseline and at defined time points (3months up to 24months) after treatment start are depicted. Percentages refer to the total number of received questionnaires for the respective time point.

Source: PAZOREAL TFL: Figure 14.3.8b-1-1.1 EQ-5D-5L: Mobility - 1st line pazopanib, Figure 14.3.8b-2-1.1 EQ-5D-5L: Self-Care - 1st line pazopanib, Figure 14.3.8b-3-1.1 EQ-5D-5L: Usual activity - 1st line pazopanib, Figure 14.3.8b-4-1.1 EQ-5D-5L: Pain / Discomfort - 1st line pazopanib, Figure 14.3.8b-5-1.1 EQ-5D-5L: Anxiety / Depression - 1st line pazopanib

Subgroup analyses: Age

Response levels of subgroups analyses by age groups (<65 years / ≥65 years) are provided in Table 10-29. At baseline, age groups <65 years and ≥65 years composed of 77 patients and 142 patients, respectively. Both age groups revealed similar proportions of response categories (“no problems”, “problems”) for each time point (analysis visit) and respective dimension. Note, at 6 months after treatment start, evaluable questionnaires decreased up to less than 50% compared to baseline and after 12 months up to less than 25%, respectively.

Table 10-29 EQ-5D-5L 1st-line pazopanib by age groups (<65 years / ≥65 years)

			FAS (QS,P) (N=279)		
	Analysis visit		**<65 years**	**≥65 years**	**Total**
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	----------Total----------	77	142	219
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	No Problems	39 (50.6%)	77 (54.2%)	116
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	Problems	34 (44.2%)	55 (38.7%)	89

			FAS (QS,P) (N=279)		
	Analysis visit		**<65 years**	**≥65 years**	**Total**
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	Missing value	4	10	14
EQ-5D-5L: Mobility (transformed items) by age group	6 Months	----------Total----------	36	72	108
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	No Problems	19 (52.8%)	32 (44.4%)	51
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	Problems	16 (44.4%)	33 (45.8%)	49
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	Missing value	1	7	8
EQ-5D-5L: Mobility (transformed items) by age group	12 Months	----------Total----------	17	41	58
EQ-5D-5L: Mobility (transformed items) by age group		No Problems	9 (52.9%)	19 (46.3%)	28
EQ-5D-5L: Mobility (transformed items) by age group		Problems	7 (41.2%)	21 (51.2%)	28
EQ-5D-5L: Mobility (transformed items) by age group		Missing value	1	1	2

Source: PAZOREAL TFL: Table 14.3.8c-6-1.1 EQ-5D-5L: Mobility (transformed items) by age group - 1st line pazopanib

			FAS (QS,P) (N=279)		
	Analysis visit		**<65 years**	**≥65 years**	**Total**
EQ-5D-5L: Self-Care (transformed items) by age group	Baseline	----------Total----------	77	142	219
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	No Problems	53 (68.8%)	99 (69.7%)	152
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	Problems	21 (27.3%)	35 (24.6%)	56
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	Missing value	3	8	11
EQ-5D-5L: Mobility (transformed items) by age group	6 Months	----------Total----------	36	72	108
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	No Problems	31 (86.1%)	57 (79.2%)	88
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	Problems	5 (13.9%)	15 (20.8%)	20
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	Missing value	-	-	-
EQ-5D-5L: Mobility (transformed items) by age group	12 Months	----------Total----------	17	41	58

			FAS (QS,P) (N=279)		
	Analysis visit		**<65 years**	**≥65 years**	**Total**
EQ-5D-5L: Mobility (transformed items) by age group		No Problems	15 (88.2%)	34 (82.9%)	49
EQ-5D-5L: Mobility (transformed items) by age group		Problems	2 (11.8%)	6 (14.6%)	8
EQ-5D-5L: Mobility (transformed items) by age group		Missing value	0	1	1

Source PAZOREAL TFL: Table 14.3.8c-7-1.1 EQ-5D-5L: Self-Care (transformed items) by age group - 1st line pazopanib

			FAS (QS,P) (N=279)		
	Analysis visit		**<65 years**	**≥65 years**	**Total**
EQ-5D-5L: Usual activity (transformed items) by age group	Baseline	----------Total----------	77	142	219
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	No Problems	29 (37.7%)	65 (45.8%)	94
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	Problems	46 (59.7%)	72 (50.7%)	118
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	Missing value	2	5	7
EQ-5D-5L: Mobility (transformed items) by age group	6 Months	----------Total----------	36	72	108
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	No Problems	10 (27.8%)	23 (31.5%)	33
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	Problems	26 (72.2%)	47 (65.3%)	73
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	Missing value	0	2	2
EQ-5D-5L: Mobility (transformed items) by age group	12 Months	----------Total----------	17	41	58
EQ-5D-5L: Mobility (transformed items) by age group		No Problems	6 (35.3%)	17 (41.5%)	23
EQ-5D-5L: Mobility (transformed items) by age group		Problems	11 (64.7%)	23 (56.1%)	34
EQ-5D-5L: Mobility (transformed items) by age group		Missing value	0	1	1

Source PAZOREAL TFL: Table 14.3.8c-8-1.1 EQ-5D-5L: Usual activity (transformed items) by age group - 1st line pazopanib

EQ-5D-5L: Pain/ Discomfort (transformed items) by age group	Baseline	----------Total----------	77	142	219
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	No Problems	14 (18.2%)	48 (33.8%)	62

			FAS (QS,P) (N=279)		
	Analysis visit		**<65 years**	**≥65 years**	**Total**
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	Problems	61 (79.2%)	88 (61.9%)	149
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	Missing value	2	6	8
EQ-5D-5L: Mobility (transformed items) by age group	6 Months	----------Total----------	36	72	108
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	No Problems	6 (16.7%)	20 (27.8%)	26
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	Problems	30 (83.3%)	52 (72.2%)	82
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	Missing value	-	-	-
EQ-5D-5L: Mobility (transformed items) by age group	12 Months	----------Total----------	17	41	58
EQ-5D-5L: Mobility (transformed items) by age group		No Problems	5 (29.4%)	13 (31.7%)	18
EQ-5D-5L: Mobility (transformed items) by age group		Problems	12 (70.6%)	25 (60.9%)	37
EQ-5D-5L: Mobility (transformed items) by age group		Missing value	0	3	3

Source PAZOREAL TFL: Table 14.3.8c-9-1.1 EQ-5D-5L: Pain/ Discomfort (transformed items) by age group - 1st line pazopanib

			FAS (QS,P) (N=279)		
	Analysis visit		**<65 years**	**≥65 years**	**Total**
EQ-5D-5L: Anxiety/ Depression (transformed items) by age group	Baseline	----------Total----------	77	142	219
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	No Problems	35 (45.5%)	70 (49.3%)	105
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	Problems	39 (50.6%)	65 (45.8%)	104
EQ-5D-5L: Mobility (transformed items) by age group	Baseline	Missing value	3	7	10
EQ-5D-5L: Mobility (transformed items) by age group	6 Months	----------Total----------	36	72	108
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	No Problems	21 (58.3%)	32 (44.4%)	53
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	Problems	15 (41.7%)	39 (54.2%)	54
EQ-5D-5L: Mobility (transformed items) by age group	3 Months	Missing value	0	1	1
EQ-5D-5L: Mobility (transformed items) by age group	12 Months	----------Total----------	17	41	58

			FAS (QS,P) (N=279)		
	Analysis visit		**<65 years**	**≥65 years**	**Total**
EQ-5D-5L: Mobility (transformed items) by age group		No Problems	10 (58.8%)	21 (51.2%)	31
EQ-5D-5L: Mobility (transformed items) by age group		Problems	7 (41.2%)	18 (43.9%)	25
EQ-5D-5L: Mobility (transformed items) by age group		Missing value	0	2	2

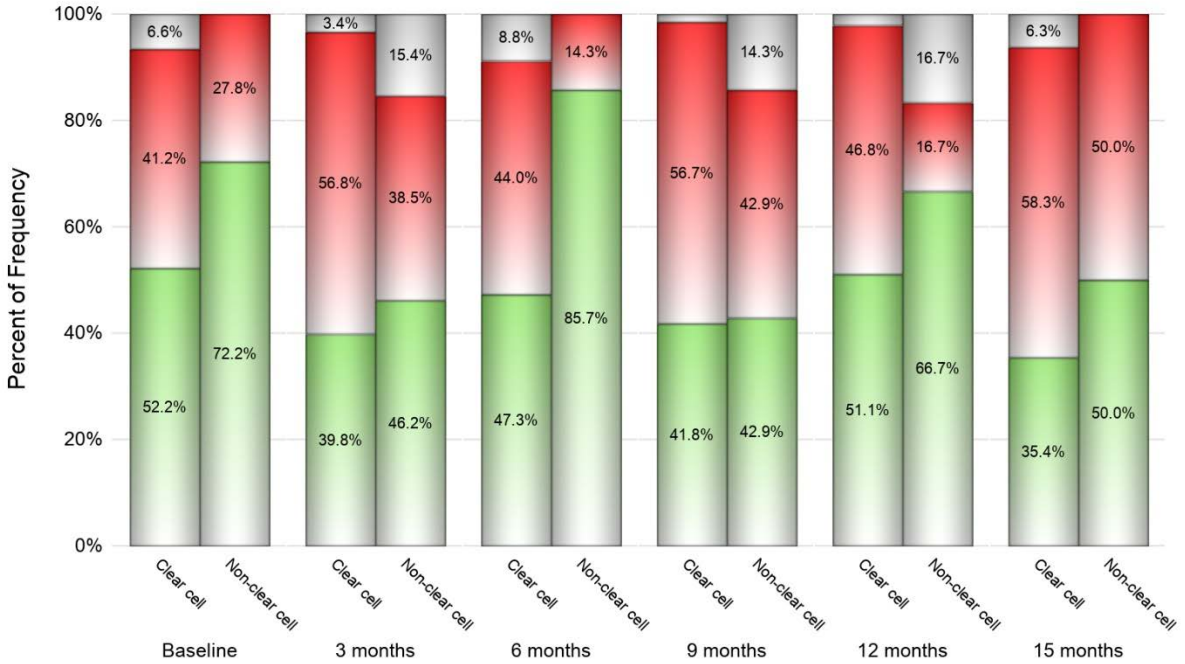
Source PAZOREAL TFL: Table 14.3.8c-10-1.1 EQ-5D-5L: Anxiety/ Depression (transformed items) by age group - 1st line pazopanib
(Percent values refer to total number of patients for Analyses visit and age groups, respectively.)

Subgroup analyses: histology

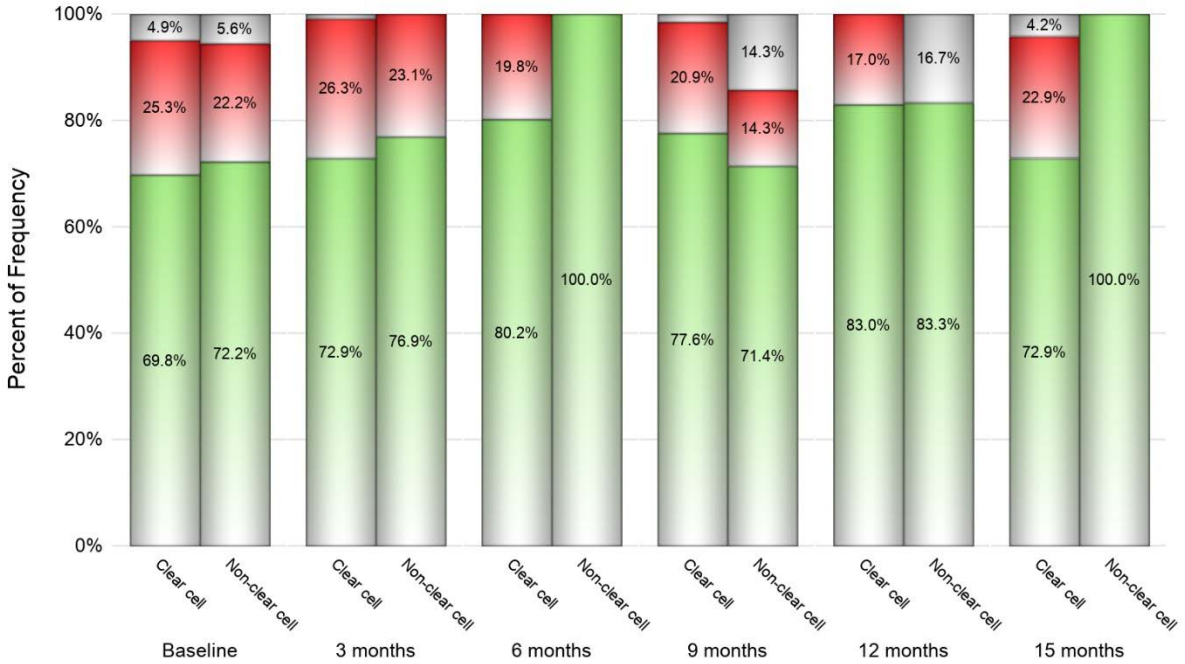
Detailed response levels of both histology subgroups (clear cell / non-clear cell) are provided in Figure 10.20 and in Appendix *PAZOREAL TFL: Tables 14.2.8b-11 up to -15-1.1*. At baseline histology groups clear cell and non-clear cell composed of 182 patients and 18 patients, respectively. Both histology subgroups revealed similar proportions of response categories ("no problems", "problems") for each time point (analysis visit) and the respective dimension. For details refer to appendix *PAZOREAL TFL: Tables 14.3.8c-11 up to -15-1.1*.

Note, that i) the number of non-clear cell patients was comparable small compared to clear cell patients and ii) at 6 months after treatment start, respective evaluable questionnaires decreased up to less than 50% compared to baseline.

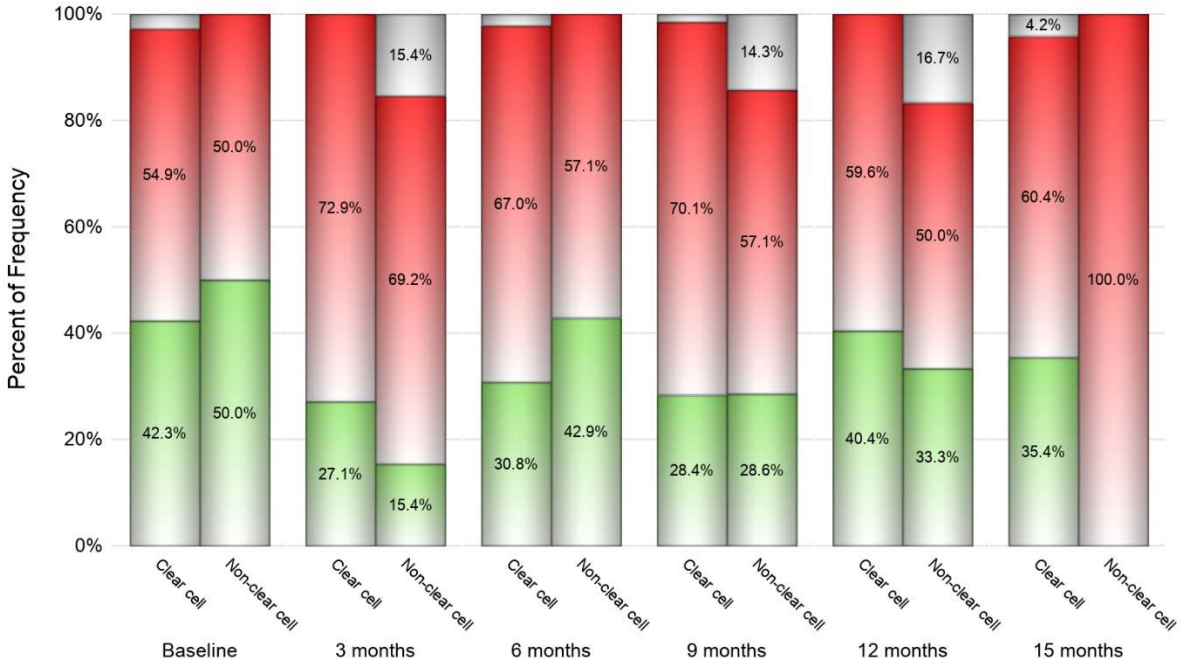
Mobility – I have ... problems walking / I am ... to walk



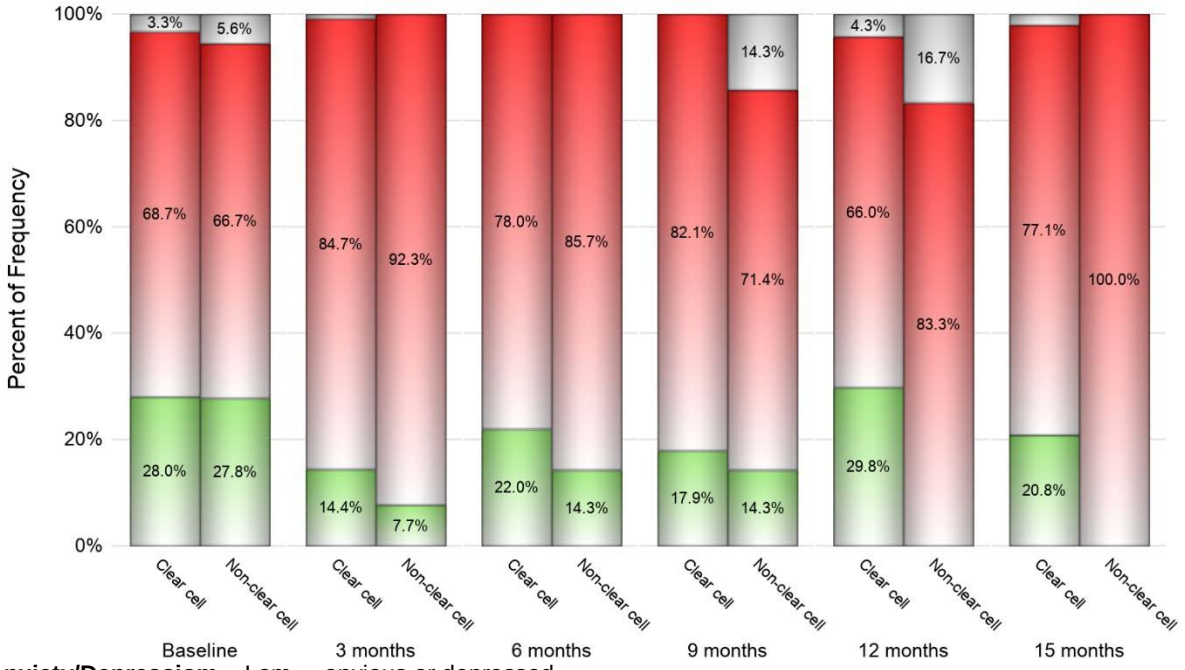
Self-Care – I have ... problems washing or dressing myself / I am ... to wash or dress myself



Usual activity – I have ... problems doing my usual activities / I am ... to do my usual activities



Pain/Discomfort – I have ... pain or discomfort



Anxiety/Depressiom – I am ... anxious or depressed

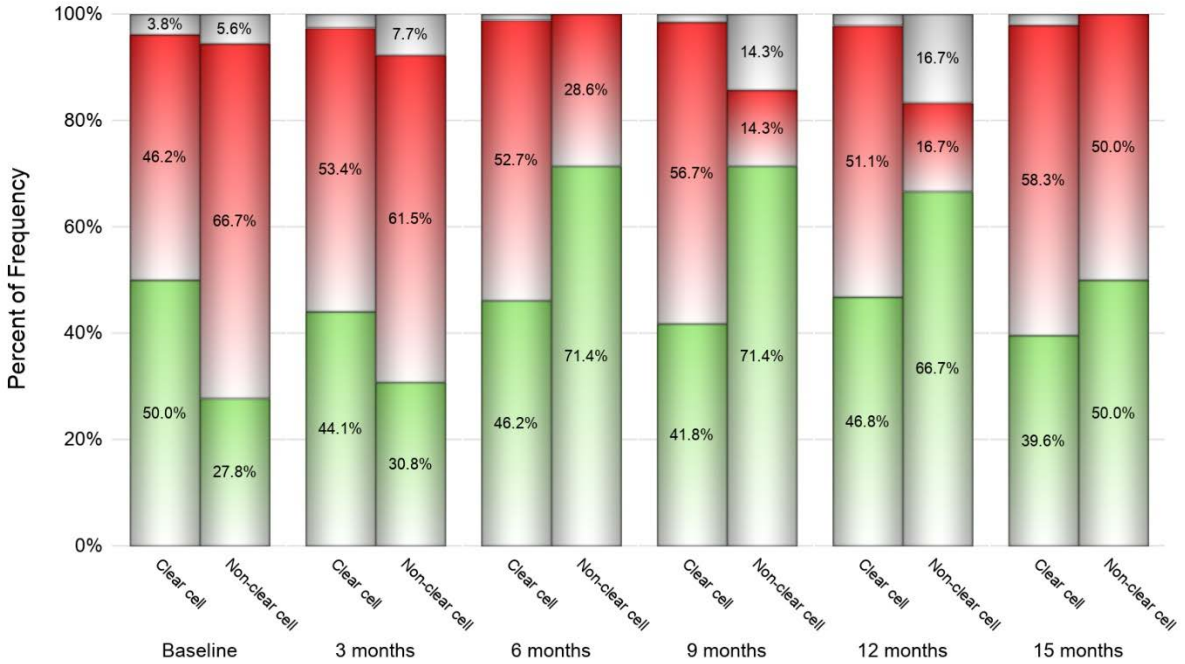


Figure 10.20 EQ-5D-5L 1st-line pazopanib by histology groups

Transformed response levels: green color - no problems; red color – problems; grey color – missing. Number of evaluable questionnaires clear cell/non-clear cell: baseline: 182/18; 3 months: 118/13; 6 months: 91/7; 9 months: 67/7; 12 months: 47/6; 15 months: 48/2.

Source PAZOREAL TFL: Figures Figure 14.3.8-6-1.1 EQ-5D-5L: Mobility by histology - 1st line pazopanib, Figure 14.3.8-7-1.1 EQ-5D-5L: Self-Care by histology - 1st line pazopanib, Figure 14.3.8-8-1.1 EQ-5D-5L: Usual activity by histology - 1st line pazopanib, Figure 14.3.8-9-1.1 EQ-5D-5L: Pain / Discomfort by histology - 1st line pazopanib, Figure 14.3.8-10-1.1 EQ-5D-5L: Anxiety / Depression by histology - 1st line pazopanib.

Subgroup analyses: Participation in a Patient Education Program

At baseline subgroups participation and no participation composed of 2 patients and 121 patients, respectively. For more details about response levels for each dimension refer to *PAZOREAL TFL: Tables 14.3.8b-16 up to -20-1.1* in the appendix.

Subgroup analyses: Distance

At baseline distance subgroups <10km and ≥10km composed of 36 patients and 70 patients, respectively. Detailed response levels of both distance subgroups are provided in the appendix *PAZOREAL TFL: Tables 14.3.8b-21 up to -25-1.1*. Both subgroups revealed similar proportions of response levels for each time point (analysis visit) and dimension. Note, that i) the number of "distance <10km" patients was about half of the number of "distance ≥10km" patients and ii) at 12 months after treatment start, respective evaluable questionnaires decreased up to about 25% and 50% compared to baseline.

EQ-5D-5L Visual analogue scale

The visual analogue scale (VAS) was evaluable for 211 patients at baseline, 141, 107, 80, 57, 54 patients at 3 months, 6 months, 9 months, 12 months and 15 months of 1st line pazopanib treatment. Baseline VAS was in mean 65.3 and in median 70.0 (lower and upper quartiles: 50, 80). Both, mean and median values remained relatively stable over the course of 15 months. (cf. Figure 10.21) VAS at 15 months was in mean 69.1 and in median 75.0 (lower and upper quartiles: 55, 80). Details are provided in the appendix *PAZOREAL TFL: Tables 14.3.8d-1-1.1.*

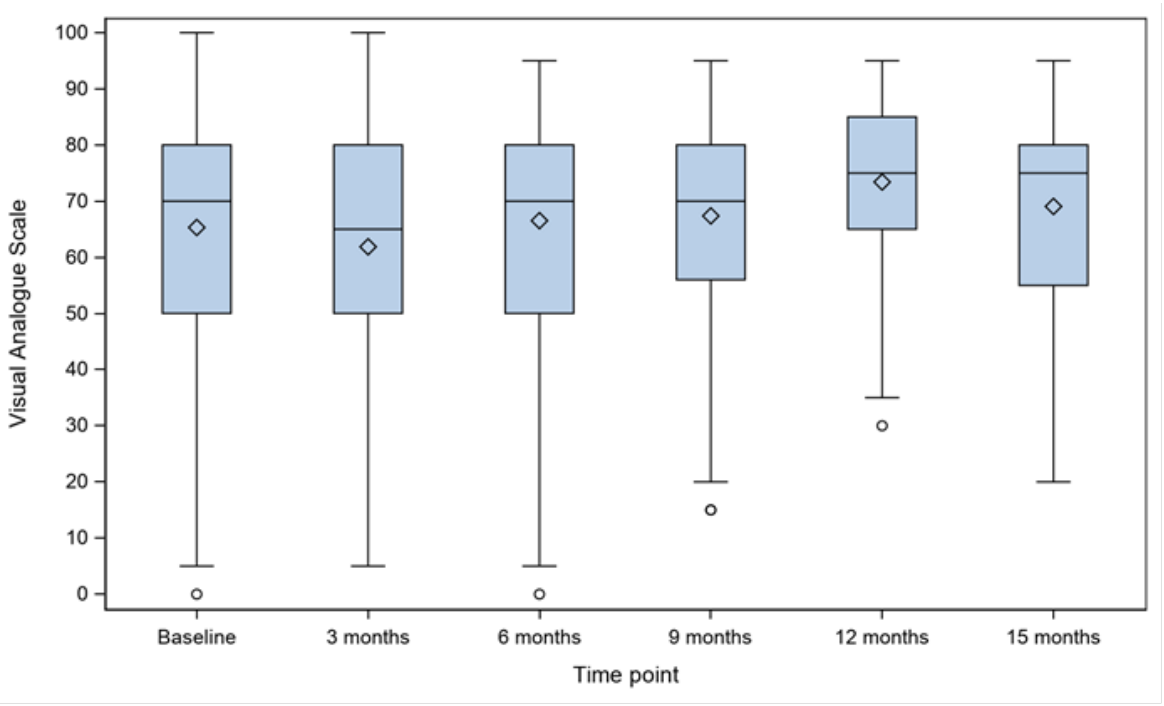


Figure 10.21 EQ-5D-5L Visual Analogue Scale – 1st-line pazopanib

Box: lower to upper quartile, horizontal line inside box: median, diamond inside box: mean, whisker: minimum/maximum value within lower quartile minus 1.5x interquartile range (IQR) / upper quartile plus 1.5x IQR, respectively, circles: outliers outside of lower quartile minus 1.5x IQR / upper quartile plus 1.5x IQR, respectively (IQR = interquartile range) *Source: PAZOREAL TFL: Figures 14.3.9-1-1.1*

Subgroup analysis: Histology

At baseline histology subgroubs clear cell and non-clear cell subtype composed of 174 and 18 patients, respectively. Detailed VAS levels of both subgroups are provided in the appendix *PAZOREAL TFL: Table 14.3.8d-3-1.1*. VAS levels were similar between both groups, slightly lower for the non-clear cell group. Note that the non-clear cell group was relatively small, particularly for later time points.

Subgroup analysis: Participation in a Patient Education Program

At baseline the subgroups participation and no participation were composed of 2 patients and 118 patients, respectively. Detailed VAS levels of both subgroups are provided in the appendix *PAZOREAL TFL: Table 14.3.8d-4-1.1.*

Subgroup analysis: Distance

At baseline distance subgroups <10km and ≥10km composed of 35 patients and 69 patients, respectively. Detailed VAS levels of both subgroups are provided in the appendix *PAZOREAL TFL: Table 14.3.8d-5-1.1.*

10.5.2 Cohort I: 2nd-line nivolumab

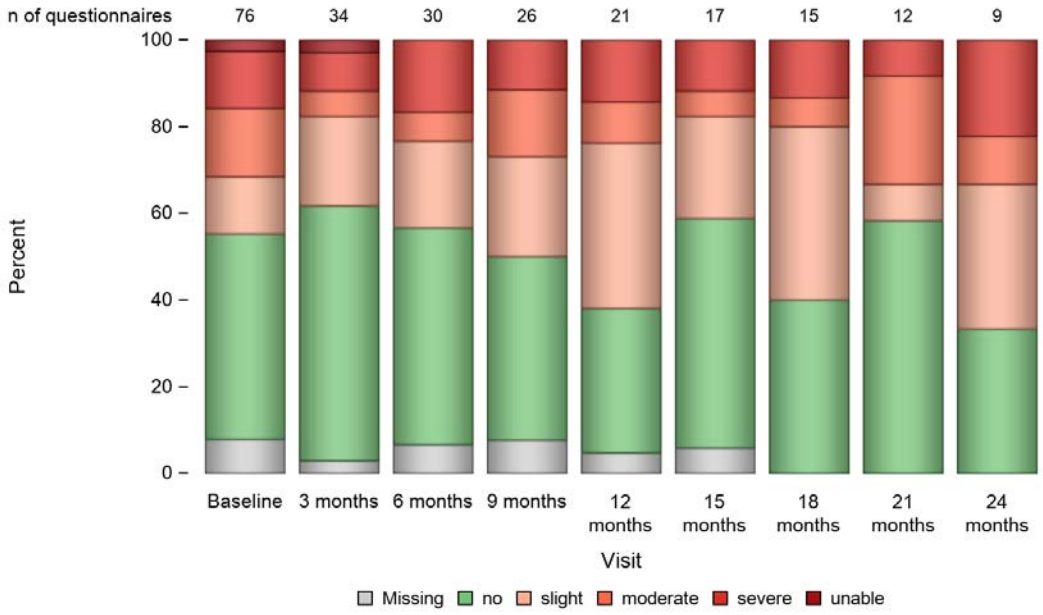
Evaluable questionnaires

Of patients with 2nd-line nivolumab treatments (FAS(N)) 146 patients (89.6%) qualified for the questionnaire project and were assigned to FAS (QS, N) and of those, 82 patients were handed out the baseline-questionnaire (see appendix: *PAZOREAL TFL: Table 14.3.8a-1-1.3 Overview of patients qualifying for the questionnaire project - 2nd line nivolumab, Table 14.3.8a-2-1.3 Number of patients with questionnaires sent - 2nd line nivolumab*). The overview of evaluable questionnaires per time period is provided in appendix *PAZOREAL TFL: Table 14.3.8a-3-1.3 Number of filled questionnaires - 2nd line nivolumab*. At baseline 76 questionnaires (52.1%) were available for analysis, after 3 months the number deceased to 34 evaluable questionnaires (23.3%), after 24 months the number was reduced to 9 questionnaires and after 24 months the QoL of only 6.2% of patients (FAS(QS,N)) could be analyzed.

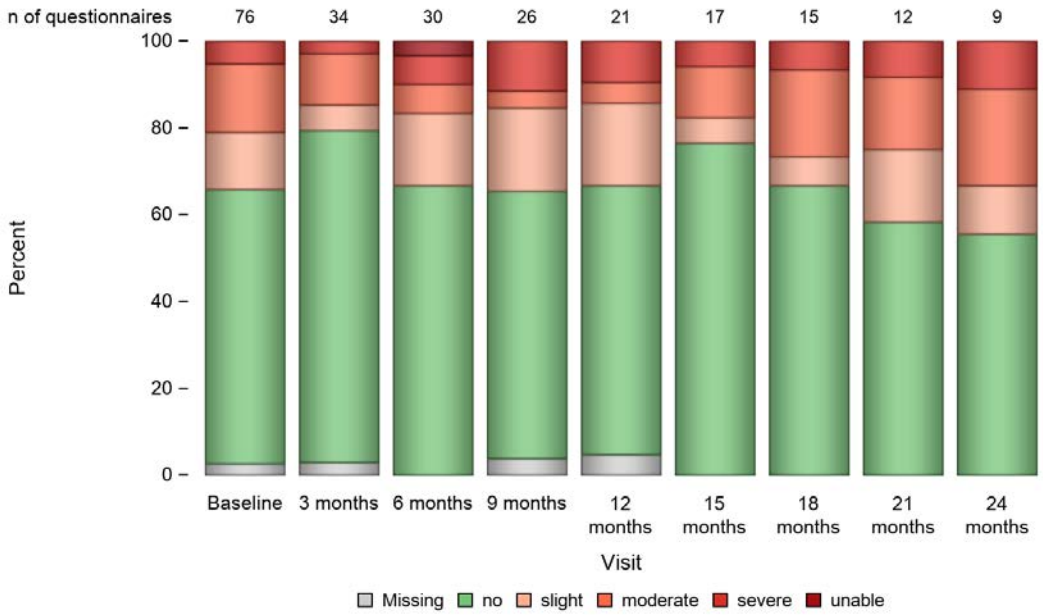
EQ-5D-5L- scores

The reported response levels for each dimension at baseline and during 2nd-line nivolumab treatment are depicted in Figure 10.22 and the EQ-5D-5L- scores generally remained unchanged under treatment: most patients reported “no” problems with regard to self-care, while for dimensions Pain/Discomfort most proportion of patients reported “slight” up to “extremely” problems. For dimensions Mobility, Usual activity and Anxiety/Depression about half of patients reported “no” problems. Compared to resepective analyses for 1st-line pazopanib treatement the proportion of response levels “severe/severely” and “unable/extreme/extremely” numerically increases. Details on reported response levels for each dimension are depicted in appendix *PAZOREAL TFL: Table 14.3.8b-1 up to -5-1.3.* Details on transformed reported response levels into two categories “no problems” (i.e. response level “no”) and “problems” (i.e. response levels “slight/slightly” up to “unable/extreme/extremely”) for each dimension are depicted in appendix *PAZOREAL TFL: Table 14.3.8c-1 up to -5-1.3.*

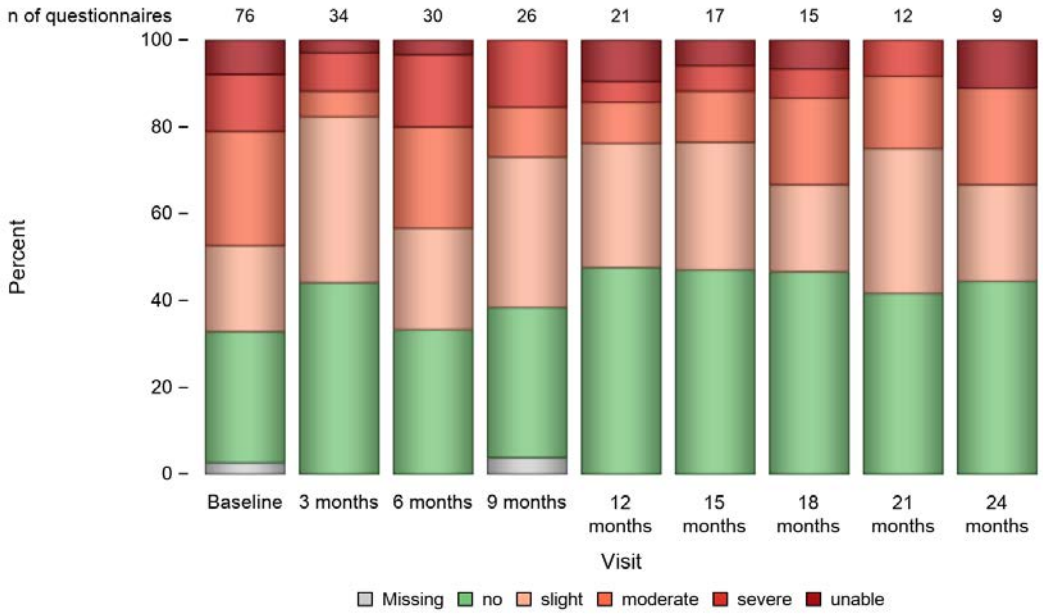
Mobility – I have ... problems walking / I am ... to walk



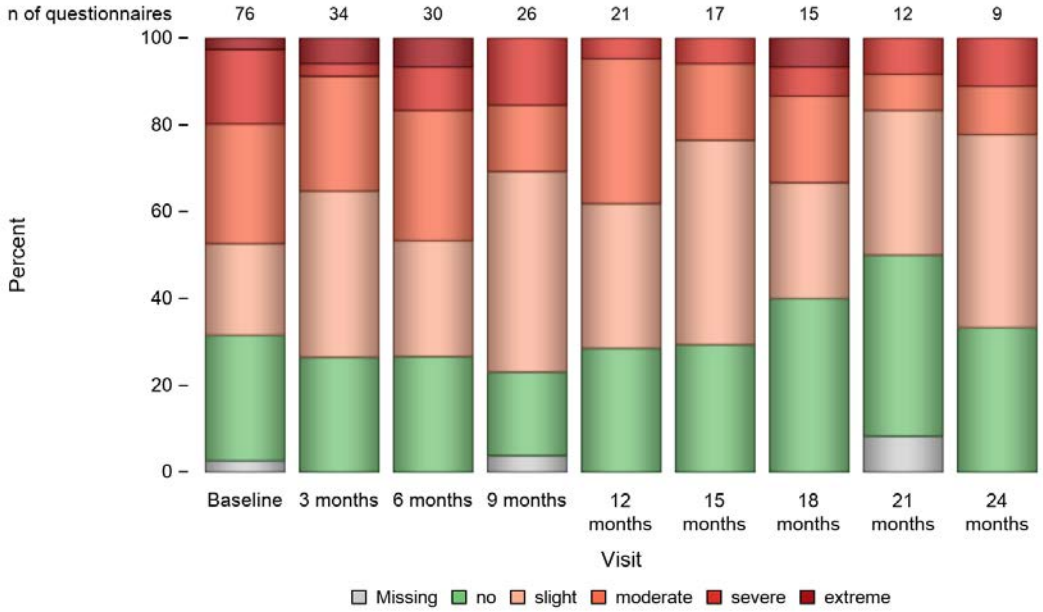
Self-Care – I have ... problems washing or dressing myself / I am ... to wash or dress myself



Usual activity – I have ... problems doing my usual activities / I am ... to do my usual activities



Pain/Discomfort – I have ... pain or discomfort



Anxiety/Depressiom – I am ... anxious or depressed

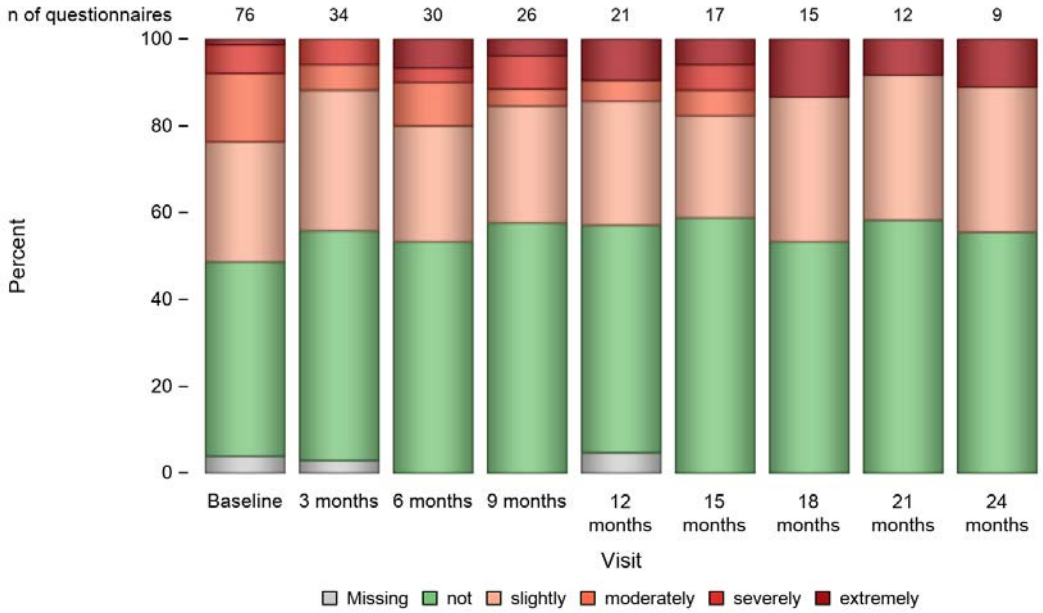


Figure 10.22 EQ-5D-5L 2nd-line nivolumab

For each dimension the proportion of levels (not, slight/slightly, moderate/moderately, severe/severely, unable/extreme/extremely) at baseline and at defined time points (3 months up to 24 months) after treatment start are depicted. Percentages refer to the total number of received questionnaires for the respective time point.

Source: PAZOREAL TFL: Figure 14.3.8b-1-1.3 EQ-5D-5L: Mobility - 2nd line nivolumab, Figure 14.3.8b-2-1.3 EQ-5D-5L: Self-Care - 2nd line nivolumab, Figure 14.3.8b-3-1.3 EQ-5D-5L: Usual activity - 2nd line nivolumab, Figure 14.3.8b-4-1.3 EQ-5D-5L: Pain / Discomfort - 2nd line nivolumab, Figure 14.3.8b-5-1.3 EQ-5D-5L: Anxiety / Depression – 2nd line nivolumab

Subgroup analyses: Age

Response levels and transformed response levels of subgroup analyses by age groups (<65 years / ≥65 years) are provided in *PAZOREAL TFL: Table 14.3.8b-6 up to -10-1.3* and *Table 14.3.8c-6 up to -10-1.3* in appendix. At baseline, age groups <65 years and ≥65 years composed of 24 patients and 52 patients, respectively. Both age groups revealed similar proportions of response categories (“no problems”, “problems”) for each time point (analysis visit) and respective dimension. Note, that 12 months after treatment start the number of evaluable questionnaires decreased to only 10 and 11 patients of respective age group.

Subgroup analyses: histology

Response levels and transformed response levels of subgroups analyses by histology (non-clear cell/clear cell) are provided in *PAZOREAL TFL: Table 14.3.8b-11 up to -15-1.3* and *Table 14.3.8c-11 up to -15-1.3* in the appendix. At baseline, histology groups non-clear cell and clear cell composed of 12 patients and 60 patients, respectively. Both groups revealed similar proportions of response levels and response categories (“no problems”, “problems”) for each time point (analysis visit) and respective dimension. Note, that 6 months after treatment start the number of evaluable questionnaires decreased to only 5 and 23 patients of respective histology group.

Subgroup analyses: Participation in a Patient Education Program

At baseline subgroups participation and no participation composed of 2 patients and 51 patients, respectively. For more details about response levels for each dimension refer to *PAZOREAL TFL: Tables 14.2.8b-16 up to -20-1.3* in the appendix.

Subgroup analyses: Distance

At baseline distance subgroups <10km and ≥10km composed of 18 patients and 32 patients, respectively. Detailed response levels of both distance subgroups are provided in the appendix *PAZOREAL TFL: Tables 14.2.8b-21 up to -25-1.3*. Both subgroups revealed similar proportions of response levels for each time point (analysis visit) and dimension. Note, that i) the number of "distance <10km" patients was about half of the number of "distance ≥10km" patients and ii) at 12 months after treatment start, evaluable questionnaires decreased up to about 10 questionnaires, respectively.

EQ-5D-5L Visual analogue scale

VAS was evaluable in 70 patients at baseline, at the beginning of 2nd-line nivolumab treatment, and in 34, 30, 26, 21, 17 patients at 3 months, 6 months, 9 months, 12 months, 15 months, respectively (Figure 10.23). Baseline VAS showed a mean of 56.3 and median of 56.5 (lower and upper quartiles: 40.0, 75.0), VAS levels remained comparable with a tendency to slightly higher values over the course of 2nd-line nivolumab treatment. At 15 months, the VAS mean was 70.8 and median 70.0 (lower and upper quartiles: 55.0, 90.0). Details are provided in the appendix *PAZOREAL TFL: Tabels 14.3.8d-1-1.3.*

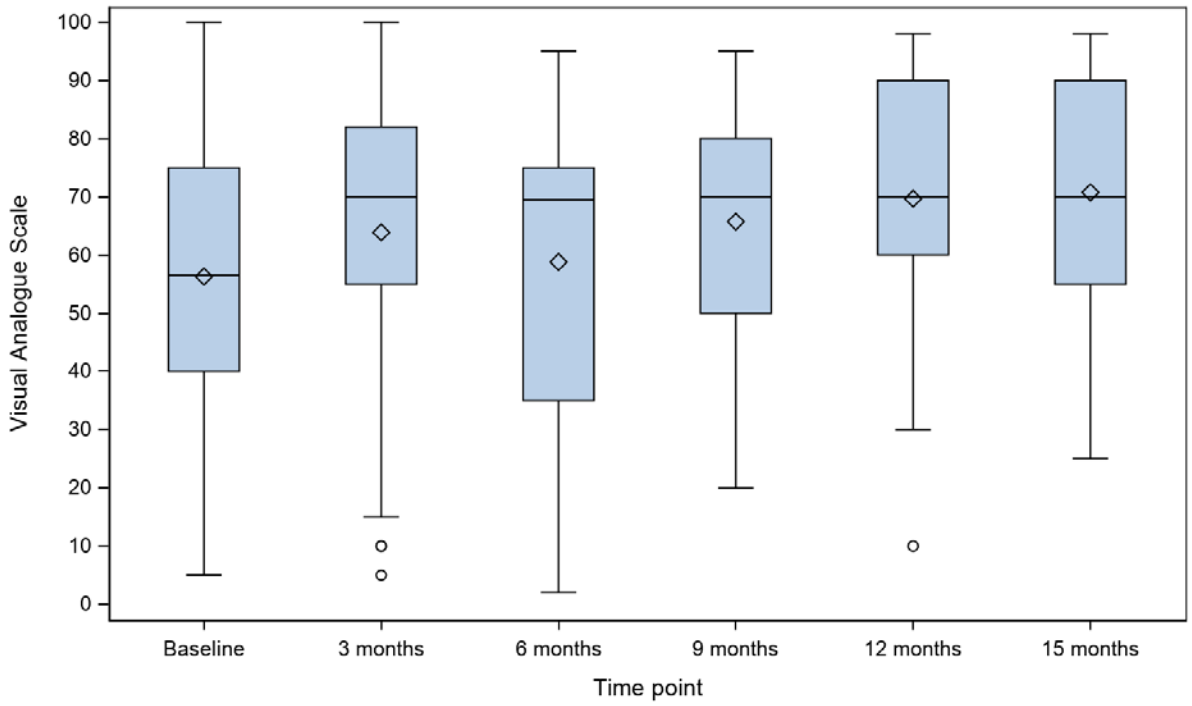


Figure 10.23 EQ-5D-5L Visual Analogue Scale 2nd-line nivolumab

Box: lower to upper quartile, horizontal line inside box: median, diamond inside box: mean, whisker: minimum/maximum value within lower quartile minus 1.5x IQR / upper quartile plus 1.5x IQR, respectively, circles: outliers outside of lower quartile minus 1.5x IQR / upper quartile plus 1.5x IQR, respectively (IQR = interquartile range) Source: PAZOREAL TFL: Figures Figure 14.3.9-1-1.2.

Subgroup analyses: histology

At baseline, histology groups non-clear cell and clear cell were composed of 12 patients and 54 patients, respectively. Detailed VAS levels by subgroup are provided in the appendix in *PAZOREAL TFL: Table 14.3.8d-3*-1.3.

Subgroup analyses: Participation in a Patient Education Program

At baseline subgroups participation and no participation composed of 2 patients and 47 patients, respectively. For more details about response levels for each dimension refer to *PAZOREAL TFL: Table 14.3.8d-4-1.3* in the appendix.

Subgroup analyses: Distance

At baseline distance, subgroups <10km and ≥10km composed of 17 patients and 29 patients, respectively. Detailed response levels of both distance subgroups are provided in appendix *PAZOREAL TFL: Table 14.3.8d-5-1.3* in the appendix.

10.5.3 Cohort I: 2nd-line or 3rd-line everolimus

For patients with 2nd-line or 3rd-line everolimus respective details of the questionnaire analyses are provided in appendix *PAZOREAL TFL: Table 14.3.8a-1-1.2+5, Table 14.3.8a-2-1.2+5 and Table 14.3.8a-3-1.2+5*. For respective details of EQ-5D-5L response levels and response categories of each dimensions refer to appendix *PAZOREAL TFL: Table 14.3.8b-1 up to -5-1.2* and *Table 14.3.8c-1 up to -5-1.2* for 2nd-line everolimus; and *Table 14.3.8b-1 up to -5-1.5 and Table 14.3.8c-1 up to -5-1.5* for 3rd-line everolimus.

For respective details of EQ-5D-5L visual analogue scales refer to appendix *PAZOREAL TFL: Table 14.3.8d-1-1.2* for 2nd-line everolimus and *PAZOREAL TFL: Table 14.3.8d-1-1.5* for 3rd-line everolimus.

Cohort II

10.5.4 Cohort II: 3rd-line everolimus

EQ-5D-5L- scores

For cohort II, respective details of the questionnaire analyses are provided in appendix: *PAZOREAL TFL: Table 14.3.8a-1-2.2, Table 14.3.8a-2-2.2 and 14.3.8a-3-2.2*. For respective details of EQ-5D-5L response levels and response categories of each dimensions refer to appendix *PAZOREAL TFL: Table 14.3.8b-1 up to -5-2.2* and *Table 14.3.8c-1 up to -5-2.2*.

EQ-5D-5L visual analogue scale

For details of EQ-5D-5L visual analogue scales of cohort II, i.e. patients with 3rd-line everolimus refer to appendix *PAZOREAL TFL: Table 14.3.8d-1-2.2*.

10.6 Safety Evaluation

Safety analyses were performed for all patients in the SAF. The SAF set includes all patients who received at least one dose of pazopanib, everolimus or nivolumab in the respective line and for whom at least one further post-baseline information (e.g. laboratory) was available. The SAF study cohort was defined in Section 9.8.1.1. Overall, a total of 375 patients were included in the SAF(all). This population is relevant for all safety parameters.

Trial eligibility

In SAF (P) study population (n=375) 146 patients (38.9%) were identified as “trial-eligible” patients who fulfilled none of the three “trial-ineligibility criteria”, i.e. Karnofsky Performance Status <70%, Haemoglobin < Lower Limit of Normal, Non-clear Cell Carcinoma Histology. 184 patients (49.1%) were identified as not trial-eligible. 45 patients (12.0%) could not be assigned due to the missing of one of the three “trial-ineligibility criteria” (*PAZOREAL TFL: Table 14.1.1c-7-3.1 Overview of trial-eligible patients - 1st line pazopanib*).

In the SAF (N) study population (n=163) 64 patients (39.3%) were identified as “trial-eligible” patients, 81 (49.7%) patients as not trial-eligible and 18 patients (11.0%) could not be assigned

due to the missing of one of the three "trial-ineligibility criteria" *PAZOREAL TFL: Table 14.1.1c-7-3.3 Overview of trial-eligible patients - 2nd line nivolumab*).

For patients from cohort I treated 2nd- and 3rd-line everolimus respective details to trial eligibility are provided in the appendix (*Table 14.1.1c-7-3.2 Overview of trial-eligible patients - 2nd line everolimus, Table 14.1.1c-7-3.5 Overview of trial-eligible patients - 3rd line everolimus)*

Overview of trial eligible patients of SAF population of cohort II is provided in the appendix *PAZOREAL TFL: Table 14.1.1c-7-4.2 Overview of trial-eligible patients - 3rd line everolimus*.

10.6.1 Main reason for end of treatment

Cohort I

1st-line pazopanib

For 349 patients (93.1%) of the safety analysis population (SAF(P)) end of treatment was documented. Reasons for end of therapy documentation were as follows: Progressive disease (n=197, 52.5%), toxicity (therapy-related) (n=51, 13.6%), death (n=22, 5.9%), (Serious) adverse event (not therapy-related) (n=22, 5.9%), patient's wish (not toxicity, not therapy-related) (n=21, 5.6%), investigator's decision (not toxicity, not therapy-related) (n=15, 4.0%) and lost to follow-up (n=9, 2.4%). For one patient (0.3%) the end of treatment was documented reasoned by non-compliance and for 11 patients (2.9%) end of treatment was reasoned by other reasons, see also *PAZOREAL TFL: Table 14.1.1b-1-3.1 Main reason for end of treatment – 1st line pazopanib* in appendix. For 23 patients (6.1%) treatment was ongoing after end of study observation and for 3 patients (0.8%) reason for end of treatment was missing.

2nd -line nivolumab

For 143 patients (87.7%) with 2nd-line nivolumab of the safety analysis population (SAF(N)) end of treatment was documented. For most of the patients end of treatment was documented with the reason progressive disease (n=87, 53.4%). For 14 patients (8.6%) the reason toxicity (therapy-related) and for 11 patients (6.7%) the reason death was documented. The reasons (serious) adverse event (not therapy-related), patient's wish (not toxicity, not therapy-related), investigator's decision (not toxicity, not therapy-related) were documented for 7 patients (4.3%), respectively. The respective reason lost to follow-up and non-compliance were stated in 2 (1.2%) patients and one (0.6%) patient, respectively. For 7 patients (4.3%) end of treatment was reasoned by other reasons, for one patients (0.6%) the reason for end of treatment was missing and for 19 patients (11.7%) the treatment was ongoing after end of study observation, see also *PAZOREAL TFL: Table 14.1.1b-1-3.3 Main reason for end of treatment – 2nd line nivolumab* in appendix.

2nd-line or 3rd-line everolimus

Details of main reasons for end of treatment of patients who received 2nd-line therapy everolimus and for patients who received 3rd-line therapy everolimus in cohort I are provided

in the appendix (*PAZOREAL TFL: Table 14.1.1b-1-3.2 Main reason for end of treatment - 2nd line everolimus, Table 14.1.1b-1-3.5 Main reason for end of treatment - 3rd line everolimus).*

Cohort II

2nd-line nivolumab and 3rd-line everolimus

Details of main reasons for end of treatment of patients receiving 2nd-line therapy nivolumab and 3rd-line therapy everolimus in cohort II are provided in the appendix *PAZOREAL TFL: Table 14.1.1b-1-4.1 Main reason for end of treatment - 2nd line nivolumab and Table 14.1.1b-1-4.2 Main reason for end of treatment - 3rd line everolimus..*

10.6.2 Cause of death

Cohort I

In cohort I, SAF(all), i.e. including all patients from the safety set entering the study in the first-line setting, a total of 174 deaths occurred, and 201 patients were documented as still alive at date of end of study (28 February 2021). Cause of deaths are provided in Table 10-30

Table 10-30 Cause of death – cohort I

			SAF (all) (N=375)
	Line		
Cause of death	1st line	(Serious) Adverse event (not therapy-related)	28 (7.5%)
		Concomitant disease	1 (0.3%)
		Progression	47 (12.5%)
		Unknown	26 (6.9%)
	2nd line (E)	Progression	3 (0.8%)
		Unknown	1 (0.3%)
	2nd line (N)	(Serious) Adverse event (not therapy-related)	12 (3.2%)
		Progression	38 (10.1%)
		Unknown	9 (2.4%)
		Other:	2 (0.5%)
	3rd line	(Serious) Adverse event (not therapy-related)	1 (0.3%)
		Progression	6 (1.6%)
	N.A.	Patients still alive	201 (53.6%)

Data as recorded on the form '*Überlebensstatus / Datum des letzten Kontaktes'.*

Source: PAZOREAL TFL: Table 14.3.1f-3.1 Cause of death

Cohort II

In cohort II, SAF(all) a total of 5 deaths occurred, and 1 patient was documented as still alive. Cause of deaths are provided in Table 10-31.

Table 10-30

Table 10-31 Cause of death cohort II

			SAF (all) (N=6)
	Line		
Cause of death	3rd line	Progression	4 (66.7%)
		Unknown	1 (16.7%)
	N.A.	Patients still alive	1 (16.7%)

Data as recorded on the form 'Überlebensstatus / Datum des letzten Kontaktes'.

Source: PAZOREAL TFL: Table 14.3.1f-4.1 Cause of death

10.6.3 BMI

An overview of BMI at start of treatment as well as the highest and the lowest value during 1st-line pazopanib and 2nd-line nivolumab is given in Table 10-32. Between SAF(P) and SAF(N) of cohort I similar median BMI values were observed. During course of respective 1st and 2nd-line treatment no remarkable changes in BMI-values were observed, since highest and lowest values did not differ from values observed at start of treatment.

Table 10-32 BMI 1st-line pazopanib and 2nd-line nivolumab of cohort I

	1st-line pazopanib (N=375)			**2nd-line nivolumab (N=163)**		
SAF	at start of treatment	highest value	lowest value	at start of treatment	highest value	lowest value
Patients (N)	290	311	311	129	129	129
Median [kg/m²] [25%-75% quantile]	25.8 [23.4–29.1]	26.2 [23.8-29.4]	24.9 [22.3-27.8]	25.3 [22.8-28.1]	26.2 [23.0-29.4]	24.9 [22.5-27.8]
min-max	18.2-58.4	17.2-58.4	16.3-51.9	17.1-51.9	17.1- 56.8	17.1- 47.9

Source: PAZOREAL TFL: Table 14.3.5a-1-3.1 BMI [kg/m²] at start of treatment - 1st line pazopanib, Table 14.3.5a-2-3.1 BMI [kg/m²]: highest value during treatment with pazopanib - 1st line pazopanib, Table 14.3.5a-3-3.1 BMI [kg/m²]: lowest value during treatment with pazopanib - 1st line pazopanib, Table 14.3.5a-1-3.3 BMI [kg/m²] at start of treatment - 2nd line nivolumab, Table 14.3.5a-2-3.3 BMI [kg/m²]: highest value during treatment with nivolumab - 2nd line nivolumab, Table 14.3.5a-3-3.3 BMI [kg/m²]: lowest value during treatment with nivolumab - 2nd line nivolumab

For respective details of BMI for cohort I and cohort II and each study drug refer to appendix *PAZOREAL TFL: Table 14.3.5a*.

10.6.4 Heart rate

Patients' heart rate at start of treatment as well as the highest and the lowest value during 1st-line pazopanib and 2nd-line nivolumab are depicted in Table 10-33. Between SAF(P) and SAF(N) of cohort I heart rate values were observed. Heart rate of patients remained stable during course of respective 1st and 2nd-line treatment, since highest and lowest values did hardly differ from values observed at start of treatment.

Table 10-33 Heart rate for 1st-line pazopanib and 2nd-line nivolumab of cohort I

	1st-line pazopanib (N=375)			2nd-line nivolumab (N=163)		
SAF	at start of treatment	highest value	lowest value	at start of treatment	highest value	lowest value
Patients (N)	236	236	236	83	83	83
Median [beats/min] [25%-75% quantile]	72 [66–83]	79 [71-87]	68 [60-77]	72 [66-80]	76 [71-86]	68 [61-76]
min-max [beats/min]	50-129	51-129	47-129	55-106	56-106	46-106

Source: PAZOREAL TFL: Table 14.3.5b-1-3.1 Heart rate [beats/min] at start of treatment - 1st line pazopanib, Table 14.3.5b-2-3.1 Heart rate [beats/min]: highest value during treatment with pazopanib - 1st line pazopanib, Table 14.3.5b-3-3.1 Heart rate [beats/min]: lowest value during treatment with pazopanib - 1st line pazopanib, Table 14.3.5a-1-3.3 BMI [kg/m²] at start of treatment - 2nd line nivolumab, Table 14.3.5b-2-3.3 Heart rate [beats/min]: highest value during treatment with nivolumab - 2nd line nivolumab, Table 14.3.5b-3-3.3 Heart rate [beats/min]: lowest value during treatment with nivolumab - 2nd line nivolumab

For respective details of heart rate for cohort I and cohort II and each study drug refer to appendix *PAZOREAL TFL: Table 14.3.5b*.

10.6.5 Blood pressure levels

Proportions of measured patients' blood pressure levels at start of treatment as well as the highest during 1st-line pazopanib and 2nd-line nivolumab of cohort I are depicted in Table 10-34. At start of 1st-line pazopanib and 2nd-line nivolumab treatment blood pressure was not measured in 36% and 53% of patients, respectively. Similarly, during treatment in around 63% of patients no blood pressure measurement was documented. Irrespective of the type of antineoplastic treatment, (out of patients with measured blood pressure levels) the highest proportion of patients had high blood pressure levels and a lowest proportion of patients had normal blood pressure levels.

Table 10-34 Blood pressure level for 1st-line pazopanob and 2nd-line nivolumab

SAF	1st-line pazopanib (N=375)		2nd-line nivolumab (N=163)	
	at start of treatment	highest value	at start of treatment	highest value

normal, N (%)	20 (5.3%)	13 (3.5%)	10 (6.1%)	7 (4.3%)
prehypertension, N (%)	86 (22.9%)	34 (9.1%)	32 (19.6%)	22 (13.5%)
high, N (%)	130 (34.7%)	89 (23.7%)	35 (21.5%)	30 (18.4%)
not done, N (%)	136 (36.3%)	236 (62.9%)	86 (52.8%)	104 (63.8%)
missing, N (%)	3 (0.8%)	3 (0.8%)	-	-

For details to categorization of blood pressure levels refer to SAP v4.1 from 14 November 2019, Table 3: Blood pressure categories.
Source: PAZOREAL TFL: Table 14.3.5c-1-3.1 Blood pressure levels at start of treatment - 1st line pazopanib, Table 14.3.5c-2-3.1 Blood pressure levels: highest value during treatment with pazopanib - 1st line pazopanib, Table 14.3.5c-1-3.3 Blood pressure levels at start of treatment - 2nd line nivolumab, Table 14.3.5c-2-3.3 Blood pressure levels: highest value during treatment with nivolumab - 2nd line nivolumab

For respective details of blood pressure levels for cohort I and cohort II and each study drug refer to appendix *PAZOREAL TFL: Table 14.3.5c.*

Baseline to worst on treatment measure in patients with antihypertensive therapy

For patients receiving an antihypertensive therapy (treatment start after start of 1st-line pazopanib treatment) the blood pressure categories from baseline were compared to worst on treatment values and are depicted in Table 10-35. In most patients blood pressure level measurements were not performed. One patient with prehypertension at start of treatment had a high blood pressure level as worst value on treatment, seven patients with high blood pressure at start of treatment had also a high blood pressure level as worst level value on treatment.

Table 10-35 Blood pressure levels: patients with antihypertensive therapy – 1st-line pazopanib

	Worst on treatment					
At start of treatment	**Normal**	**Prehypertension**	**High**	**Not done**	**Missing**	**Total**
Prehypertension			1 (0.3%)	4 (1.1%)		5 (1.3%)
High blood pressure			7 (1.9%)	9 (2.4%)		16 (4.3%)
Not done				6 (1.6%)		6 (1.6%)

Percentages refer to the total number of patients included in the SAF(P), N = 375 .

Source: PAZOREAL TFL: Table 14.3.5c-3-3.1 Blood pressure levels: baseline to worst on treatment (patients with antihypertensive therapy) - 1st line pazopanib

10.6.6 ECOG

ECOG values at start of treatment as well as the highest during 1st-line pazopanib and 2nd-line nivolumab are depicted in Table 10-34. At start of treatment the proportions of 1st-line pazopanib patients with ECOG 0 at start of treatment is with 40.3% higher than the respective proportion of 2nd-line nivolumab patients (28.8%). Patients with 2nd-line nivolumab mostly presented with ECOG 1 at start of treatment. During treatment most patients had a highest

ECOG value of 1 and a lowest EGOC value of 0 in both 1st-line pazopanib and 2nd-line nivolumab groups.

Table 10-36 ECOG– 1st-line pazopanib and 2nd-line nivolumab – cohort I

SAF	1st-line pazopanib (N=375) n (%)			2nd-line nivolumab (N=163) n (%)		
ECOG performance status	at start of treatment	highest value	lowest value	at start of treatment	highest value	lowest value
0	151 (40.3%)	105 (28.0%)	183 (48.8%)	47 (28.8%)	36 (22.1%)	67 (41.1%)
1	126 (33.6%)	147 (39.2%)	114 (30.4%)	58 (35.6%)	72 (44.2%)	51 (31.3%)
2	31 (8.3%)	72 (19.2%)	33 (8.8%)	19 (11.7%)	25 (15.3%)	15 (9.2%)
3	6 (1.6%)	9 (2.4%)	3 (0.8%)	-	-	-
4	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.6%)	1 (0.6%)	1 (0.6%)
not done	58 (15.5%)	39 (10.4%)	39 (10.4%)	38 (23.3%)	29 (17.8%)	29 (17.8%)
missing	2 (0.5%)	2 (0.5%)	2 (0.5%)	-	-	-

Source: PAZOREAL TFL: Table 14.3.5d-1-3.1 ECOG performance status at start of treatment - 1st line pazopanib, Table 14.3.5d-2-3.1 ECOG performance status: highest value during treatment with pazopanib - 1st line pazopanib, Table 14.3.5d-3-3.1 ECOG performance status: lowest value during treatment with pazopanib - 1st line pazopanib, Table 14.3.5d-1-3.3 ECOG performance status at start of treatment - 2nd line nivolumab, Table 14.3.5d-2-3.3 ECOG performance status: highest value during treatment with nivolumab - 2nd line nivolumab, Table 14.3.5d-3-3.3 ECOG performance status: lowest value during treatment with nivolumab - 2nd line nivolumab

For respective details of ECOG for cohort I and cohort II and each study drug refer to appendix *PAZOREAL TFL: Table 14.3.5d*.

Time to reduction of ECOG performance status – 1st-line pazopanib

In this time-to-event analysis, 108 patients (SAF(P) 31.5%) had an event and the median time to reduction was 14.8 months, cf. Table 10-37. However, 235 patients (68.5%) were censored due to missing baseline ECOG performance status, i.e. no assessment of the ECOG during treatment, or without a reduction of the ECOG performance status.

Table 10-37 Time to reduction of the ECOG - 1st-line pazopanib

		Total (N = 343)
Time to reduction of the ECOG performance status [months]	Events (n[%])	108 (31.5%)
	Censored (n[%])	235 (68.5%)
	25%-Quantile [95% CI] (months)	3.8 (3.0 - 5.5)

		Total (N = 343)
	50%-Quantile (Median) [95% CI] (months)	14.8 (9.0 - 23.4)
	75%-Quantile [95% CI] (months)	NA (30.9 - NA)

The reduction of the ECOG performance status for at least one point (compared to the status at treatment start) was defined as event. Only patients with a recorded baseline value were taken into account. Patients without event at the end of the pazopanib treatment were censored

Source PAZOREAL TFL: Table 14.3.5e-1-1.1 Time to reduction of the ECOG performance status [months] - 1st line pazopanib

10.6.7 Blood count test

At baseline, 84% of patients (n=315, SAF(P)) with 1st-line pazopanib had one documented blood count test, while for 16% of the patients (n=60) no test was performed (see in the appendix *PAZOREAL TFL: Table 14.3.6a-1-01 Overview of performed blood count tests (Baseline) - 1st line pazopanib*). During treatment the number of performed blood count tests generally decreased: while at the visit one 79.2% of patients had at least one documented blood count test, at visit 4 only 32.3% of patients and at visit 8 only 15.2% of patients had at least one documented test. (cf. Table 10-38). This trend applied also for performed blood count tests in patients of cohort I with subsequent 2nd-line nivolumab treatment (SAF(N)), while the proportion of patients with at least one documented test remained stable compared to 1st-line treatment period, for details refer to appendix *PAZOREAL TFL: Table 14.3.6a-1-3.3 Overview of performed blood count tests - 2nd line nivolumab*.

Table 10-38 Overview of performed blood count tests – 1st-line pazopanib

		Number of performed tests					
Visits*	**No test performed**	**1**	**2**	**3**	**4**	**≥5**	**Total****
Visit 01	76 (20.3%)	226 (60.3%)	26 (6.9%)	14 (3.7%)	10 (2.7%)	21 (5.6%)	373 (99.5%)
Visit 02	30 (8.0%)	165 (44.0%)	17 (4.5%)	13 (3.5%)	6 (1.6%)	3 (0.8%)	234 (62.4%)
Visit 03	22 (5.9%)	120 (32.0%)	9 (2.4%)	9 (2.4%)	3 (0.8%)	1 (0.3%)	164 (43.7%)
Visit 04	18 (4.8%)	104 (27.7%)	10 (2.7%)	5 (1.3%)	1 (0.3%)	1 (0.3%)	139 (37.1%)
Visit 05	17 (4.5%)	79 (21.1%)	4 (1.1%)	3 (0.8%)		1 (0.3%)	104 (27.7%)
Visit 06	16 (4.3%)	58 (15.5%)	8 (2.1%)	2 (0.5%)	2 (0.5%)		86 (22.9%)
Visit 07	13 (3.5%)	53 (14.1%)	7 (1.9%)	1 (0.3%)	1 (0.3%)		75 (20.0%)
Visit 08	11 (2.9%)	49 (13.1%)	6 (1.6%)	2 (0.5%)			68 (18.1%)
Visit 09	12 (3.2%)	43 (11.5%)	1 (0.3%)		1 (0.3%)		57 (15.2%)

	Number of performed tests						
Visits*	**No test performed**	**1**	**2**	**3**	**4**	**≥5**	**Total****
Visit 10	7 (1.9%)	35 (9.3%)	2 (0.5%)	1 (0.3%)			45 (12.0%)
Visit 11	6 (1.6%)	33 (8.8%)		2 (0.5%)			41 (10.9%)
Visit 12	7 (1.9%)	28 (7.5%)	1 (0.3%)	1 (0.3%)	1 (0.3%)		38 (10.1%)
Visit 13	8 (2.1%)	23 (6.1%)	3 (0.8%)		1 (0.3%)		35 (9.3%)
Visit 14	7 (1.9%)	24 (6.4%)			2 (0.5%)		33 (8.8%)
Visit 15	6 (1.6%)	18 (4.8%)		1 (0.3%)			25 (6.7%)
Visit 16	5 (1.3%)	12 (3.2%)	1 (0.3%)	1 (0.3%)			19 (5.1%)

* The displayed visits equal the documented 'Verlaufsvisiten' from the edc.
** This column shows the total number of patients for those at least one information concerning laboratory tests is available for the respective visit.

For respective details of blood count tests for cohort I and cohort II and each study drug refer to appendix *PAZOREAL TFL: Table 14.3.6a-1*.

Abnormal blood count test results

An overview of abnormal blood count test results per documentation period (i.e. baseline, visit 01- visit 04) is provided in appendix *PAZOREAL TFL: Table 14.3.6c-1-3.1-5 and 14.3.6c-1-4.2*. For 1st-line pazopanib the rate of abnormal blood count test results per documentation period is depicted in Table 10-39. At baseline, before 1st-line pazopanib treatment for 315 patients the data for blood count test results were documented and in 130 patients no abnormal (rate 0%), and in 185 patients an abnormal result (rate 100%) was detected. During treatment the available data for blood count test results deceased, while independed of number of performed tests, rate of detected abnormal test result remained stable.

Table 10-39 Rate of abnormal blood count test results per documentation period – 1st-line pazopanib

Rate	Baseline	Visit 01	Visit 02	Visit 03	Visit 04
Total**	375	373	234	164	139
0 %	130	135	105	75	64
20.00 %		1			
25.00 %		2			
33.33 %		6	2		
40.00 %		2			
50.00 %		9	5	2	1
66.67 %		5	5		1

Rate	Baseline	Visit 01	Visit 02	Visit 03	Visit 04
71.43 %			1		
75.00 %		3	2	1	
80.00 %		2			
88.89 %			1		
100 %	185	146	86	68	56
No test performed	60	62	27	18	17

Data is based on the reported information on the eCRF form 'Laborbefunde'. According to SAP only the first four documentation periods per substance were considered for this analysis: Baseline period = 0-3 months, visit 01 = 3-6 months, visit 02 = 6-9 months after start of treatment, and so on (+/- 1.5 months each).
** Total number of patients for whom data on laboratory tests in the respective period was available / reported in the eCRF.

During 2nd-line treatment with nivolumab at visit 01 the number of patients with documented data for blood count test results was reduced to 163 patients, while in 37 patients no test was performed, in 40 patients each performed test led to no abnormal results (rate 0%), and in 81 patients each performed tests resulted in an abnormal value (rate 100%). During the course of treatment the number of patients with available data for abnormal blood count test results decreased (cf. Table 10-40).

Table 10-40 Rate of abnormal blood count test results per documentation period – 2nd-line nivolumab

Rate	Baseline	Visit 01	Visit 02	Visit 03	Visit 04
	N.A.*				
Total**		163	97	62	47
0 %		40	35	25	23
50.00 %		3	1	1	
66.67 %		1		1	1
75.00 %		1			
85.71 %					1
100 %		81	54	30	17
No test performed		37	7	5	5

Data is based on the reported information on the eCRF form 'Laborbefunde'.
Baseline period = 0-3 months, visit 01 = 3-6 months, visit 02 = 6-9 months after start of treatment, and so on (+/- 1.5 months each).
* For this period no laboratory test was performed.
** Total number of patients for whom data on laboratory tests in the respective period was available / reported in the eCRF.
Source: PAZOREAL TFL: Table 14.3.6c-2-3.3 Rate of abnormal blood count test results per documentation period - 2nd line nivolumab

For respective details of rate of abnormal blood count tests results for cohort I and cohort II and each study drug refer to appendix *PAZOREAL TFL: Table 14.3.6c-3-3.1-5 and Table 14.3.6c-4-3.1*.

10.6.8 Liver function test (LFT)

Before 1st-line pazopanib treatment, at baseline, 81.1% of patients (n=304, SAF(P)) had a documented LFT, while for 18.9% of patients (n=71) no test was performed (see *PAZOREAL TFL: Table 14.3.6a-2-01 Overview of performed liver function tests (Baseline) - 1st line pazopanib* in the appendix). During treatment the number of performed LFTs generally decreased: while at visit one 75.2% of patients had at least one documented LFT, at visit 4 only 31.7% of patients and at visit 8 only 15.2% of patients had at least one documented test, cf. Table 10-41. This trend applied also for performed LFTs in patients with subsequent 2nd-line nivolumab treatment (SAF(N)), while generally the proportion of patients with at least one documented test remained stable compared to 1st-line treatment period, for details refer to appendix *PAZOREAL TFL: Table 14.3.6a-2-3.3 Overview of performed liver function tests - 2nd line nivolumab*.

Table 10-41 Overview of performed LFTs – 1st-line pazopanib

		Number of performed tests					
Visits*	**No test performed**	**1**	**2**	**3**	**4**	**≥5**	**Total****
Visit 01	91 (24.3%)	215 (57.3%)	25 (6.7%)	13 (3.5%)	9 (2.4%)	20 (5.3%)	373 (99.5%)
Visit 02	36 (9.6%)	162 (43.2%)	16 (4.3%)	11 (2.9%)	6 (1.6%)	3 (0.8%)	234 (62.4%)
Visit 03	24 (6.4%)	119 (31.7%)	8 (2.1%)	9 (2.4%)	3 (0.8%)	1 (0.3%)	164 (43.7%)
Visit 04	20 (5.3%)	101 (26.9%)	11 (2.9%)	5 (1.3%)	1 (0.3%)	1 (0.3%)	139 (37.1%)
Visit 05	21 (5.6%)	76 (20.3%)	4 (1.1%)	2 (0.5%)		1 (0.3%)	104 (27.7%)
Visit 06	14 (3.7%)	60 (16.0%)	8 (2.1%)	2 (0.5%)	2 (0.5%)		86 (22.9%)
Visit 07	16 (4.3%)	50 (13.3%)	7 (1.9%)	1 (0.3%)	1 (0.3%)		75 (20.0%)
Visit 08	11 (2.9%)	49 (13.1%)	6 (1.6%)	2 (0.5%)			68 (18.1%)
Visit 09	13 (3.5%)	42 (11.2%)	1 (0.3%)		1 (0.3%)		57 (15.2%)
Visit 10	8 (2.1%)	34 (9.1%)	2 (0.5%)	1 (0.3%)			45 (12.0%)
Visit 11	7 (1.9%)	32 (8.5%)		2 (0.5%)			41 (10.9%)
Visit 12	8 (2.1%)	27 (7.2%)	1 (0.3%)	1 (0.3%)	1 (0.3%)		38 (10.1%)
Visit 13	7 (1.9%)	24 (6.4%)	3 (0.8%)		1 (0.3%)		35 (9.3%)
Visit 14	8 (2.1%)	23 (6.1%)			2 (0.5%)		33 (8.8%)
Visit 15	4 (1.1%)	20 (5.3%)		1 (0.3%)			25 (6.7%)
Visit 16	5 (1.3%)	12 (3.2%)	1 (0.3%)	1 (0.3%)			19 (5.1%)

(continued)

* The displayed visits equal the documented 'Verlaufsvisiten' from the edc.

** This column shows the total number of patients for those at least one information concerning laboratory tests is available for the respective visit.

The table should be read as follows: e.g. 215 patient(s) had 1 test documented during visit 1 of 1st-line treatment.
All percentages refer to the total number of patients included in the Safety Set - 1st-line pazopanib (N=375).

Source PAZOREAL TFL: Table 14.3.6a-2-3.1 Overview of performed liver function tests - 1st line pazopanib

For respective details of LFTs for cohort I and cohort II and each study drug refer to appendix *PAZOREAL TFL: Table 14.3.6a-2*.

Abnormal LFT result

An overview of abnormal LFT results per documentation period (i.e. baseline, visit 01- visit 04) is provided in appendix *PAZOREAL TFL: Table 14.3.6c-4-3.1-5 and 14.3.6c-4-4.2*.

Before 1st-line pazopanib treatment, for 375 patients available data on LFT were documented, while for 92 patients no test was performed, in 180 patients each performed test detected no abnormal LFT result and in 103 patients each performed test discovered an abnormal LFT result. During treatment for the majority of patients the rate of abnormal LFT results is either 0% or 100% (Table 10-42). This applies also for rate of abnormal LFT results during 2nd-line nivolumab treatment (cf. Table 10-43)

Table 10-42 Rate of abnormal LFT results per documentation period – 1st-line pazopanib

Rate	Baseline	Visit 01	Visit 02	Visit 03	Visit 04
Total**	375	373	234	164	139
0 %	180	126	108	92	79
16.67 %		1			
20.00 %		1			
25.00 %		1	1		
33.33 %		5	2	2	
40.00 %		2	1		
50.00 %		6	4	1	1
66.67 %		2	1		
75.00 %		4	1	1	
80.00 %		1			
83.33 %		1			
100 %	103	148	81	49	36
No test performed	92	75	35	19	23

Data is based on the reported information on the eCRF form 'Laborbefunde'.
Baseline period = 0-3 months, visit 01 = 3-6 months, visit 02 = 6-9 months after start of treatment, and so on (+/- 1.5 months each).
* For this period no laboratory test was performed.
** Total number of patients for whom data on laboratory tests in the respective period was available / reported in the eCRF.
Source: PAZOREAL TFL: Table 14.3.6c-4-3.1 Rate of abnormal liver function test results per documentation period - 1st line pazopanib

Table 10-43 Rate of abnormal LFT results per documentation period – 2nd-line nivolumab

Rate	Baseline	Visit 01	Visit 02	Visit 03	Visit 04
	N.A.*				
Total**		163	97	62	47
0 %		64	60	39	27

Rate	Baseline	Visit 01	Visit 02	Visit 03	Visit 04
25.00 %		1			
33.33 %				1	
42.86 %			1		
50.00 %			1		
66.67 %		3			
75.00 %		1		1	
83.33 %					1
85.71 %					1
100 %		44	23	15	10
No test performed		50	12	6	8

Data is based on the reported information on the eCRF form 'Laborbefunde'.
Baseline period = 0-3 months, visit 01 = 3-6 months, visit 02 = 6-9 months after start of treatment, and so on (+/- 1.5 months each).
* For this period no laboratory test was performed.
** Total number of patients for whom data on laboratory tests in the respective period was available / reported in the eCRF.

Source: PAZOREAL TFL: Table 14.3.6c-4-3.3 Rate of abnormal liver function test results per documentation period - 2nd line nivolumab

For respective details of rate of abnormal liver function tests results for cohort I and cohort II and each study drug refer to appendix *PAZOREAL TFL: Table 14.3.6c-4-3.1-5 and Table 14.3.6c-4-4.2*.

10.6.9 Effect of frequent lab analyses on frequency and severity of AEs, with focus on liver-related AEs

The crosstable illustrating the number of performed LFTs and the number of recorded liver-related AEs per therapy line, per documentation period (visit ~ every 12 weeks) for cohort I is provided in appendix *PAZOREAL TFL: Table 14.3.7a-1-1.1 Effect of frequent lab analyses on frequency of AEs - 1st line pazopanib*. During treatment with pazopanib number of performed LFTs generally decreased and most of patients received one liver function test per visit, cf. Figure 10.24 and Figure 10.25.

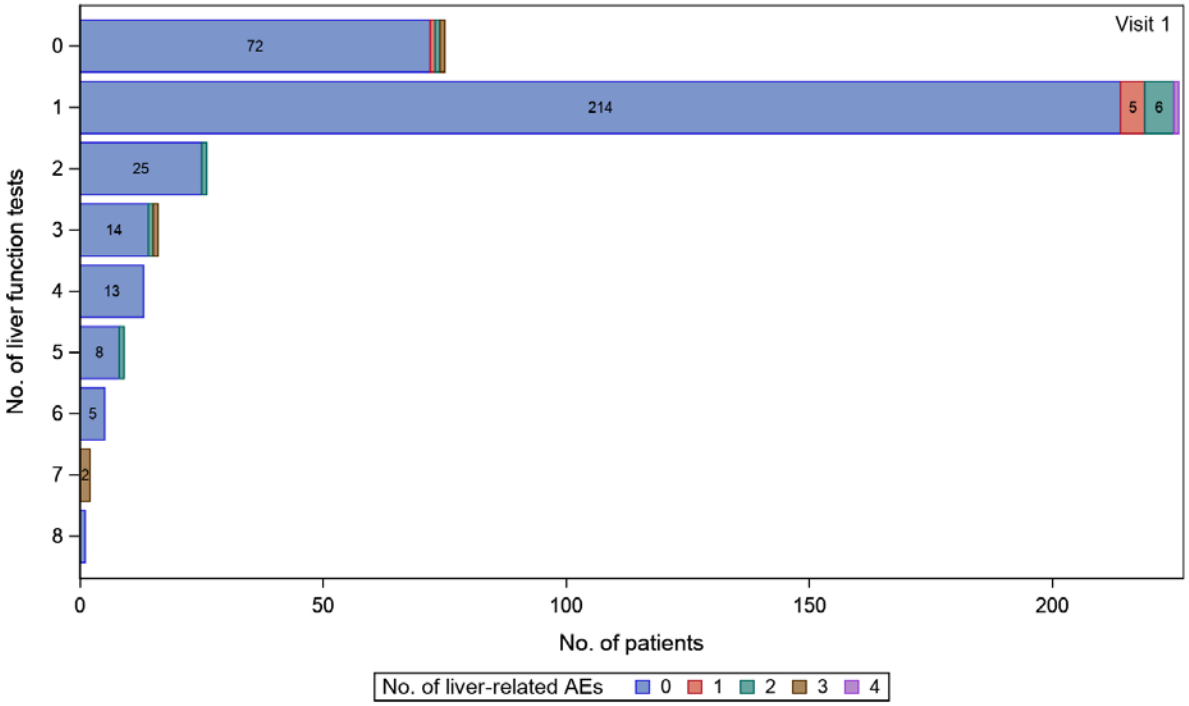
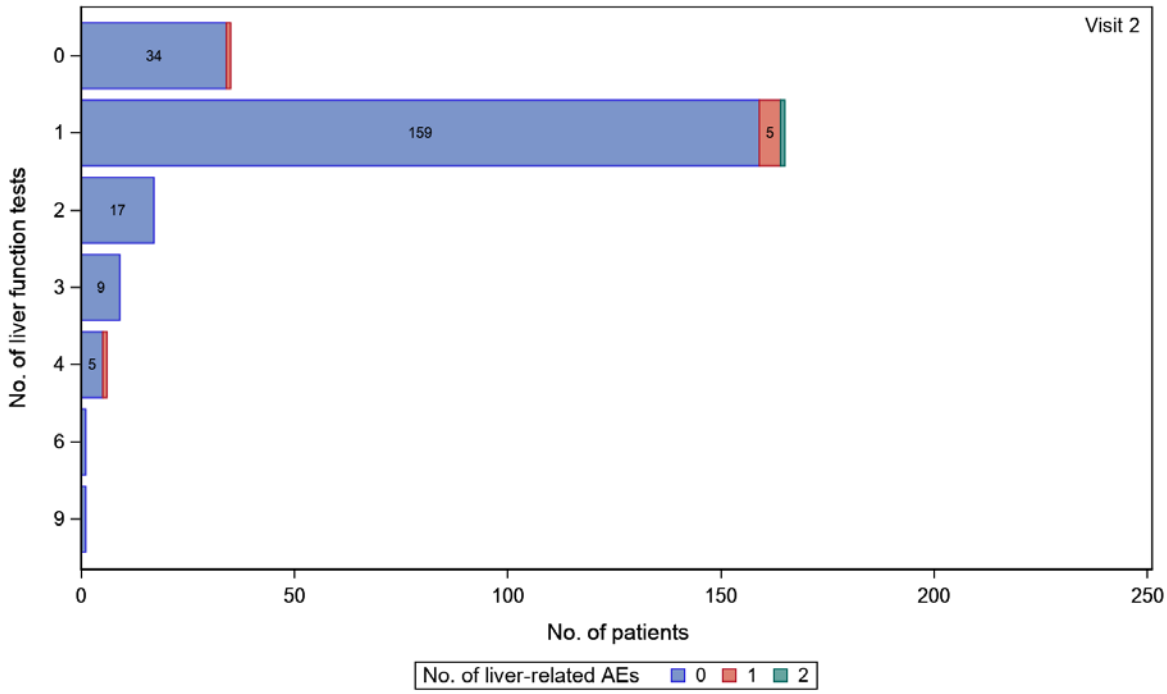
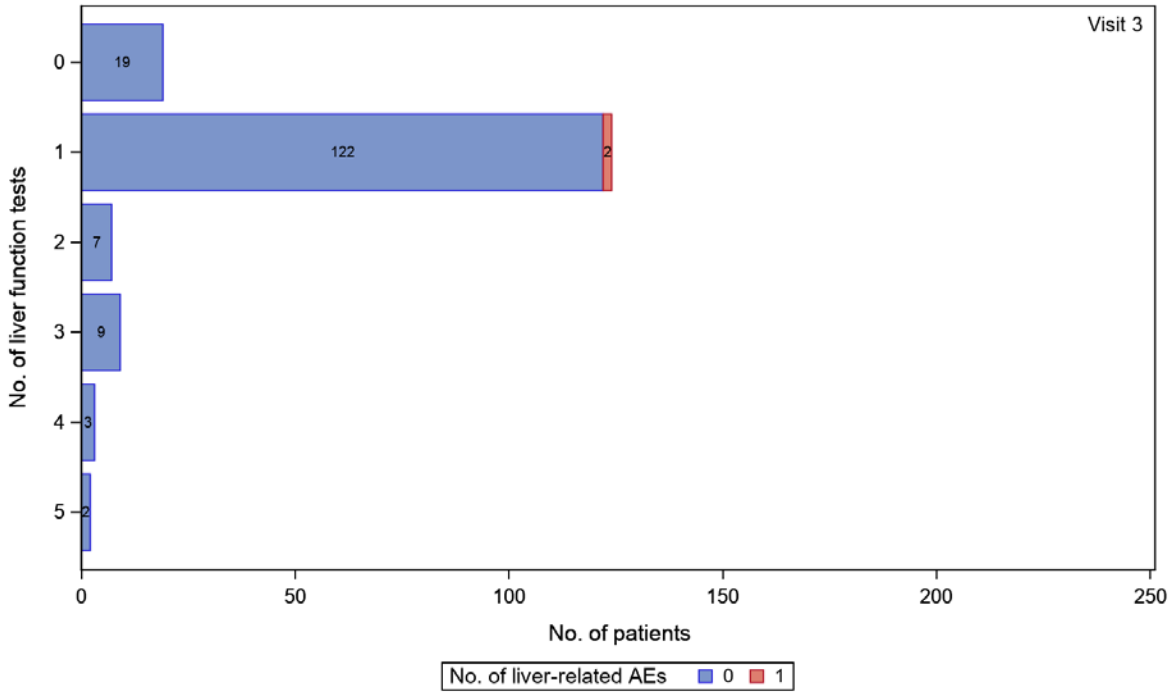
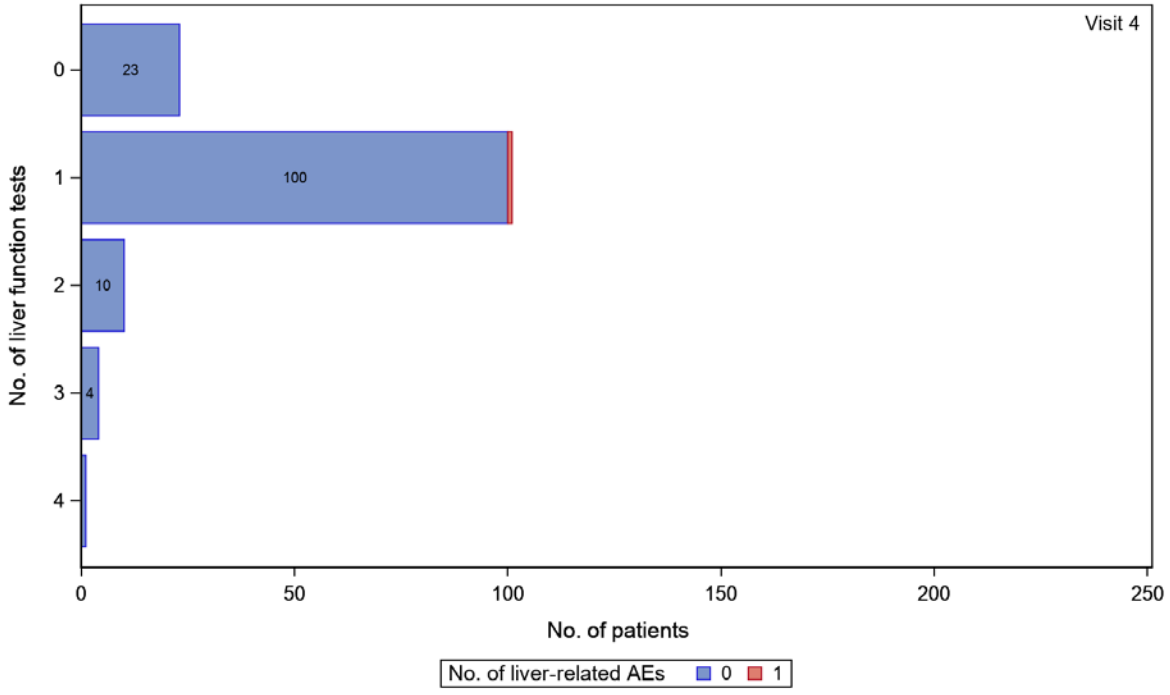


Figure 10.24 Effect of frequent lab analyses on frequency of AEs - Visit 01

Source: PAZOREAL TFL: Figure 14.3.7-1-3.1 Effect of frequent lab analyses on frequency of AEs - 1st line pazopanib




Visit 3
No. of liver function tests
0
1
2
3
4
5
19
122
2
7
9
3
2
0
50
100
150
200
250
No. of patients
No. of liver-related AEs
0
1


Visit 4
No. of liver function tests
0
1
2
3
4
23
100
10
4
0
50
100
150
200
250
No. of patients
No. of liver-related AEs
0
1

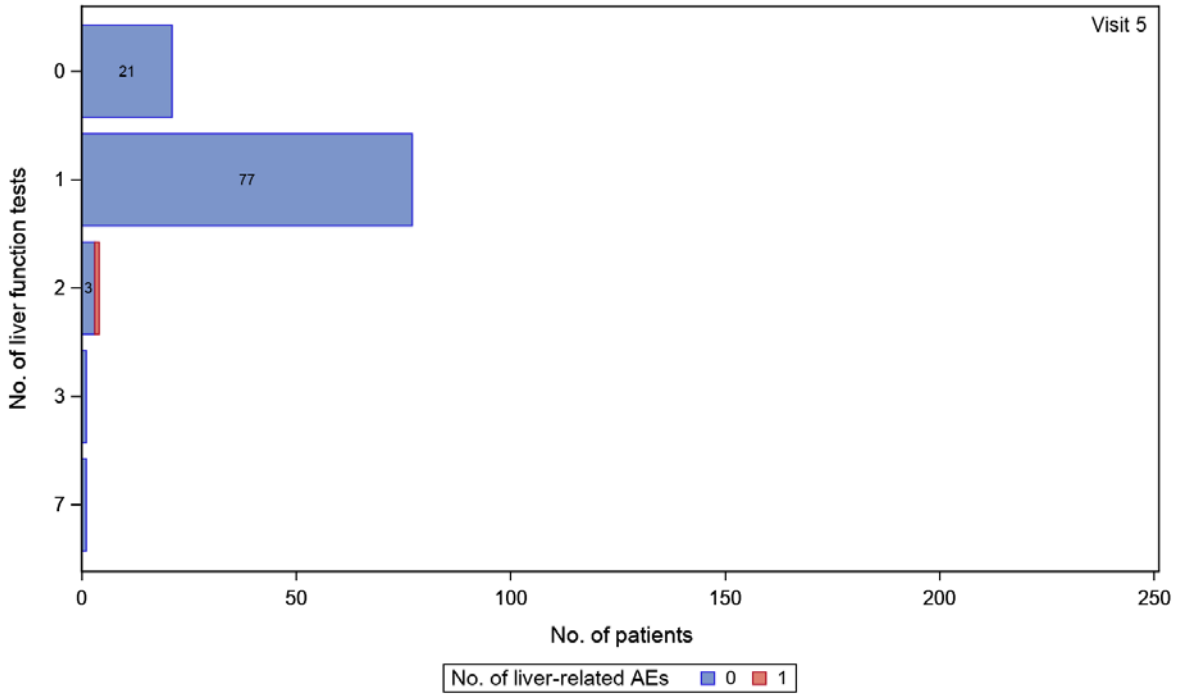


Figure 10.25 Effect of frequent lab analyses on frequency of AEs - Visit 2-Visit 5

Source: PAZOREAL TFL: Figure 14.3.7-1-3.1 Effect of frequent lab analyses on frequency of AEs - 1st line pazopanib

Overview of patients with liver monitoring according to SmPC

Out of 375 patients (SAF(P)), 7 (1.9%) patients have been monitored for liver events as prescribed in the German SmPC (LFTs according to SmPC) and 368 patients (98.1%) not (cf. Table 10-44).

Table 10-44 Overview of patients with liver monitoring according to SmPC – 1st-line pazopanib

		SAF (P) (N=375)
Overview of patients with liver monitoring according to SmPC	LFTs according to SmPC	7 (1.9%)
Overview of patients with liver monitoring according to SmPC	LFTs not according to SmPC	368 (98.1%)

NOTE: According to SmPC, liver function tests (from serum) should be performed in week 3, 5, 7 and 9 and in month 3 and 4 after start of pazopanib therapy.
A patient qualifying for group “LFTs according to SmPC” thus needs to have documentation of liver monitoring as follows (day 1 = first intake of pazopanib):
one test between day 15 and day 21, one test between day 29 and day 35,
one test between day 43 and day 49, one test between day 57 and day 63,
one test between day 64 and day 94, and one test between day 95 and day 125.
Source PAZOREAL TFL: Table 14.3.7b-1-1.1 Overview of patients with liver monitoring according to SmPC - 1st line pazopanib

AEs related to liver toxicity - 1st line pazopanib

Frequency of liver-related AEs in patients with LFTs according to SmPC and in patients with LFTs not according to SmPC are depicted in Table 10-45.

Table 10-45 AEs related to liver toxicity – 1st-line pazopanib

	LFTs according to SmPC	LFTs not according to SmPC
Total:	4	41
Alanine aminotransferase increased	1	14
Aspartate aminotransferase increased	2	14
Bilirubin conjugated increased	0	1
Blood alkaline phosphatase increased	1	9
Blood bilirubin increased	2	5
Gamma-glutamyltransferase increased	2	22
Liver disorder	0	1
Liver function test abnormal	0	10

Source: PAZOREAL TFL: Table 14.3.7c-1-1.1 AEs related to liver toxicity - 1st line pazopanib

Treatment discontinuation due to Liver toxicity – 1st-line pazopanib

Out of 7 patients with LFTs according to SmPC one patient (14.3%) and out of 368 patients without LFTs according SmPC 16 patients (4.3%) had a documented treatment discontinuation due to liver toxicity, respectively.

Table 10-46 Treatment discontinuation due to Liver toxicity – 1st-line pazopanib

	LFTs according to SmPC	LFTs not according to SmPC
Treatment discontinuation due to liver toxicity	1	16
No treatment discontinuation due to liver toxicity	6	352

Source: PAZOREAL TFL: Table 14.3.7d-1-1.1 Treatment discontinuation due to Liver toxicity - 1st line pazopanib

10.6.1 Clinical chemistry tests

At baseline, 75.5% of patients (n=285, SAF(P)) had a documented clinical chemistry test, while for 24.5% of patients (n=92) no test was performed (*PAZOREAL TFL: Table 14.3.6a-3-01 Overview of performed clinical chemistry tests (Baseline) - 1st line pazopanib*).

During treatment the number of performed clinical chemistry tests generally decreased: while at visit one 75.5% of patients had at least one documented test, at visit 4 only 30.4% of patients and at visit 8 only 14.7% of patients had at least one documented test, cf. Table 10-41. This trend applied also for performed tests in patients with subsequent 2nd-line nivolumab treatment

(SAF(N)), while generally the proportion of patients with at least one documented test remained stable compared to 1st-line treatment period, for details refer to appendix *PAZOREAL TFL: Table 14.3.6a-3-3.3 Overview of performed clinical chemistry tests - 2nd line nivolumab*.

Table 10-47 Overview of performed clinical chemistry tests – 1st-line pazopanib

		Number of performed tests					
Visits*	**No test performed**	**1**	**2**	**3**	**4**	**≥5**	**Total****
Visit 01	90 (24.0%)	214 (57.1%)	26 (6.9%)	12 (3.2%)	10 (2.7%)	21 (5.6%)	373 (99.5%)
Visit 02	40 (10.7%)	158 (42.1%)	17 (4.5%)	11 (2.9%)	6 (1.6%)	2 (0.5%)	234 (62.4%)
Visit 03	23 (6.1%)	119 (31.7%)	9 (2.4%)	9 (2.4%)	3 (0.8%)	1 (0.3%)	164 (43.7%)
Visit 04	25 (6.7%)	98 (26.1%)	10 (2.7%)	5 (1.3%)	1 (0.3%)		139 (37.1%)
Visit 05	22 (5.9%)	75 (20.0%)	4 (1.1%)	2 (0.5%)		1 (0.3%)	104 (27.7%)
Visit 06	17 (4.5%)	60 (16.0%)	6 (1.6%)	2 (0.5%)	1 (0.3%)		86 (22.9%)
Visit 07	16 (4.3%)	50 (13.3%)	7 (1.9%)	1 (0.3%)	1 (0.3%)		75 (20.0%)
Visit 08	12 (3.2%)	49 (13.1%)	5 (1.3%)	2 (0.5%)			68 (18.1%)
Visit 09	15 (4.0%)	40 (10.7%)	1 (0.3%)		1 (0.3%)		57 (15.2%)
Visit 10	11 (2.9%)	31 (8.3%)	2 (0.5%)	1 (0.3%)			45 (12.0%)
Visit 11	11 (2.9%)	28 (7.5%)		2 (0.5%)			41 (10.9%)
Visit 12	8 (2.1%)	27 (7.2%)	1 (0.3%)	1 (0.3%)	1 (0.3%)		38 (10.1%)
Visit 13	8 (2.1%)	23 (6.1%)	3 (0.8%)		1 (0.3%)		35 (9.3%)
Visit 14	10 (2.7%)	21 (5.6%)			2 (0.5%)		33 (8.8%)
Visit 15	7 (1.9%)	17 (4.5%)		1 (0.3%)			25 (6.7%)
Visit 16	6 (1.6%)	12 (3.2%)		1 (0.3%)			19 (5.1%)

(Continued)

* The displayed visits equal the documented 'Verlaufsvisiten' from the edc.

** This column shows the total number of patients for those at least one information concerning laboratory tests is available for the respective visit.

The table should be read as follows: e.g. 214 patient(s) had 1 test documented during visit 1 of 1st-line treatment.

All percentages refer to the total number of patients included in the Safety Set - 1st-line pazopanib (N=375).

Source PAZOREAL TFL: Table 14.3.6a-3-3.1 Overview of performed clinical chemistry tests - 1st line pazopanib

For respective details of clinical chemistry tests for cohort I and cohort II and each study drug refer to appendix *PAZOREAL TFL: Table 14.3.6a-3*.

Abnormal clinical chemistry test results

An overview of abnormal results per documentation period (i.e. baseline, visit 01- visit 04) is provided in appendix *PAZOREAL TFL: Table 14.3.6c-5-3.1 – 5 and 14.3.6c-5-4.2*.

Before 1st-line pazopanib treatment for 375 patients available data on clinical chemistry tests were documented, while for 71 patients no test was performed, in 99 patients each performed test detected no abnormal result and in 205 patients each performed test discovered an abnormal result. During treatment for the majority of patients the rate of abnormal results is 100%. (cf. Table 10-48) This applies also for respective rate of abnormal results during 2nd-line nivolumab treatment (cf. Table 10-49)

Table 10-48 Rate of abnormal clinical chemistry test results per documentation period – 1st-line pazopanib

Rate	Baseline	Visit 01	Visit 02	Visit 03	Visit 04
Total**	375	373	234	164	139
0 %	99	90	69	64	40
16.67 %		1			
33.33 %		1	1	1	1
40.00 %		1			
50.00 %		6	2	4	3
57.14 %		1			
60.00 %		4			
66.67 %		3	3		
75.00 %		1			
80.00 %		4			
83.33 %		1		1	
85.71 %		1			
90.00 %			1		
100 %	205	183	127	74	75
No test performed	71	76	31	20	20

Data is based on the reported information on the eCRF form 'Laborbefunde'.
Baseline period = 0-3 months, visit 01 = 3-6 months, visit 02 = 6-9 months after start of treatment, and so on (+/- 1.5 months each).
* For this period no laboratory test was performed.
** Total number of patients for whom data on laboratory tests in the respective period was available / reported in the eCRF.

Source: PAZOREAL TFL: Table 14.3.6c-6-3.1 Rate of abnormal clinical chemistry test results per documentation period - 1st line pazopanib

Table 10-49 Rate of abnormal clinical chemistry test results per documentation period – 2nd-line nivolumab

Rate	Baseline	Visit 01	Visit 02	Visit 03	Visit 04
	N.A.*				
Total**		163	97	62	47
0 %		26	28	16	14
33.33 %		1			
50.00 %		1			1
66.67 %		1			
80.00 %		1			
85.71 %			1		1
100 %		87	57	40	25
No test performed		46	11	6	6

Data is based on the reported information on the eCRF form 'Laborbefunde'.
Baseline period = 0-3 months, visit 01 = 3-6 months, visit 02 = 6-9 months after start of treatment, and so on (+/- 1.5 months each).
* For this period no laboratory test was performed.
** Total number of patients for whom data on laboratory tests in the respective period was available / reported in the eCRF.

Source: PAZOREAL TFL: Table 14.3.6c-6-3.3 Rate of abnormal clinical chemistry test results per documentation period - 2nd line nivolumab

For respective details of rate of abnormal clinical chemistry test results for cohort I and cohort II and each study drug refer to appendix *PAZOREAL TFL: Table 14.3.6c-6-3.1-5 and Table 14.3.6c-6-4.2*.

10.7 Adverse events/adverse reactions

Evaluation of adverse events was performed for all patients in the SAF (N=375), cohort I.
Details for adverse events for FAS^{ext} are provided in the appendix (*PAZOREAL TFL: Table 14.3.1b-c labeled with SAF(extended)).*

10.7.1 Brief summary of Adverse Events

Cohort I: 1st-line pazopanib

Data on TEAEs are summarized in Table 10-50.

In 337 (89.9%) patients with 1st line pazopanib treatment 1923 TEAEs were documented and of those 1038 (54.0%) were judged to be related to pazopanib. These 1038 events occurred in 270 patients (72.0%). Furthermore, 368 serious TEAEs (19.1%) in 176 patients (46.9%) were reported. Of these 368 serious TEAEs, 89 (4.6%) were assessed as being related to pazopanib in 55 patients (14.7%).

There were 368 TEAEs grade 3/4 (19.1%) occurring in 179 patients (47.7%), out of which 151 TEAEs grade 3/4 (7.9%) in 95 patients (25.3%) were assessed as being related to pazopanib.

223 TEAEs (11.6%) in 129 patients (34.4%) led to discontinuation of treatment. Of these, 115 (6.0%) were assessed to be related to pazopanib and were experienced by 66 patients (17.6%).

75 fatal TEAEs (3.9%) were reported in 71 (18.9%) patients. Of these 75 fatal TEAEs, 3 (0.2%) occurring in 3 patients (0.8%) were assessed as being related to pazopanib.

Table 10-50 Summary of adverse events (treatment-emergent) - 1st-line pazopanib

	Patients N=375	Cases N=1923
TEAE	337 (89.9%)	1923 (100.0%)
Related TEAE	270 (72.0%)	1038 (54.0%)
TESAE	176 (46.9%)	368 (19.1%)
Related TESAE	55 (14.7%)	89 (4.6%)
TEAE grade 3/4	179 (47.7%)	368 (19.1%)
Related TEAE grade 3/4	95 (25.3%)	151 (7.9%)
TEAE leading to discontinuation of treatment	129 (34.4%)	223 (11.6%)
Related TEAE leading to discontinuation of treatment	66 (17.6%)	115 (6.0%)
Fatal TEAE	71 (18.9%)	75 (3.9%)
Related fatal TEAE	3 (0.8%)	3 (0.2%)

An adverse event is classified as Treatment Emergent Adverse Event (TEAE) if it is temporally related to the study medication, administered in the respective therapy line.
Temporally means from the day of first dose of study medication to 30 days after last dose of study medication within the therapy line.
For the determination of a fatal Adverse Event the following points were considered:
- CTCAE severity grade = 5 and/or
- Outcome of AE = fatal and/or
- Reason for seriousness = death

Source: PAZOREAL TFL: Table 14.3.1a-1-3.1 Summary of adverse events (treatment-emergent) - 1st line pazopanib

In the population of trial-eligible patients receiving 1st-line treatment with Pazopanib 133 (91.1%) out of 146 patients experienced 708 TEAEs (cf. Table 10-51). Of these, 427 (60.3%) TEAEs were judged as related to Pazopanib, occurring in 114 patients (78.1%). 108 TEAEs were assessed as serious, emerging in 57 (39.0%) patients. 19 (13.0%) patients experienced serious TEAEs which were judged to be related to Pazopanib. The total number of related TESAEs was 31 (4.4%).

119 (16.8%) TEAEs grade 3/4 happened to 65 patients (44.5%), of which 61 (8.6%) were assessed as related to Pazopanib, occurring in a total of 39 (26.7%) patients.

79 (11.2%) TEAEs led to discontinuation of treatment with Pazopanib and were experienced by 42 (28.8%) patients. For 28 (19.2%) out of these 42 patients 54 (7.6%) TEAEs leading to dscontinuation were assessed as related to Pazopanib.

The number of fatal TEAEs was 20 (13.7%), occurring in 21 (3.0%) patients including 1 (0.1%) fatal TEAE in 1 (0.7%) patient that was assessed as related to Pazopanib.

Table 10-51 Summary of TEAE of trial-eligible patients – 1st-line pazopanib

	Patients N=146	Cases
TEAE	133 (91.1%)	708 (100.0%)
Related TEAE	114 (78.1%)	427 (60.3%)
TESAE	57 (39.0%)	108 (15.3%)
Related TESAE	19 (13.0%)	31 (4.4%)
TEAE grade 3/4	65 (44.5%)	119 (16.8%)
Related TEAE grade 3/4	39 (26.7%)	61 (8.6%)
TEAE leading to discontinuation of treatment	42 (28.8%)	79 (11.2%)
Related TEAE leading to discontinuation of treatment	28 (19.2%)	54 (7.6%)
Fatal TEAE	20 (13.7%)	21 (3.0%)
Related fatal TEAE	1 (0.7%)	1 (0.1%)

An adverse event is classified as Treatment Emergent Adverse Event (TEAE) if it is temporally related to the study medication, administered in the respective therapy line.
Temporally means from the day of first dose of study medication to 30 days after last dose of study medication within the therapy line.
For the determination of a fatal Adverse Event the following points were considered:
- CTCAE severity grade = 5 and/or
- Outcome of AE = fatal and/or
- Reason for seriousness = death

Source: PAZOREAL TFL: Table 14.3.1a-2-3.1 Summary of adverse events (treatment-emergent) of trial-eligible patients - 1st line pazopanib

For a detailed summary of TEAEs of trial-ineligible patients refer to appendix *PAZOREAL TFL: Table 14.3.1a-3-3.1 Summary of adverse events (treatment-emergent) of trial-ineligible patients - 1st line pazopanib.*

Cohort I: 2nd-line nivolumab

For 163 patients receiving 2nd line nivolumab after 1st line treatment with pazopanib a total number of 400 TEAEs were reported occurring in 120 (73.6%) patients (cf. Table 10-52). Of these 400 TEAEs, 105 (26.3%) were assessed as being related to nivolumab and were recorded for 56 (34.4%) patients. Furthermore, 64 (39.3%) patients experienced 105 (26.3%) serious TEAEs, out of which 20 (5.0%) were judged to be related to nivolumab. These 20 related TESAEs happened to 15 (9.2%) patients.

86 (21.5%) TEAEs grade 3/4 were reported in this population that were experienced by 53 (32.5%) patients. Out of these, 23 (14.1%) patients experienced 28 (7.0%) TEAEs grade 3/4 which were assessed as being related to nivolumab.

In sum 56 (14.0%) TEAEs leading to discontinuation of treatment which was documented in 38 (23.3%) patients. Of these 19 (4.8%) TEAES were assessed as related to nivolumab.

In sum 22 (5.5%) fatal TEAEs were reported, occurring in 22 (13.5%) patients. No fatal TEAE was judged to be related to nivolumab.

Table 10-52 Summary of TEAE – 2nd-line nivolumab

	Patients N=163	Cases N=400
TEAE	120 (73.6%)	400 (100.0%)
Related TEAE	56 (34.4%)	105 (26.3%)
TESAE	64 (39.3%)	105 (26.3%)
Related TESAE	15 (9.2%)	20 (5.0%)
TEAE grade 3/4	53 (32.5%)	86 (21.5%)
Related TEAE grade 3/4	23 (14.1%)	28 (7.0%)
TEAE leading to discontinuation of treatment	38 (23.3%)	56 (14.0%)
Related TEAE leading to discontinuation of treatment	15 (9.2%)	19 (4.8%)
Fatal TEAE	22 (13.5%)	22 (5.5%)
Related fatal TEAE	0 (0.0%)	0 (0.0%)

An adverse event is classified as Treatment Emergent Adverse Event (TEAE) if it is temporally related to the study medication, administered in the respective therapy line.
Temporally means from the day of first dose of study medication to 30 days after last dose of study medication within the therapy line.
For the determination of a fatal Adverse Event the following points were considered:
- CTCAE severity grade = 5 and/or
- Outcome of AE = fatal and/or
- Reason for seriousness = death

Source: PAZOREAL TFL: Table 14.3.1a-1-3.3 Summary of adverse events (treatment-emergent) – 2nd line nivolumab

Cohort I: 2nd-line everolimus and 3rd-line everolimus

Due to the limited number of patients receiving 2nd line everolimus or 3rd line everolimus in cohort I, summarized data of treatment-emergent adverse events are provided in appendix *PAZOREAL TFL: Table 14.3.1a-1-3.2 Summary of adverse events (treatment-emergent) – 2nd line everolimus and Table 14.3.1a-1-3.5 Summary of adverse events (treatment-emergent) - 3rd line everolimus*.

Cohort II: 3rd-line everolimus

For an overview of treatment-emergent adverse events in cohort II, 3rd line Everolimus refer to appendix *PAZOREAL TFL: Table 14.3.1a-1-4.2 Summary of adverse events (treatment-emergent) - 3rd line everolimus*.

10.7.2 Summary of TEAEs in subgroups

Cohort I: 1st-line pazopanib

Table 10-53 shows a summary of TEAEs in 1st line Pazopanib by gender. For both groups the relative number of TEAEs is similar. 227 (88.7%) out of 256 male patients experienced TEAEs. This compares with 110 (92.4%) out of 119 female patients in which occurred TEAEs. For 25 (21.0%) female patients fatal TEAEs were recorded, with 2 (1.7%) of them being assessed as related to Pazopanib. On the other hand 46 (18.0%) male patients experienced fatal TEAEs, with 1 (0.4%) judged as related to Pazopanib.

Table 10-53 Summary of TEAE by gender – 1st-line pazopanib

	Patients in Safety population (N=375)	
	Female (N=119)	**Male (N=256)**
TEAE	110 (92.4%)	227 (88.7%)
Related TEAE	92 (77.3%)	178 (69.5%)
TESAE	57 (47.9%)	119 (46.5%)
Related TESAE	19 (16.0%)	36 (14.1%)
TEAE grade 3/4	55 (46.2%)	124 (48.4%)
Related TEAE grade 3/4	33 (27.7%)	62 (24.2%)
TEAE leading to discontinuation of treatment	45 (37.8%)	84 (32.8%)
Related TEAE leading to discontinuation of treatment	25 (21.0%)	41 (16.0%)
Fatal TEAE	25 (21.0%)	46 (18.0%)
Related fatal TEAE	2 (1.7%)	1 (0.4%)

An adverse event is classified as Treatment Emergent Adverse Event (TEAE) if it is temporally related to the study medication, administered in the respective therapy line.
Temporally means from the day of first dose of study medication to 30 days after last dose of study medication within the therapy line.
For the determination of a fatal Adverse Event the following points were considered:
- CTCAE severity grade = 5 and/or
- Outcome of AE = fatal and/or
- Reason for seriousness = death

Source: PAZOREAL TFL: Table 14.3.2a-1-3.1 Summary of adverse events (treatment-emergent) by gender - 1st line pazopanib

A more detailed overview of TEAEs in 1st-line Pazopanib by age at start of therapy line, by BMI at enrollment and by MSKCC score at enrollment is provided in the appendix *PAZOREAL*

TFL: Table 14.3.2a-2-3.1 Summary of adverse events (treatment-emergent) by age at start of therapy line - 1st line pazopanib, *Table 14.3.2a-3-3.1 Summary of adverse events (treatment-emergent) by BMI at enrollment - 1st line pazopanib* and *Table 14.3.2a-4-3.1 Summary of adverse events (treatment-emergent) by MSKCC Score at enrollment - 1st line pazopanib*.

Cohort I: 2nd-line nivolumab

In 2nd line nivolumab the relative number of patients with TEAEs was comparable in both patient-subgroups '<65 years' and '≥65 years' of age (cf. Table 10-54). 84 (73.7%) out of 114 patients ≥65 years experienced any TEAE, compared to 36 (73.5%) out of 49 patients <65 years. Of these 36 patients <65 years, 16 (32.7%) had TEAEs that were considered related to nivolumab, whereas 40 (35.1%) patients aged ≥65 years had TEAEs assessed as related to nivolumab. The number of patients <65 years with TEAEs leading to discontinuation of treatment was 9 (18.4%), with 2 (4.1%) being assessed as related to nivolumab. In the group of patients aged ≥65 years, 29 (25.4%) experienced TEAEs that led to discontinuation and for 13 (11.4%) patients these TEAEs were judged as being related to Nivolumab.

Appendix *PAZOREAL TFL: Table 14.3.2a-1-3.3 Summary of adverse events (treatment-emergent) by gender - 2nd line nivolumab* provides information for TEAEs by gender in 2nd line Nivolumab.

Table 10-54 Summary of TEAEs by age at start of therapy line – 2nd-line nivolumab

	Patients in Safety population (N=163)	
	<65 years (N=49)	≥65 years (N=114)
TEAE	36 (73.5%)	84 (73.7%)
Related TEAE	16 (32.7%)	40 (35.1%)
TESAE	18 (36.7%)	46 (40.4%)
Related TESAE	4 (8.2%)	11 (9.6%)
TEAE grade 3/4	14 (28.6%)	39 (34.2%)
Related TEAE grade 3/4	6 (12.2%)	17 (14.9%)
TEAE leading to discontinuation of treatment	9 (18.4%)	29 (25.4%)
Related TEAE leading to discontinuation of treatment	2 (4.1%)	13 (11.4%)
Fatal TEAE	6 (12.2%)	16 (14.0%)

An adverse event is classified as Treatment Emergent Adverse Event (TEAE) if it is temporally related to the study medication, administered in the respective therapy line.
Temporally means from the day of first dose of study medication to 30 days after last dose of study medication within the therapy line.
For the determination of a fatal Adverse Event the following points were considered:
- CTCAE severity grade = 5 and/or
- Outcome of AE = fatal and/or
- Reason for seriousness = death

Source: PAZOREAL TFL: Table 14.3.2a-2-3.3 Summary of adverse events (treatment-emergent) by age at start of therapy line - 2nd line nivolumab

10.7.3 Adverse events classified by CTCAE grade

Cohort I: 1st-line pazopanib

The most common TEAEs in 1st-line pazopanib are shown in Table 10-55. 337 (89.9%) patients had any event whereof 299 (79.7%) patients experienced grade 1/2 events and 179 (47.7%) patients grade 3/4 events. Gastrointestinal disorders were most frequently reported by patients as adverse events of any grade, with diarrhoea experienced by 138 (36.8%) patients, nausea by 84 (22.4%) patients and vomiting by 27 (7.2%) patients. Furthermore, 72 (19.2%) patients presented with fatigue, 47 (12.5%) patients with decreased appetite and 46 (12.3%) patients with hypertension. For a sorted overview of grade 1/2 events experienced by most of the patients refer to Table 10-56 and to Table 10-57 for grade 3/4 events, respectively.

Diarrhoea, which occurred in 130 (34.7%) patients, was the most commonly reported grade 1/2 adverse event, followed by nausea, reported by 75 (20.0%) patients and fatigue, reported by 66 (17.6%) patients, whereas hypertension, which occurred in 17 (4.5%) patients, was the most frequent grade 3/4 adverse event, followed by hypertensive crisis, reported by 12 (3.2%) patients, and increased gamma-glutamyltransferase, reported by 11 (2.9%) patients.

Table 10-55 TEAEs experienced by most of the patients – 1st-line pazopanib

	Total N=375		
Preferred Term	**Any CTCAE grade**	**Grade 1/2**	**Grade 3/4**
Patients with any event	337 (89.9%)	299 (79.7%)	179 (47.7%)
Diarrhoea	138 (36.8%)	130 (34.7%)	6 (1.6%)
Nausea	84 (22.4%)	75 (20.0%)	9 (2.4%)
Fatigue	72 (19.2%)	66 (17.6%)	5 (1.3%)
Decreased appetite	47 (12.5%)	46 (12.3%)	1 (0.3%)
Hypertension	46 (12.3%)	29 (7.7%)	17 (4.5%)
Dysgeusia	44 (11.7%)	43 (11.5%)	1 (0.3%)
Hair colour changes	34 (9.1%)	33 (8.8%)	1 (0.3%)
Malignant neoplasm progression	34 (9.1%)	1 (0.3%)	3 (0.8%)
Weight decreased	29 (7.7%)	27 (7.2%)	2 (0.5%)
Vomiting	27 (7.2%)	23 (6.1%)	4 (1.1%)
Hypothyroidism	21 (5.6%)	21 (5.6%)	
Thrombocytopenia	21 (5.6%)	13 (3.5%)	5 (1.3%)
Gamma-glutamyltransferase increased	20 (5.3%)	9 (2.4%)	11 (2.9%)
Palmar-plantar erythrodysaesthesia syndrome	19 (5.1%)	18 (4.8%)	1 (0.3%)
Stomatitis	19 (5.1%)	19 (5.1%)	

All numbers displayed in this table are based on the data which is available by the form 'Adverse Events'.

		Total N=375	
Preferred Term	**Any CTCAE grade**	**Grade 1/2**	**Grade 3/4**

Adverse event terms were encoded according to MedDRA version 20.0.

If a Preferred Term is reported more than once per patient the respective term with the highest reported severity grade is considered for the analysis.

Source: PAZOREAL TFL: Table 14.3.1b-6-3.1 Adverse events (treatment-emergent) experienced by most of the patients - 1st line pazopanib

Table 10-56 TEAEs of CTCAE grade 1/2 experienced by most of the patients - 1st-line pazopanib

CTCAE severity grade	Preferred Term	Total N=375
Grade 1/2	**Patients with any event**	299 (79.7%)
Grade 1/2	Diarrhoea	130 (34.7%)
Grade 1/2	Nausea	75 (20.0%)
Grade 1/2	Fatigue	66 (17.6%)
Grade 1/2	Decreased appetite	46 (12.3%)
Grade 1/2	Dysgeusia	43 (11.5%)
Grade 1/2	Hair colour changes	33 (8.8%)
Grade 1/2	Hypertension	29 (7.7%)
Grade 1/2	Weight decreased	27 (7.2%)
Grade 1/2	Vomiting	23 (6.1%)
Grade 1/2	Hypothyroidism	21 (5.6%)
Grade 1/2	Stomatitis	19 (5.1%)
Grade 1/2	Palmar-plantar erythrodysaesthesia syndrome	18 (4.8%)
Grade 1/2	Ageusia	16 (4.3%)
Grade 1/2	Blood pressure increased	15 (4.0%)
Grade 1/2	Dizziness	15 (4.0%)

All numbers displayed in this table are based on the data which is available by the form 'Adverse Events'.

Adverse event terms were encoded according to MedDRA version 20.0.

If a Preferred Term is reported more than once per patient the respective term with the highest reported severity grade is considered for the analysis.

Source: PAZOREAL TFL: Table 14.3.1b-4-3.1 Adverse events (treatment-emergent) of CTCAE grade 1/2 experienced by most of the patients - 1st line pazopanib

Table 10-57 TEAEs of CTCAE grade 3/4 experienced by most of the patients - 1st-line pazopanib

CTCAE severity grade	Preferred Term	Total N=375
Grade 3/4	**Patients with any event**	179 (47.7%)
Grade 3/4	Hypertension	17 (4.5%)

CTCAE severity grade	Preferred Term	Total N=375
Grade 3/4	Hypertensive crisis	12 (3.2%)
Grade 3/4	Gamma-glutamyltransferase increased	11 (2.9%)
Grade 3/4	Anaemia	9 (2.4%)
Grade 3/4	Nausea	9 (2.4%)
Grade 3/4	General physical health deterioration	8 (2.1%)
Grade 3/4	Pneumonia	7 (1.9%)
Grade 3/4	C-reactive protein increased	6 (1.6%)
Grade 3/4	Diarrhoea	6 (1.6%)
Grade 3/4	Hyperkalaemia	6 (1.6%)
Grade 3/4	Hyponatraemia	6 (1.6%)
Grade 3/4	Alanine aminotransferase increased	5 (1.3%)
Grade 3/4	Aspartate aminotransferase increased	5 (1.3%)
Grade 3/4	Dyspnoea	5 (1.3%)
Grade 3/4	Fatigue	5 (1.3%)

All numbers displayed in this table are based on the data which is available by the form 'Adverse Events'.

Adverse event terms were encoded according to MedDRA version 20.0.

If a Preferred Term is reported more than once per patient the respective term with the highest reported severity grade is considered for the analysis.

Source: PAZOREAL TFL: Table 14.3.1b-5-3.1 Adverse events (treatment-emergent) of CTCAE grade 3/4 experienced by most of the patients - 1st line pazopanib

A summary of all TEAEs of CTCAE grade 1/2, grade 3/4 and grade 5 in 1st-line Pazopanib is provided in appendix *PAZOREAL TFL: Table 14.3.1b-1-3.1, Table 14.3.1b-2-3.1* and *Table 14.3.1b-3-3.1*.

Cohort I: 2nd-line nivolumab

In 2nd-line nivolumab 120 (73.6%) patients experienced adverse events of any CTCAE grade. Thereof 96 patients (58.9%) had adverse events grade 1/2 and 53 (32.5%) patients had adverse events grade 3/4. Table 10-58 lists the most frequent reported preferred terms in 2nd line nivolumab. Gastrointestinal disorders were most often observed, followed by neoplasms. Diarrhoea was reported in 14 (8.6%) patients and nausea and vomiting each in 7 (4.3%) patients. 10 (6.1%) patients experienced a malignant neoplasm progression and 5 (3.1%) patients experienced a neoplasm progression.

A list of the most common adverse events sorted by frequency is provided in Table 10-59 for TEAEs of grade 1/2 and in Table 10-60 for TEAEs of grade 3/4. Gastrointestinal disorders as diarrhoea in 12 (7.4%) patients and nausea and vomiting both in 7 (4.3%) patients were the

adverse event of grade 1/2 that were most often reported, followed by skin disorders like rash in 8 (4.9%) patients and pruritus in 6 (3.7%) patients.

The most frequent reported adverse event of grade 3/4 was oedema peripheral which occurred in 4 (2.5%) patients.

Table 10-58 TEAEs experienced by most of the patients – 2nd-line nivolumab

	Total N=163		
Preferred Term	**Any CTCAE grade**	**Grade 1/2**	**Grade 3/4**
Patients with any event	120 (73.6%)	96 (58.9%)	53 (32.5%)
Diarrhoea	14 (8.6%)	12 (7.4%)	1 (0.6%)
Malignant neoplasm progression	10 (6.1%)	1 (0.6%)	
Oedema peripheral	9 (5.5%)	5 (3.1%)	4 (2.5%)
Rash	8 (4.9%)	8 (4.9%)	
Dyspnoea	7 (4.3%)	5 (3.1%)	2 (1.2%)
Fatigue	7 (4.3%)	7 (4.3%)	
Nausea	7 (4.3%)	7 (4.3%)	
Vomiting	7 (4.3%)	7 (4.3%)	
Anaemia	6 (3.7%)	5 (3.1%)	1 (0.6%)
Dizziness	6 (3.7%)	6 (3.7%)	
General physical health deterioration	6 (3.7%)	2 (1.2%)	3 (1.8%)
Pruritus	6 (3.7%)	6 (3.7%)	
Back pain	5 (3.1%)	5 (3.1%)	
Gamma-glutamyltransferase increased	5 (3.1%)	4 (2.5%)	1 (0.6%)
Neoplasm progression	5 (3.1%)	2 (1.2%)	

All numbers displayed in this table are based on the data which is available by the form 'Adverse Events'.

Adverse event terms were encoded according to MedDRA version 20.0.

If a Preferred Term is reported more than once per patient the respective term with the highest reported severity grade is considered for the analysis.

Source: PAZOREAL TFL: Table 14.3.1b-6-3.3 Adverse events (treatment-emergent) experienced by most of the patients - 2nd line nivolumab

Table 10-59 TEAEs of CTCAE grade 1/2 experienced by most of the patients - 2nd-line nivolumab

CTCAE severity grade	Preferred Term	Total N=163
Grade 1/2	**Patients with any event**	96 (58.9%)
Grade 1/2	Diarrhoea	12 (7.4%)
Grade 1/2	Rash	8 (4.9%)
Grade 1/2	Fatigue	7 (4.3%)

CTCAE severity grade	Preferred Term	Total N=163
Grade 1/2	Nausea	7 (4.3%)
Grade 1/2	Vomiting	7 (4.3%)
Grade 1/2	Dizziness	6 (3.7%)
Grade 1/2	Pruritus	6 (3.7%)
Grade 1/2	Anaemia	5 (3.1%)
Grade 1/2	Back pain	5 (3.1%)
Grade 1/2	Dyspnoea	5 (3.1%)
Grade 1/2	Oedema peripheral	5 (3.1%)
Grade 1/2	Arthralgia	4 (2.5%)
Grade 1/2	Constipation	4 (2.5%)
Grade 1/2	Gamma-glutamyltransferase increased	4 (2.5%)
Grade 1/2	Hypothyroidism	4 (2.5%)

All numbers displayed in this table are based on the data which is available by the form 'Adverse Events'.

Adverse event terms were encoded according to MedDRA version 20.0.

If a Preferred Term is reported more than once per patient the respective term with the highest reported severity grade is considered for the analysis.

Source: PAZOREAL TFL: Table 14.3.1b-4-3.3 Adverse events (treatment-emergent) of CTCAE grade 1/2 experienced by most of the patients - 2nd line nivolumab

Table 10-60 TEAEs of CTCAE grade 3/4 experienced by most of the patients – 2nd-line nivolumab

CTCAE severity grade	Preferred Term	Total N=163
Grade 3/4	**Patients with any event**	53 (32.5%)
Grade 3/4	Oedema peripheral	4 (2.5%)
Grade 3/4	Acute kidney injury	3 (1.8%)
Grade 3/4	General physical health deterioration	3 (1.8%)
Grade 3/4	Pain	3 (1.8%)
Grade 3/4	Pneumonia	3 (1.8%)
Grade 3/4	C-reactive protein increased	2 (1.2%)
Grade 3/4	Dyspnoea	2 (1.2%)
Grade 3/4	Pneumonitis	2 (1.2%)
Grade 3/4	Abscess limb	1 (0.6%)
Grade 3/4	Adrenal insufficiency	1 (0.6%)
Grade 3/4	Anaemia	1 (0.6%)
Grade 3/4	Anaemia of malignant disease	1 (0.6%)
Grade 3/4	Aphthous ulcer	1 (0.6%)
Grade 3/4	Aspartate aminotransferase increased	1 (0.6%)

CTCAE severity grade	Preferred Term	Total N=163
Grade 3/4	Asthenia	1 (0.6%)

All numbers displayed in this table are based on the data which is available by the form 'Adverse Events'.

Adverse event terms were encoded according to MedDRA version 20.0.

If a Preferred Term is reported more than once per patient the respective term with the highest reported severity grade is considered for the analysis.

Source: PAZOREAL TFL: Table 14.3.1b-5-3.3 Adverse events (treatment-emergent) of CTCAE grade 3/4 experienced by most of the patients - 2nd line nivolumab

For a fully detailed overview of all TEAEs of CTCAE grade 1/2, grade 3/4 and grade 5 in 2nd line nivolumab see appendix *PAZOREAL TFL: Table 14.3.1b-1-3.3, Table 14.3.1b-2-3.3 and Table 14.3.1b-3-3.3*.

Cohort I: 2nd-line everolimus and 3rd-line everolimus

A summary of all TEAEs of CTCAE grade 1/2, grade 3/4 and grade 5 in 2nd-line everolimus is provided in appendix *PAZOREAL TFL: Table 14.3.1b-1-3.2, Table 14.3.1b-2-3.2 and Table 14.3.1b-3-3.2*.

Details of TEAEs with CTCAE grade 1/2, grade 3/4 and grade 5 in 3rd line Everolimus are provided in appendix *PAZOREAL TFL: Table 14.3.1b-1-3.5, Table 14.3.1b-2-3.5 and Table 14.3.1b-3-3.5*.

Cohort II: 3rd line Everolimus

Appendix *PAZOREAL TFL: Table 14.3.1b-1-4.2, Table 14.3.1b-2-4.2 and Table 14.3.1b-3-4.2* show a complete list of all TEAEs of grade 1/2, grade 3/4 and grade 5 in 3rd line Everolimus after 2nd-line nivolumab.

10.7.4 Related adverse events

Cohort I: 1st-line pazopanib

In Table 10-61 treatment-emergent adverse events of grade 1/2 related to pazopanib are displayed which occurred in more than 5.0% of patients in the SAF.

Gastrointestinal disorders were the most common TEAEs grade 1/2 assessed as related to pazopanib with 167 (44.5%) patients being affected by at least one adverse event in this SOC, followed by general disorders and administration site conditions and skin and subcutaneous tissue disorders, each with at least one documented adverse event in 75 (20.0%) patients. Specifically, diarrhoea was observed in 116 (30.9%) patients and nausea in 60 (16.0%) patients. Furthermore, fatigue was reported as TEAE with causal relationship to pazopanib for 47 (12.5%) patients. 39 (10.4%) patients experienced dysgeusia which was assessed as related to

pazopanib, while 35 (9.3%) patients reported decreased appetite which was judged as related to pazopanib. Pazopanib-related hypertension was documented for 25 (6.7%) patients.

The full patient-based list of all related TEAEs grade 1/2 in 1st-line pazopanib is provided in appendix *PAZOREAL TFL: Table 14.3.1c-1-3.1 Related adverse events (treatment-emergent) of CTCAE grade 1/2 - 1st line pazopanib*.

Table 10-61 TEAEs of CTCAE grade 1/2 – 1st-line pazopanib

CTCAE severity grade	Primary System Organ Class	Preferred Term	Total N=375
Grade 1/2	**Patients with any event**		250 (66.7%)
	Gastrointestinal disorders	**Patients with any event**	167 (44.5%)
		Diarrhoea	116 (30.9%)
		Nausea	60 (16.0%)
		Stomatitis	19 (5.1%)
	General disorders and administration site conditions	**Patients with any event**	75 (20.0%)
		Fatigue	47 (12.5%)
	Skin and subcutaneous tissue disorders	**Patients with any event**	75 (20.0%)
		Hair colour changes	33 (8.8%)
	Nervous system disorders	**Patients with any event**	71 (18.9%)
		Dysgeusia	39 (10.4%)
	Metabolism and nutrition disorders	**Patients with any event**	40 (10.7%)
		Decreased appetite	35 (9.3%)
	Vascular disorders	**Patients with any event**	34 (9.1%)
		Hypertension	25 (6.7%)

All numbers displayed in this table are based on the data which is available by the form 'Adverse Events'.

Adverse event terms were encoded according to MedDRA version 20.0.

If a Preferred Term is reported more than once per patient the respective term with the highest reported severity grade is considered for the analysis.

Source: PAZOREAL TFL: Table 14.3.1c-1-3.1 Related adverse events (treatment-emergent) of CTCAE grade 1/2 - 1st line pazopanib

The most frequently reported TEAEs of CTCAE grade 3/4 with causal relationship to pazopanib are shown in Table 10-62. Data presented were adjusted for all events that occurred in at least 5 patients.

For the full data set of all related TEAEs grade 3/4 in 1st-line pazopanib refer to appendix *PAZOREAL TFL: Table 14.3.1c-2-3.1 Related adverse events (treatment-emergent) of CTCAE grade 3/4 - 1st line pazopanib*.

Overall, 95 (25.3%) patients experienced TEAEs grade 3/4 related to pazopanib. Most related TEAEs grade 3/4 in 1st-line pazopanib involved investigations and vascular disorders with 28 (7.5%) patients in each of the two SOCs affected by at least one adverse event of CTCAE grade 3/4. Hypertension, experienced by 16 (4.3%) patients and hypertensive crisis, experienced by 9 (2.4%) patients were the most common preferred terms reported as TEAE grade 3/4 with causal relationship to pazopanib. Gastrointestinal disorders of grade 3/4 which were assessed as related to pazopanib occurred less frequently than those of grade 1/2.

Three (0.8%) patients experienced fatal TEAEs of grade 5 that were judged as related to pazopanib by the respective investigators: For 1 (0.3%) patient each, death (reported event verbatim: death without witnesses), disease progression or neoplasm progression was reported. The CTCAE grade for adverse events related to pazopanib was completely missing in 6 (1.6%) patients (cf. appendix *PAZOREAL TFL: Table 14.3.1c-3-3.1 Related adverse events (treatment-emergent) of CTCAE grade 5 - 1st line pazopanib* for more details).

Table 10-62 TEAEs of CTCAE grade 3/4 – 1st-line pazopanib

CTCAE severity grade	Primary System Organ Class	Preferred Term	Total N=375
Grade 3/4	**Patients with any event**		95 (25.3%)
	Investigations	**Patients with any event**	28 (7.5%)
		Gamma-glutamyltransferase increased	8 (2.1%)
		Alanine aminotransferase increased	5 (1.3%)
		Aspartate aminotransferase increased	5 (1.3%)
	Vascular disorders	**Patients with any event**	28 (7.5%)
		Hypertension	16 (4.3%)
		Hypertensive crisis	9 (2.4%)
	Gastrointestinal disorders	**Patients with any event**	19 (5.1%)
		Nausea	7 (1.9%)
		Diarrhoea	6 (1.6%)
	General disorders and administration site conditions	**Patients with any event**	11 (2.9%)
		Fatigue	5 (1.3%)

All numbers displayed in this table are based on the data which is available by the form 'Adverse Events'.

Adverse event terms were encoded according to MedDRA version 20.0.

If a Preferred Term is reported more than once per patient the respective term with the highest reported severity grade is considered for the analysis.

Source: PAZOREAL TFL: Table 14.3.1c-2-3.1 Related adverse events (treatment-emergent) of CTCAE grade 3/4 - 1st line pazopanib

Cohort I: 2nd-line nivolumab

Altogether, 40 (24.5%) patients in 2nd-line nivolumab experienced TEAEs of CTCAE grade 1/2 with causal relationship to nivolumab. Gastrointestinal disorders, which occurred in 14 (8.6%) patients, and skin and subcutaneous tissue disorders, which occurred in 13 (8.0%) patients, were reported most frequently, with diarrhoea in 9 (5.5%) patients being the most common preferred term. As no related TEAEs grade 1/2 other than diarrhoea occurred in more than 5.0% of patients, the full list is provided in appendix *PAZOREAL TFL: Table 14.3.1c-1-3.3 Related adverse events (treatment-emergent) of CTCAE grade 1/2 - 2nd line nivolumab* only.

For 23 (14.1%) patients at least one TEAE of grade 3/4 was assessed as related to nivolumab. No specific TEAE was reported for more than 2 (1.2%) patients. Therefore the full list is shown in appendix *PAZOREAL TFL: Table 14.3.1c-2-3.3 Related adverse events (treatment-emergent) of CTCAE grade 3/4 - 2nd line nivolumab*.

No fatal TEAEs grade 5 related to nivolumab occurred in this non-interverntional study. For 2 (1.2%) patients a TEAE was reported which was assessed as related to nivolumab but the CTCAE grade was missing (cf. appendix *PAZOREAL TFL: Table 14.3.1c-3-3.3 Related adverse events (treatment-emergent) of CTCAE grade 5 - 2nd line nivolumab*).

Cohort I: 2nd-line everolimus and 3rd-line everolimus

In 2nd line Everolimus no TEAEs of any grade were assessed as related to Everolimus (cf. appendix *PAZOREAL TFL: Table 14.3.1c-1-3.2, Table 14.3.1c-2-3.2 and Table 14.3.1c-3-3.2*).

For 5 (55.6%) patients in 3rd-line everolimus investigators assessed at least one TEAE grade 1/2 as related to everolimus and for 2 (22.2%) patients at least one TEAE grade 3/4 as related to everolimus. No patient experienced a related TEAE grade 5 in 3rd-line everolimus. Refer to appendix *PAZOREAL TFL: Table 14.3.1c-1-3.5, Table 14.3.1c-2-3.5 and Table 14.3.1c-3-3.5* for more details.

Cohort II: 3rd-line everolimus

As data for 3rd-line everolimus after 2nd-line nivolumab (cohort II) are limited, the results of TEAEs related to everolimus are provided in appendix *PAZOREAL TFL: Table 14.3.1c-1-4.2, Table 14.3.1c-2-4.2 and Table 14.3.1c-3-4.2* only.

10.7.5 Adverse events with relationship to concomitant medication

In 1st-line pazopanib 27 (7.2%) patients experienced adverse events, for which the investigator suspected a causal relationship to concomitant medication. Gastrointestinal complaints were most often associated with the patient´s concomitant medication. For 12 (7.4%) patients in 2nd-line nivolumab the investigator assessed TEAEs as possibly related to concomitant medication. Due to the limited number of patients in lines with Everolimus investigators only evaluated TEAEs for 1 (11.1%) patient with causal relationship to concomitant medication in 3rd-line everolimus (cohort I).

A complete overview for all lines in cohort I and cohort II is shown in appendix *PAZOREAL TFL: Table 14.3.1d-3.1* to *Table 14.3.1d-3.5* and *Table 14.3.1d-4.2*.

10.7.6 Related adverse events leading to discontinuation of treatment

The most important related adverse events grade 1/2 leading to discontinuation of pazopanib treatment are displayed in Table 10-63. Overall, for 44 (11.7%) patients a CTCAE grade 1/2 TEAE was responsible for end of treatment in 1st-line pazopanib. Most often, the discontinuation of pazopanib treatment was caused by gastrointestinal disorders related to pazopanib which happened in 17 (4.5%) patients, followed by increased laboratory values associated with pazopanib and other related adverse events involved in investigations in 13 (3.5%) patients. For the complete summary refer to appendix *PAZOREAL TFL: Table 14.3.1e-1-3.1 Related adverse events of CTCAE grade 1/2 leading to treatment discontinuation - 1st line pazopanib*.

Increased liver values associated with pazopanib and other related adverse events involved in investigations, which occurred in 14 (3.7%) patients, were the main related adverse events grade 3/4 leading to discontinuation of pazopanib treatment (cf. Table 10-64). In total, 35 (9.3%) patients experienced a grade 3/4 TEAE that caused the end of treatment. The full table is provided in appendix *PAZOREAL TFL: Table 14.3.1e-2-3.1 Related adverse events of CTCAE grade 3/4 leading to treatment discontinuation - 1st line pazopanib*.

Table 10-63 Related AEs of CTCAE grade 1/2 leading to treatment discontinuation – 1st-line pazopanib

CTCAE severity grade	Primary System Organ Class	Preferred Term	Total N=375
Grade 1/2	**Patients with any event**		44 (11.7%)
	Gastrointestinal disorders	**Patients with any event**	17 (4.5%)
		Diarrhoea	6 (1.6%)
		Nausea	5 (1.3%)
		Abdominal pain	3 (0.8%)
		Vomiting	3 (0.8%)
	Investigations	**Patients with any event**	13 (3.5%)
		Blood lactate dehydrogenase increased	3 (0.8%)
		Liver function test abnormal	3 (0.8%)
	General disorders and administration site conditions	**Patients with any event**	7 (1.9%)
		Fatigue	4 (1.1%)

All numbers displayed in this table are based on the data which is available by the form 'Adverse Events'.

Adverse event terms were encoded according to MedDRA version 20.0.

If a Preferred Term is reported more than once per patient the respective term with the highest reported severity grade is considered for the analysis.

Source: PAZOREAL TFL: Table 14.3.1e-1-3.1 Related adverse events of CTCAE grade 1/2 leading to treatment discontinuation - 1st line pazopanib

Table 10-64 Related AEs of CTCAE grade 3/4 leading to treatment discontinuation – 1st-line pazopanib

CTCAE severity grade	Primary System Organ Class	Preferred Term	Total N=375
Grade 3/4	**Patients with any event**		35 (9.3%)
	Investigations	**Patients with any event**	14 (3.7%)
		Aspartate aminotransferase increased	4 (1.1%)
		Alanine aminotransferase increased	3 (0.8%)
		Gamma-glutamyltransferase increased	3 (0.8%)
		Liver function test increased	3 (0.8%)
	Hepatobiliary disorders	**Patients with any event**	6 (1.6%)
		Drug-induced liver injury	2 (0.5%)
	General disorders and administration site conditions	**Patients with any event**	4 (1.1%)
		Fatigue	3 (0.8%)

All numbers displayed in this table are based on the data which is available by the form 'Adverse Events'.

Adverse event terms were encoded according to MedDRA version 20.0.

If a Preferred Term is reported more than once per patient the respective term with the highest reported severity grade is considered for the analysis.

Source: PAZOREAL TFL: Table 14.3.1e-2-3.1 Related adverse events of CTCAE grade 3/4 leading to treatment discontinuation - 1st line pazopanib

A summary of all related adverse events of CTCAE grade 1/2 and grade 3/4, respectively, that led to discontinuation of Nivolumab treatment in 2nd line Nivolumab is provided in appendix *PAZOREAL TFL: Table 14.3.1e-1-3.3 Related adverse events of CTCAE grade 1/2 leading to treatment discontinuation - 2nd line nivolumab* and *Table 14.3.1e-2-3.3 Related adverse events of CTCAE grade 3/4 leading to treatment discontinuation - 2nd line nivolumab*.

Due to the limited number of patients in 2nd-line everolimus and 3rd-line everolimus in cohort I and 3rd-line everolimus in cohort II, no related adverse events of CTCAE grade 1/2 and grade 3/4, respectively, leading to discontinuation of everolimus treatment were recorded in these lines (cf. appendix *PAZOREAL TFL: Table 14.3.1e-1-3.2, Table 14.3.1e-2-3.2, Table 14.3.1e-1-3.5, Table 14.3.1e-2-3.5, Table 14.3.1e-1-4.2* and *Table 14.3.1e-2-4.2*.

11 Discussion

11.1 Key results

These data from the final analysis of PAZOREAL give an insight into the effectiveness, tolerability, safety and health-related QoL in patients with unresectable or metastatic RCC starting with either their first systemic therapy with pazopanib or 3rd-line everolimus following nivolumab within treatment reality of practice-based oncologists in Germany.

Between 10-Dec-2015 and 22-Dec-2017, 427 patients were enrolled in PAZOREAL and 398 patients were treated. In the analysis population FAS, 376 patients were assigned to cohort I and were treated with pazopanib in 1st-line setting (FAS(P)), while 6 patients were assigned to cohort II (i.e. observation start: treatment with everolimus in 3rd-line setting). After 1st-line pazopanib, 163 patients were treated with nivolumab in 2nd-line (FAS(N)) and of these 9 patients received the 3rd-line treatment everolimus. During the course of the study, 174 patients of cohort I and 5 patients of cohort II died. The median observation time (first prescription of pazopanib for cohort I until last contact or death) was 44.6 months (95% CI: 43.2 – 47.1).

Patients' characteristics are comparable to other studies: At enrollment, the majority of patients were male (n=257, 68.4%) and had a median body mass index (BMI) of 26.4 kg/m² (range 16.8-58.4) (Goebell et al., 2018a). Most of the patients had an ECOG performance status of 0 or 1 (n=301, 80.1%), indicating a good baseline performance status (Escudier et al., 2014). Median time from primary diagnosis of RCC to the first administration of pazopanib was 11.0 months (Goebell et al., 2018a; Cora N Sternberg et al., 2010) with a broader range of 0.2 to 339.3 months than previously reported 0 to 184.0 months (Cora N Sternberg et al., 2010).

The majority of the patients presented with metastatic disease (n=353, 93.9%). The main sites for metastases were lung, bone, liver and lymph nodes (58.0%, 25.5%, 16.2%, 26.1%) (Cora N Sternberg et al., 2010; Sternberg et al., 2013).

The vast majority of tumors showed a clear cell histology (80.9%).(Cora N Sternberg et al., 2010) Compared to pivotal studies (Cora N Sternberg et al., 2010; Sternberg et al., 2014, 2013) with reported median age of 59 years (range 28.0-85.0 years, VEG105192, clinicaltrial.gov identifier NCT00334282) and of 65years (range 25.0-80.0 years, VEG107769, clinicaltrial.gov identifier NCT00387764) in PAZOREAL the median age was comparable higher: at baseline, in cohort I the median age was 69.7 years (range 38.5-89.2 years) and most of the patients receiving 1st-line pazopanib, FAS(P) were older than 65 years (n=244, 64.9%). Also, patients receiving subsequent 2nd-line nivolumab (FAS(N)) were mostly older than 65 years (n=114, 69.9%).

In the FAS(P), 146 patients (38.8%) identified as trial-eligible (i.e. not meeting any of the trial-ineligibility criteria KPS<70, Haemoglobin < lower limit of normal, non-clear cell carcinoma histology) and in the FAS (N) study population 64 patients (39.3%). The proportion of trial-eligible patients is comparable smaller than previously reported data of prospective, multicenter German cohort study with 57% "trial-ineligible" patients (Marschner et al., 2017).

The MSKCC risk score was available in 85 (22.6%) patients and could be unambiguously categorized according to the MSKCC criteria. Of those, 20 patients (23.5%) had favorable risk, 52 patients (61.2%) were assigned to the intermediate-risk group, and 13 patients (15.3%) were

categorized as poor risk. Of note, available proportion of MSKCC risk groups is distinct from reported MSKCC risk groups, i.e. 39%, 55% and 3% of patients with favorable, intermediate and poor risk in the pivotal study (Cora N Sternberg et al., 2010).

The overall mToD for 1st-line pazopanib, i.e. start date of first pazopanib administration until end date of last administration of any study medication (i.e. either 1st-line pazopanib, 2nd-line everolimus or nivolumab or 3rd-line everolimus), was 10.0 (95% CI: 8.5-11.7) months. The 6-month time on drug rate was 66.7% (95% CI: 61.6-71.2%). In the respective trial-eligible population, overall mToD was 11.3 (95% CI: 9.2-14.3) months and the 6-month time on drug rate was 70.5% (95% CI: 62.4-77.2%).

In the FAS(P), pazopanib 1st-line mToD was 6.3 (95% CI: 5.6-7.4) months and in accordance to previous data (Cora N Sternberg et al., 2010). However mToD observed in other previous studies were comparably longer with 8.1months (COMPARZ-study, clinicaltrials.gov identifier NCT00720941 (Motzer et al., 2014, 2013)) and 9.7 months (Sternberg et al., 2013). The 6-month time on drug rate was 52.2% (95% CI: 47.0 - 57.1%). In the respective trial-eligible population, the mToD was 7.7 (95% CI: 6.1-9.0) months and the 6-month time on drug rate was 58.9% (95% CI: 50.5 - 66.4%). Sensititvity analyses revealed no differences between subgroups, e.g. tumor histology seems to have no impact on mToD.

In the FAS(N), nivolumab 2nd-line mToD was 4.8 (95% CI: 3.7-6.5) months and in accordance to previous data months (5.5 months, range, <0.1 to 29.6, (Motzer et al., 2015c)) and the 6-month time on drug rate was 43.9% (95% CI: 36.1 - 51.4%). For respective trial-eligible patients mToD was 3.9 (95% CI: 3.1-6.7) months and the 6-month time on drug rate was 42.2% (95% CI: 30.0 - 53.8%). Again, subgroup analyses revealed no differences.

The overall mOS for patients started with 1st-line pazopanib (mOS1) was 35.9 (95% CI: 28.2-48.3) months whereas trial- eligible patients achived a mOS of 53.2 (95% CI: 38.9-NA) months. Of note, 12-month OS rate of both populations were similar with 71.5% (95% CI: 66.4-76.0%) and 77.9% (95% CI: 69.9-84.0%). However, while present mOS1 is longer compared to previous data of the phase III non-inferiority study COMPARZ (comparing pazopanib to sunitinib) with a mOS of 28.3 (26.0, 35.5) months (Motzer et al., 2014), present mOS1 is accordance with previously reported mOS of 34.4 months, (95% CI: 29.5–39.3) of the retrospective, observational study PAMERIT (Mosca et al., 2021). Further, other studies showed a prolongiation of mOS with the sequential use of everolimus (4.9months (Motzer et al., 2010)) or nivolumab (25months (Motzer et al., 2015c)).

Median OS after start of 2nd-line treatment (mOS2) was 30.4 months (95% CI: 22.6-NA) with nivolumab and 26.6 months (95% CI: 9.6-NA) with other 2nd-line treatments. Sensitivity analyses showed no difference between subgoups. Present mOS2 for patients started with 2nd-line nivolumab is similar to previously reported mOS for 2nd-line nivolumab (25.0 months, 95% CI: 21.8-NA) (Motzer et al., 2015a).

In FAS (P) CR as best response was achieved in 36 patients (9.57%) and SD, definded as non-CR or non-PD, in 178 patients (47.34%). PD was the best response in 81 patients (21.54%). Tumor response in the real world setting showed a DCR (comprised by patients with CR and SD) of 56.91% (95% CI: 51.86-61.83%) with 1st-line pazopanib. Treatment with 2nd-line nivolumab achieved a DCR of 43.56% (95% CI: 36.18-51.23%).

Of patients with 1st-line pazopanib treatment 212 patients (56.4%) had a progressive disease and of these 127 patients (33.8%) received the subsequent 2nd-line treatment with either nivolumab or everolimus. Of patients with 2nd-line nivolumab treatment 96 patients (58.9%) had a progressive disease and of these 9 patients (5.5%) received the subsequent 3rd-line treatment with everolimus and 54 patients (33.1%) received an other subsequent antineoplastic therapy.

The majority of patients (66%, FAS (P)) started with full dose pazopanib (800 mg/day). This is similar to reported real world data showing a initial daily dose of 800mg in 76.4% of patients (Mosca et al., 2021). The lowest documented dose during the course of treatment was 800 mg/day in 39.6%, 400 mg/day in 43.6%, while only <10% of patients received less than 400 mg as lowest administered dose. For most of patients (69.7%) no dose interruption was necessary. Documented dose interruptions were mostly due to adverse events (13.3%) or toxicity (14.9%). Dose reductions mainly resulted from the treating physician's decisions (42.0%) rather than from adverse events (6.1%) or toxicity (29.0%). EOT was mainly caused by progressive disease in about half of the patients (52.4%), other EOT reasons were toxicity (13.6%), adverse events (5.9%) and death (5.9%).

Before start of 1st-line pazopanib treatment, 81.1% of patients (SAF(P)) had a documented LFT, while for 18.9% of patients (n=71) no test were performed. During treatment the number of performed LFTs decreased from 75.2% at first visit to 15.2% at eighth visit.

In 1st line Pazopanib, 337 patients (89.9%) in the SAF experienced TEAEs. A total of 1923 TEAEs occurred, of which 1038 (54.0%) were judged to be related to Pazopanib. There were 368 TEAEs grade 3/4 (19.1%) occurring in 179 patients (47.7%), out of which 151 TEAEs grade 3/4 (7.9%) were assessed as being related to Pazopanib. 75 fatal TEAEs (3.9%) were reported in 71 (18.9%) patients, with 3 assessed as being related to pazopanib. In agreement with the SmPC of pazopanib (June 2021, Reference ID: 014815-67235) most frequent TEAEs of any grade were gastrointestinal disorders with diarrhoea (36.8%), nausea (22.4%) and vomiting (7.2%) as well as fatigue (19.2%), decreased appetite (12.5%) and hypertension (12.3%).

Of patients with 1st-line pazopanib treatment (FAS(P)) 279 patients (74.2%) were identified as qualifying for the questionnaire project and were assigned to FAS (QS,P). At baseline 219 (78.5%) questionnaires were available for analysis, after 3 months and 24 months the number of evaluable questionnaires deceased to 141 (50.5%) and 31 (11.1%). Of patients with 2nd-line nivolumab treatments (FAS(N)) 146 patients (89.6%) qualified for the questionnaire project and were assigned to FAS (QS, N) and of those, 82 patients were handed out the baseline-questionnaire. Health-related QoL assessed by EQ-5D-5L did not change from baseline: patients were mainly bothered by pain/discomfort and the patients' mobility and usual activity were affected by the disease. Sensitivity analyses showed no difference between subgroups. Accordingly, EQ-5D-5L-VAS levels merely remained stable throughout treatment.

11.2 Limitations

Due to the non-interventional character of this study, all associated limitations as well as advantages apply. The internal validity of the data collected is limited, as no predefined schedule and only minimal inclusion criteria were present. A standardized tumor response

evaluation (e.g. according to RECIST) was not required. As a consequence, tumor evaluations were not uniform and were performed at arbitrary time points or were not performed at all. In addition, the significant attrition of patients over the course of the study has to be taken into account.

The time interval from primary diagnosis to first administration of pazapanib was calculated in the present real world patient population composed of both, i) patients which were treated in curative setting before entering the present study and ii) patients which were presented with advanced or metastasized disease at their primary diagnosis.

Patients with documented nephrectomy comprised patients underwent either curative or palliative nephrectomy. A clear distinction between curative and palliative nephrectomy is not possible.

Subgroup analyses performed in this study should be interpreted with caution, in cases where the number of patients per subgroup was small.

With regard to QoL evaluation, many patients did not complete all questionnaires and did not answer all items of the questionnaires. More importantly, it is reasonable that patients that are doing rather well under therapy were still able to complete questionnaires at later time points, whereas patients with a poor prognosis and short therapy duration might have only completed questionnaires at early time points. Additionally, fitter patients might generally be more willing to take part in activities such as answering the QoL questionnaires. Therefore, results of QoL scores might not be fully representative of the whole patient collective.

11.3 Interpretation

The non-interventional PAZOREAL (Pazopanib and Everolimus in a Real-world Setting) study was aimed to observe the real-world use of pazopanib, everolimus (with or without lenvatinib) or nivolumab given in 1st-line through 3rd-line therapy for patients with mRCC.

In PAZOREAL 376 patients were assigned to cohort I and were treated with pazopanib in 1st-line setting (FAS(P)), while only 6 patients were assigned to cohort II (i.e. were treated with everolimus in 3rd-line setting, reflecting that while the sequence of pazopanib followed by nivolumab as 2nd-line treatment is commonly applied therapy strategy in patients with mRCC (Méndez-Vidal et al., 2018). Several reasons might explain the low number of patients starting with 3rd-line everolimus treatment in PAZOREAL: it is reasonable that in PAZOREAL the number of available patients being treated in 1st-line is higher than respective available patients with 3rd-line treatment [5]. Moreover, the patient enrolment for 3rd-line patients was only possible from a subpopulation of 2nd-line patients after authorisation and application of nivolumab as 2nd-line treatment[6]. Thus the first patient being enrolled for cohort II consented nearly 1 year after the first patient of cohort I (01 December 2016 for cohort II versus 10 December 2015 for cohort I). Additionally, after 1st-line pazopanib, everolimus seems to be rarely chosen as 2nd- or 3rd-line treatment option (Méndez-Vidal et al., 2018). Data of German renal carcinoma registry

[5] "Krebs - Nierenkrebs," n.d.; "Krebs in Deutschland 2009/2010 - krebs_in_deutschland_2013.pdf," n.d.; Naito et al., 2019)

[6] ("Europäische Kommission erweitert Zulassung von Opdivo® (Nivolumab) als Monotherapie bei Erwachsenen zur Behandlung des fortgeschrittenen Nierenzellkarzinoms nach Vortherapie," 2016)

CARAT showed that preferred 2nd-line treatment changed from sorafenib/temsirolimus (35%/21%, 2007-09), everolimus (33% 2010-12), everolimus/axitinib/sunitinib (29%/19%/18%, 2013-15) to nivolumab (>60% since 2016) (Goebell et al., 2019).

Present patient charcteristics were similar to previously reported typical characteristics of mRCC patients, with a tendency towards male sex, older age and higher BMI (Goebell et al., 2018b). Of note, compared to patients included in the pazopanib pivotal studies (Motzer et al., 2014, 2013)[7] present baseline characteristics were more diverse in regard to histologic tumor subtype, ECOG performance status, and age. (Motzer et al., 2013; Cora N Sternberg et al., 2010). Further, in PAZOREAL the MSKCC risk score was available in only 23% of patients reflecting that MSKCC risk score determination is not routinely performed in real world setting and that the risk score does not decide the treatment strategy.

Pazopanib 1st-line mToD was 6.3 (5.6-7.4) months in PAZOREAL cohort I, and respective mToD for trial-eligible patients was 7.7 (6.1-9.0) months which is comparable to median exposure duration of 7.4 months in the pazapanib arm of VEG105192 (Sternberg et al., 2013) and of 8.0 months in ((Motzer et al., 2013), Study VEG108844), indicating that pazopanib therapy in the real world setting can be applied somewhat shorter than in the RCT setting (Cora N Sternberg et al., 2010). Similar outcomes in patient subgroup trial-eligible hint to no impact of trial-eligibility on treatment (Motzer et al., 2013; Cora N Sternberg et al., 2010).

In PAZOREAL, the overall mOS for patients started with 1st-line pazopanib was 35.9 (28.2-48.3) months and is longer compared with previously reported data of the phase III non-inferiority study COMPARZ (comparing pazopanib to sunitinib) with a mOS of 28.3 (26.0, 35.5) months (Motzer et al., 2014). For 2nd-line nivolumab, the mOS was 30.4 months (22.6-NA) months and is similar to previously reported mOS for 2nd-line nivolumab (25.0 months, 21.8-NA) (Motzer et al., 2015a). However, present mOS1 is prolonged compared to previous reported data of German registry CARAT with a mOS for patients with start of 1st-line 2007-17 of 19 months and of 27 months if patients selected by trial eligibility criteria (Goebell et al., 2019). Of note, the approval of pazopanib was in 2010 and thus the patient population in CARAT was more diverse in regard to treatment options for 1st- and 2nd-line and subsequent setting.

In PAZOREAL most patients started with standard dosis 800 mg pazopanib. Pazopanib dose interruptions occurred in 30.3% of patients (FAS(P)) and was thus somewhat lower than in the pivotal study (Sternberg et al., 2019). There, 44% of pazopanib-treated patients had dose interruption and 24% of patients permanently discontinued the study drug because of adverse events. End of treatment due to toxicity (13.6%) or adverse events and (5.9%) was less frequent in PAZOREAL.

According to the SmPC, monitoring of liver fuction should be performed before initiation of treatment with pazopanib, at weeks 3, 5, 7 and 9, then at months 3 and 4, with additional tests as clinically indicated. The periodic testing should then continue after month 4. However, in PAZOREAL for patients receiving 1st-line pazopanib, only 81.1% of patients had a documented LFT before start of pazopanib treatment and in the course of pazopanib treatment the number of documented LFTs deceased.

[7] refer also to (Cora N Sternberg et al., 2010; Sternberg et al., 2014)

The PAZOREAL Safety data is comparable to pivotal studies and current SmPC of pazopanib (June 2021, Reference ID: 014815-67235, (Motzer et al., 2014, 2013; Sternberg et al., 2019)).

Quality of life assessed by EQ-5D-5L did not relevantly change over the course of treatment in the clinical routine setting confirming previous observations in 1st-line pazopanib setting in pivotal studies (Cora N Sternberg et al., 2010). However, previous reported QoL data of nivolumab in 2nd- and 3rd-line setting showed an QoL improvement compared to baseline (Cella et al., 2016). However, in PAZOREAL the number of patients for QoL-analyses was considerably smaller than in the study of Cella et al. 2016 (reporting number of patients at baseline: 362 (88%) of 410 patients) and present QoL data should be interpreted with caution (Cella et al., 2016).

11.4 Generalizability

12 Other information

In the time period between the first COVID-19 case in Germany (27 January 2020) and date of last-subject-last-visit (28 February 2021), 130 study subjects were observed. No subject visits were delayed or cancelled due to the COVID-19 pandemic. For one subject a COVID-19 infection (CTCAE 2) during treatment with pazopanib has been reported. Validation of the database quality was carried out by onsite monitoring. All planned onsite monitoring visits took place. All study objectives were addressed and evaluated as planned and defined in the study protocol. No protocol amendment was required due to the COVID-19 pandemic. Taken together, the COVID-19 pandemic had no impact on the conduct of the study.

13 Conclusion

the sequence of pazopanib followed by nivolumab as 2nd-line treatment is commonly applied in Germany. MSKCC risk score determination is not routinely performed and the risk score does not decide the treatment strategy. Overall, time on drug was comparable with results from clinical trials. Further, respective outcomes in the subgroup of patients considered as being trial-eligible were similar, which however hint to no impact of trial-eligibility on treatment effectiveness in the present setting. In real world, the majority of patients started with full dose pazopanib and nivolumab. Taken all safety data of the PAZOREAL study together, it can be concluded that pazopanib is well tolerated. AE pattern and death rate lie in the expected range. No new or potentially important safety issues were identified during the study. Quality of Life, as evaluated via EQ-5D-5L, is maintained during 1st-line treatment with pazopanib and 2nd-line nivolumab treatment.

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Appendices

Annex 1 – List of stand-alone documents

The following documents are available upon request.

Number	Date	Description
1	29 July 2021	List of Investigators
2	07 November 2018	Study Protocol (amendment 2)
3	14 November 2019	Statistical Analysis Plan version 4.1

Tables and Figures– Interim Analysis No. 1

4	22 June 2017	Tables
5	24 May 2017	Figures

Tables and Figures – Interim Analysis No. 2

6	06 March 2018	Tables
7	30 January 2018	Figures

Tables, Figures, and Listings – Interim Anaysis No. 3

8	25 January 2019	Listings
9	25 January 2019	Tables
10	25 January 2019	Figures

Tables, Figures, and Listings – Interim Anaysis No. 4

11	03 December 2019	Listings
12	29 November 2019	Tables
13	27 January 2020	Additional Tables
14	29 Novmeber 2019	Figures
15	27 January 2020	Additional Figures

Tables, Figures, and Listings – Final Anaysis

16	16 August 2021	Listings
17	16 August 2021	Tables
18	16 August 2021	Figures