Non-Interventional Study Protocol
B1771009

Registry for the evaluation of the safety, tolerability, and efficacy of Torisel® (Temsirolimus), Sutent® (Sunitinib), and Inlyta® (Axitinib) for the treatment of subjects with advanced renal cell carcinoma (mRCC), mantle cell lymphoma (MCL), and gastro-intestinal stroma tumor (GIST).

Statistical Analysis Plan
(SAP)

Version: **9.0**

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

Amendment from version 1.0
In the course of the NIS for patients with metastasized renal cell carcinoma treated with Torisel®, regarded treatment and regarded indication was extended. In the NIS are currently included patients with metastasized renal cell carcinoma treated with either Torisel® or Sutent®, patients with mantle cell lymphoma treated with Torisel® and patients with gastrointestinal stroma tumors treated with Sutent®.
For this reason the statistical analysis plan had to be amended from version 1.0.

Amendment from version 2.0
In the course of the NIS for patients with metastasized renal cell carcinoma treated with Torisel®, was further extended regarding treatment. Patients suffering from metastasized renal cell carcinoma being treated with Inlyta® are now also included in the NIS.
Furthermore the documentation of two patient questionnaires (Functional Assessment of Cancer Therapy - Kidney Index - 15 (FKSI-15) and EuroQoL-5D (EQ-5D)) was added for patients suffering from metastasized renal cell carcinoma.
Also the importance of the sequence of systemic treatments was strengthened leading to a new version of the case report form.
For these reasons the statistical analysis plan had to be amended from version 2.0.

Amendment from version 3.0
In the course of the NIS, the flow chart had to be updated as a starting visit for the 2nd therapy for mRCC patients was included.

Amendment in version 6.0
In the course of the NIS the following changes were implemented:
Rules for determination of therapy lines were added.
Additional plausible ranges for laboratory values were defined and actions after detections of not plausible ranges were defined.
Due to the possibility of documentation of treatment sequences, the determination of modified Motzer score was not possible without any doubt for the second treatment within a sequence. It was clarified, that modified Motzer score was determined only for 1st line patients.
The analysis on comorbidities was further specified, in order to combine data on comorbidities from old and new versions of the CRF.
Determination of time to progression and overall survival was further specified.

Amendment in version 7.0
In the course of the NIS, further specifications to determine therapy line for MCL subjects were added.

Amendment in version 7.1
In the course of the NIS, further analyses for specific subgroup were defined.

Amendment in version 7.2
In the course of the study, contents of already defined tables were further specified.

Amendment in version 8.0
In the course of the study, changes in study conduct due to amendment VI, dated Oct, 30th, 2017 had to be made.
Additionally SAP was transferred to the current Non-Interventional Statistical Analysis Plan template.

Amendment in version 9.0
In the ocurse of the study, it was recognized that the additional analyses defined in amendment VI would not be possible due to low recruitment. Thus study aims and duration of recruitment were changed. This led to necessary adoptions in this SAP.

2 INTRODUCTION

Note: in this document any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

The treatment of metastasized renal cell carcinomas (mRCC) has radically changed within short time. During the last years several new substances for the treatment of mRCC have been launched and have raised new scientific questions. Temsirolimus and Sunitinib are the current standard therapy options in the first-line treatment of mRCC. Inlyta®represents a new therapy option in mRCC patients after failure of Sunitinib or cytokines.

Since August 2009 Torisel® is available as another therapy option for patients with MCL. Sunitinib® is also suitable for the second-line therapy of patients with gastrointestinal stromal tumors (GIST).

In April 2016, the first immunoocologial therapy (Nivolumab) received approval for treatment of mRCC in adults. Furthermore, in August 2016, the combination Lenvatinib / Everolimus was approved as therapy for mRCC patients after a therapy targeted against-VEGF and in September 2016 Cabozantinib gained approval for patients with mRCC after a previous therapy targeted against VEGF.

As the treatment options have significantly changed for mRCC – as reflected in the current S3-guideline – data on the use of sunitinib followed by the new therapy options followed by axitinib in daily routine is missing. This holds regarding information on efficacy and tolerability of axitinib as third or higher line therapy.

In amendment VII it is stated to reduce the recruitment period by 12 months, as the primary application of Sunitinib® in the therapy sequence moves towards later lines of therapy due to new approvals of ICI in combination with other ICI or TKI. This also

results in later lines for the interim therapies and Axitinib®. Analyses of patient recruitment and number of subjects included into each documentation cycle showed, that the additional study objective defined in amendment VI will not be reachable within the planned study period.

2.1 STUDY DESIGN

The registry STAR-TOR is a prospective, multicenter, open-label, non-interventional observational study (registry).

At a baseline visit eligibility of patients will be checked and baseline information will be documented. Patients treated will be followed up at visits every 8 to 12 weeks until treatment with temsirolimus, sunitinib or axitinib. was discontinued or documentation was stopped for any reason. For subjects with ongoing documentation survival information on the patients should thereafter be documented 12 months after baseline and then every six months until the patient dies or cannot be reached for other reasons.
After the first documented sequence with any of the three Pfizer therapies, for patients suffering from mRCC the documentation of non Pfizer-products may follow. This documentation is much smaller with regard to content and should be filled out every 8 to 12 weeks. If another Pfizer treatment is given thereafter (in 3rd line or higher) sequences of the three therapies sunitinib, temsirolimus and axitinib can be documented. In this case the documentation will be continued with further follow-up documentations after documentation of a discontinuation form. Survival information will then be documented after the second therapy.
Detailed information on assessments for patients suffering from mRCC are presented in the following flow chart. For patients suffering from GIST or MCL documentation ends after end of first sequence.

Flow chart on documentation sequences for patients suffering from mRCC

	1st Pfizer therapy sequence			Documentation of treatment with non-Pfizer therapies	2nd Pfizer therapy sequence			Survival information
	Baseline visit	Follow-up visit every 8 – 12 weeks	Final / discontinuation of treatment	every 8 – 12 month	Baseline at time of start of 2nd Pfizer therapy	Follow-up visit every 8 – 12 weeks	Final / discontinuation of treatment	12 month after discontinuation and then every 6 months
Demography	x	x	x		x	x	x	x
In- and exclusion criteria	x							
Patient consent	x			(x)				
Tumor anamnesis	x				x			
Karnofsky Performance status / height / weight	x	x			x	x		

Therapy / Medication								
Prior medication	x							
Concomitant medication	x				x			
Tumor treatment	x	x		x	x	x		x
Safety								
Concomitant diseases / physical examination	x				x			
Laboratory values	x	x			x	x		
Blood pressure	x	x			x	x		
ECG	x	x			x	x		
Echocardiogram	x	x			x	x		
Assessment of pain	x	x			x	x		
Adverse events	x	x	x	x	x	x	x	

Efficacy								
Risk prognosis	x				x			
CT / MRT	x	x				x		
Ultrasound	x	x				x		
Chest X-ray	x	x				x		
Tumor assessment		x		x		x		
Physician's assessment of efficacy and tolerability		x				x		
Physician's overall assessment of treatment response			x	x			x	
PRO: quality of life	x	x			x	x		

Study population

It is planned to recruit 100 patients per year and treatment over a total recruitment period of 156 months, resulting in approximately 1.600 patients in summary. Patients should only be included after physician's decision to treat the patients with either Torisel®, Sutent® or Inlyta®.

2.2 STUDY OBJECTIVES

The objective of this registry study is to obtain a general impression regarding questions on efficacy, tolerability and safety of a temsirolimus, sunitinib or axitinib therapy in patient with advanced renal cell carcinoma, recurrent/refractory mantle cell lymphoma (rMCL) and GIST under routine treatment conditions in usual care. The therapeutic armamentarium for the management of advanced RCC is significantly changing and thus, for example, there is a lack of real-world data concerning the routine use of sunitinib followed by new therapeutic options followed by axitinib in order to assess the efficacy and safety of axitinib in third or later lines appropriately.

The following information is of particular interest in the course of the therapy:

- *Safety profile (overall incidence of adverse events and side effects) of patients with mRCC, rMCL and GIST treated receiving temsirolimus, sunitinib or axitinib.*
- *Tolerability of the therapy (assessment performed by treating physician)*
- *Effectiveness (maximum response, survival time, progression-free survival)*
- *Profile, comorbidities and characteristics of patients treated with temsiolimus, sunitib or axitinib.*
- *Sequences used for systemic therapies of patients with RCC, MCL and GIST.*
- *Patient questionnaires regarding quality of life of patients suffering from mRCC.*

3 INTERIM ANALYSES

Two interim analyses are planned per year. A final analysis after end of study is planned with identical content. The analyses to be performed and the tables to be presented are defined in this statistical analysis plan (SAP).

Interim analyses are performed in order to get and to present early information on safety and effectiveness of a treatment with temsirolimus, sunitinib or axitinib in the usual health care setting. Interim analyses are also performed in order to get answers on new scientific questions.

4 HYPOTHESES AND DECISION RULES

4.1 STATISTICAL HYPOTHESES

Not applicable.

4.2 STATISTICAL DECISION RULES

Not applicable.

5 ANALYSIS SETS/POPULATIONS

Analyses will be performed within each indication and treatment, e.g. one for mRCC and temsirolimus, sunitinib and axitinib, one for the non-Pfizer interim therapies and one for MCL and one for GIST.

For data from mRCC patients included prior to amendment VI of the protocol baseline data from sequence 1 will be forwarded as baseline data for sequence 2, if the respective data is not asked for in follow-up 1 of sequence 2 (tumor anamnesis at time of primary diagnosis, prior local and systemic therapies, prior and concomitant diseases, concomitant medication (other than systemic therapy)). Ongoing adverse events from sequence 1 have to be added to the list of concomitant diseases in sequence 2. Additional cancer therapy from baseline and follow-up visits of sequence 1 will be forwarded as baseline data for sequence 2 unless the therapy has been discontinued.

For patients included under amendment VI, baseline data for the second Pfizer treatment will be asked for in the CRF as changes in this data are not completely asked for in the non-Pfizer treatment periods.

For data from mRCC patients the following tables (see chapter 9): demographic information (1.2-1; 1.2-2), study periods (1.1-5.2), previous local and systemic therapy (1.5-1; 1.5-2), duration of therapy (1.6-1), overall survival (2.2-1), progression free survival (2.3-1), course of Karnofsky performance scale (2.5) and course of FKSI-15 (2.6), EQ-5D (2.7) will be repeated for the following groups of patients:

- Treatment sequence 1st sunitinib → 2nd axitinib → any further therapy
- Treatment sequence 1st temsirolimus → 2nd sunitinib → any further therapy
- Treatment sequence 1st sunitinib → any further therapy (no axitinib in 2nd line)
- Treatment sequence 1st temsirolimus → any further therapy
- Treatment sequence 1st sunitinib → no further therapy
- Treatment sequence 1st temsirolimus → no further therapy
- Any therapy → 2nd axitinib → any further therapy.

The following treatment sequences were included on the basis of amendment VI. Following the rationale in amendment VII, it was not possible to include a sufficient number of subjects for meaningful statistical conclusions. Thus no analyses will be performed for this treatment sequences, but data on demographic information, previous local and systemic therapy, duration of therapy (by Pfizer therapy, by non-Pfizer

treatment), overall survival, progression free survival, course of Karnofsky performance scale, course of FKSI-15 and EQ-5D will be listed.

- Treatment sequence 1st Pfizer treatment → non-Pfizer treatment → 3rd line axitinib
- Treatment sequence 1st fizer treatment → non-Pfizer treatment 1 → non-Pfizer treatment 2 → (possibly more non-Pfizer treatments) → 4th line or later axitinib

5.1 EFFECTIVENESS ANALYSIS SET

The effectiveness analysis set consists of all patients included into the study with at least one information on any of the following criteria: date of death, date of progression, assessment of response to therapy by the treating physician or an assessment to either effectiveness or tolerability of the therapy by the treating physician. For reporting the full analysis set will be labeled EAS.

5.2 SAFETY ANALYSIS SET

The safety analysis set consists of all prospectively documented patients included in the study with a histologically proven diagnosis of either renal cell carcinoma, MCL or GIST and at least one documented administration of temsirolimus, sunitinib or axitinib or any non-Pfizer treatment.

5.3 OTHER ANALYSIS SET

Not applicable.

5.4 SUBGROUPS

Effectiveness analyses of mRCC patients will be repeated for subgroups based on physician's prognosis of patients risk and for the risk groups according to Motzer score, modified Motzer score and Motzer score for pretreated patients.

For subjects in first line Torisel® therapy with poor prognosis according to modified Motzer the following variables will be analyzed: age, gender, Karnofsky index, organs with metastases, prior surgeries, duration of disease, histology, progression free survival and overall survival.

Effectiveness analyses of MCL patients will be repeated for subgroups based on the risk groups according to MIPI (Mantle cell lymphoma international prognostic index).

Effectiveness analyses of GIST patients will be repeated for subgroups based on physician's prognosis of patients risk and for the risk groups according to Fletcher Risk Table.

6 ENDPOINTS AND COVARIATES

6.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

Variable	Role	Operational definition
Overall survival	Outcome	presented in months
Progression free survival	Outcome	presented in months
Response to therapy	Outcome	according to RECIST / according to Cheson (for MCL)
Physician's global assessment	Outcome	
Karnofsky performance status	Outcome Subgroup identifier	not for MCL
ECOG performance score	Outcome Subgroup identifier	only for MCL

6.2 SAFETY ENDPOINTS

Variable	Role	Operational definition
Incidence and severity of treatment-emergent adverse events	Safety outcome	
Discontinuation due to adverse event	Safety outcome	
Discontinuation from Study	Safety outcome	
Serious adverse events	Safety outcome	
Death	Safety outcome	either "intensity according to NCI-CTC-criteria = grade V fatal" or "outcome = exitus" or "event term = death"
Laboratory values (if available)	Safety outcome Subgroup identifier	Hemoglobin, calcium, albumin, LDH, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, TSH, fT3, fT4, hematocrit, phosphate, HbA1c, glucose, neutrophils, lymphocytes, monocytes, eosinophils, basophils, sodium, potassium, magnesium, cholesterol, triglycerides
Global tolerability assessment	Safety outcome	

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[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]

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6.4 COVARIATES

Patients with mRCC will be grouped according to the physicians risk assessment at time of inclusion in the study and by their prognosted risk according to the Motzer score.

Patients suffering from MCL will be grouped according to the physicians risk assessment at time of inclusion in the study and by prognosted risk according to the MIPI score (at time of inclusion and at time of primary diagnosis).

Patients with GIST will be grouped according to the physicians risk assessment at time of inclusion in the study and by their prognosted risk according to Fletcher risk table at time of primary diagnosis.

6.4.1 Motzer score

Motzer score

According to the Motzer score five risk factors are defined: low Karnofsky performance status (< 80%), high LDH (> 1.5 times upper limit of normal ≡ > 300 U/L), low hemoglobin (< lower limit of normal ≡ < 13 g/dL for male patients, < 11.5 g/dL for female patients), high corrected serum calcium (> 10 mg/dL) and time from diagnosis to start of Torisel® or Sutent® treatment less than one one year. A patient without any risk factor present at baseline visit belongs to the favorable-risk group, one with one or two risk factors present at baseline belongs to the intermediate-risk group and one with three or more risk factors present at baseline belongs to the poor-risk group.

The corrected serum calcium value will be computed from the values of serum calcium and serum albumin according to the following formula:

Corrected Serum Calcium (mg/dL)

= Calcium (mmol/L) * 4.008 – 0.707 * (Albumin (g/L) / 10 – 3.4).

Modified Motzer score

The modification of the Motzer score adds one further risk factor: at least 2 sites of organ metastases. The assignment to the risk groups and the calculation of corrected serum calcium remains unchanged. Within this study modified Motzer score was only determined for 1st line patients. Only two categories were analyzed "≥ 3 = poor" and "< 3 = non poor".

Motzer score for previously treated patients

The Motzer score for previously treated patients is based on the three risk factors: low Karnofsky performance status (< 80%), low hemoglobin (< lower limit of normal ≡ < 13 g/dL for male patients, < 11.5 g/dL for female patients) and high corrected serum calcium (> 10 mg/dL). The score is only defined for patients with at least one previous systemic treatment of RCC. A patient is assigned to the favourable-risk groups, if no risk

factor is present, to the intermediate-risk group, if one risk factor is present and to the poor-risk, if two or three risk factors are present.

6.4.2 Mantle Cell Lymphoma International Prognostic Index (MIPI)

MIPI score is defined as

$$\text{Score} = 0.0353 * \text{age (yrs)} + 0.6978 * [\text{ECOG} > 1 \{\text{yes/no}\}] + 1.367 * \log_{10}(\text{LDH/ULN LDH}) + 0.9393 * \log10(\text{Leukocyte count } [/\mu l])$$

Low risk	if Score < 5.7
Intermediate risk	if 5.7 ≤ Score < 6,2
High risk	if 6.2 ≤ Score

If all data necessary to compute MIPI score are available, the calculated risk will be used for analyses of current MIPI. Otherwise and for the time of primary diagnosis the value documented by the physician will be used.

6.4.3 Fletcher Risk Table (NIH Risk Table)

The risk of recurrence or metastasis of a primary GIST may be prognosted according to the Fletcher Risk Table (Fletcher et al, 2002):

Risk prognosis	Size (largest diameter) of primary tumor	Mitotic Count (per 50 HPF)
Very low risk	< 2 cm	≤ 5
Low risk	≥ 2 - ≤ 5 cm	≤ 5
Intermediate risk	< 5 cm	6 – 10
	≥ 5 - ≤ 10 cm	≤ 5
High risk	> 5 cm	> 5
	> 10 cm	any

7 HANDLING OF MISSING VALUES

Generally, missing values still missing after performing quality improvement measures (edit checks, queries) were performed, will not be replaced

For determining the risk groups according to Motzer score, modified Motzer score and Motzer score for pretreated patients the following procedures will be kept to:

- If at least three (two for Motzer score for pretreated patients) risk factors are present, missing values for the remaining can be ignored and the patient will be assigned to the poor risk group.
- If the calcium value is given, but the albumin value is missing, than calcium will be interpreted as a risk factor if the calcium value is above 11 mg/dL.
- If the hemoglobin value is missing, but a clinically significant low hemoglobin value or anemia is documented as comorbidity, than this will be interpreted as a risk factor present.
- If the LDH value is missing, but a clinically significant high LDH value is documented as comorbidity, than this will be interpreted as a risk factor present.

With the protocol amendment including mRCC patients being treated with axitinib some additional information was asked for in the CRF. This implies missing values for patients documented under earlier versions of protocol and CRF. The percentage of missings due to this reason will not be reported in tables extra. With amendment VI interim treatment with non-Pfizer products was included. This data will only be analyzed for patients documented under amendment VI.

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

8.1.1 Analysis Of Categorical And Continuous Data

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Categorical data will be analyzed by presenting frequency tables (absolute and relative frequencies/ adjusted and not adjusted). For continuous data the sample statistics mean, standard deviation, median, minimum and maximum, and quartiles are calculated. For incidence rates 95% confidence intervals will be presented.

Data measured several times during the study are analyzed by visit presenting absolute and relative differences to baseline for numerical data and shift tables for categorical data.

Agreement between the risks assigned to patients by the risk scores and physician's prognosis of patients risk will be measured using Cohens kappa-statistic.

8.1.2 Analysis Of Survival Data

OS, PFS and treatment duration will be analyzed using Kaplan-Meier plots. Median, 25% and 75% survival times with confidence intervals for OS and PFS will be presented. For stratification according to physician's prognosis and for risk groups according to Motzer score/MIPI/Fletcher risk table, log-rank tests will be performed.

8.2 STATISTICAL ANALYSES

8.2.1 Summary of Efficacy/ Effectiveness Analyses

Not applicable

8.2.2 Safety Analyses

Adverse events will be analyzed giving absolute and relative frequencies in total and by MedDRA system organ classes and preferred term. Serious adverse events will be analyzed separately in the same manner.

Adverse events will presented within each treatment (temsirolimus, sunitinib, axitinib) and for all non-Pfizer treatments in total and by treatment.
Additionally the absolute and relative frequency of patients with premature discontinuation will be presented in total and by reason for premature discontinuation.
Prior and concomitant medication will be presented showing frequency tables.
Laboratory results and ECG results will be presented by visit.
Physician's assessment of tolerability will be analyzed presenting sample statistics.

8.2.3 Summary of Analyses

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
Demographic characteristics: age, height, weight, BMI, sex	Safety, EAS	4	None	Sample statistics	None	Excluded
Incidence of treatment-emergent adverse events	Safety	3	- Patients receiving CYP3A4 inducing concomitant medication (only patients treated with temsirolimus) - Patients receiving CYP3A4 inhibiting concomitant medication (only patients treated with temsirolimus)	Rate by SOC and PT	Non-serious AE, serious AE	Excluded
Discontinuations due to AE	Safety	3	None	Rate by SOC and PT	None	Excluded
Discontinuation from Study	Safety	3	None	Rate for reason for discontinuation	None	Excluded
Serious Adverse Events	Safety	3	None	Rate by SOC and PT	None	Excluded
Deaths	Safety	3	None	- Rates for reason for death - Listing of deaths	None	Excluded
Laboratory values	Safey	3	None	Sample statistics by parameter and visit	None	Excluded

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
Global tolerability assessment	Safety	2	None	Frequency table	None	Excluded
Overall survival	EAS	1	- 1st line patients	Kaplan-Meier estimates; Kaplan-Meier curves; Log-rank test	- indication mRCC, GIST, MCL - risk prognosis - line of treatment - low vs. high LDH - response to prior therapy - age groups (≤65 yrs; > 65 yrs)	
Progression free survival	EAS	1	- 1st line patients	Kaplan-Meier estimates; Kaplan-Meier curves	- indication mRCC, GIST, MCL - risk prognosis - line of treatment - low vs. high LDH - response to prior therapy - age groups (≤65 yrs; > 65 yrs) - histology (clear cell vs. non-clear cell)	
Response to therapy	EAS	1	- risk prognosis	Frequency table	None	Excluded
Physician's global assessment	EAS	1	None	Sample statistics by visit	Risk prognosis	Excluded
Karnofsky Performance Index	EAS	4, 5	None	Sample statistics by visit	Only GIST, mRCC	Excluded
ECOG Performance Score	EAS	4, 5	- risk prognosis	Frequency table; shift tables	Only MCL	Excluded
FKSI-15	EAS	6	- risk prognosis	Sample statistics	Only mRCC	Excluded
EQ-5D	EAS	6	- risk prognosis	Frequency table for EQ-5D, Sample statistics for EQ-5D-VAS; EQ-5D-TTO	Only mRCC	Excluded

9 LIST OF TABLES AND TABLE SHELLS

If not otherwise specified, tables will be repeated for each combination of treatment and indication.

Table No.	Title	Treatment/ Indication	Analysis set	Description
1	**Demography and Baseline Characteristics**			
1.1	**Disposition of patients**			
1.1-1.1	Number of patients screened and reason for Non-inclusion	All	All patients	Counts over all treatments and indications (total number of patients in Star-Tor, total number of patients by indication, total number of patients by indication and treatment, total number of patients by indication and treatment sequence.
1.1-1.2	Treatment sequences	mRCC	All patients	Frequency table for sequences
1.1-1.3	Age of patients screened	All	Safety	Sample statistics for patients included and patients not included
1.1-2	Number of centers and patients planned and realized	All	Safety	number centers planned:200; number patients planned: 100
1.1-3	Number of patients per center	All	Safety	include number of active centers (e.g. at least 1 subject included)
1.1-4	Reason for premature discontinuation	All	Safety	Frequency tables for major reasons and specifications
1.1-5.1	Study duration	All	Safety	First patient in / Last patient out
1.1-5.2	Study periods	All	Safety Sequence analysis	Duration of study periods (Treatment phase, survival follow-up, sequence 1, sequence 2)
1.1-6.1	Summary of patient disposition	All	Safety	Patients who - were included into the study - were included into the Safety set - were included into the Safety set documented under prior versions of protocol - were included into the EAS - were included into the EAS documented under prior versions of protocol - Reason for exclusion from analysis set (refers to most comprehensive analysis set)

Table No.	Title	Treatment/ Indication	Analysis set	Description
1.1-6.2	Number of patients by time window	All	Safety, EAS	.1 Number of patients by visit .2 Number of visits by time window (table may be omitted, if only very few documented visits were condensed into one time window)
1.2	**Demography**			
1.2-1	Demographic variables	All	Safety, EAS Sequence analysis	age, sex, body height
1.2-2	Time-varying demographic variables	All	Safety, EAS Sequence analysis	Weight, BMI by time window
1.3	**Medical and oncological history**			
CCI	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCI	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.3-1.3	Current manifestations	MCL	SAFETY, EAS	Frequency tables for locations of manifestations
1.3-1.4	Tumor anamnesis - other information	GIST	SAFETY, EAS	.1 Frequency table for size of primary tumor, sample statistics for number of mitoses, frequency table for primary mutation analysis performed?, frequency table for type of KIT-mutation .2 Frequency table for mutation analysis performed in recidive?, frequency table for type of mutation
CCI	[redacted]	[redacted]	[redacted]	[redacted]
1.3-3	ECG	mRCC, GIST	SAFETY, EAS	Frequency tables for normal/abnormal ECG by time window

Table No.	Title	Treatment/ Indication	Analysis set	Description
CCI				

Table No.	Title	Treatment/ Indication	Analysis set	Description
CCI				
				, number of transplantations, R0 resection reached

Table No.	Title	Treatment/ Indication	Analysis set	Description
CCI	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table No.	Title	Treatment/ Indication	Analysis set	Description
CCI	[redacted]			
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	**Effectiveness**			
2.1	**Response to therapy**			
2.1-1	Course of response to therapy	All	EAS	Frequency table by time window (in total and by patient risk groups)

Table No.	Title	Treatment/ Indication	Analysis set	Description
2.1-2	Best response	All	EAS	Frequency table for best response in total and confirmed / not-confirmed (the latter not for Torisel® MCL); Frequency table for best response excluding patients "not assessable" only for MCL Listing of reasons for not assessable best response; Frequency table for best response by patient risk groups
2.1-3	Used diagnosis technique	All	EAS	CT, Thorax X-ray, MRT, Ultrasonic testing, PET, Bone scan, Clinical (by time window and for best response)
2.2	**Overall survival**			
2.2-1	Kaplan-Meier estimates for Overall survival	All	EAS Sequence analysis	Time to 25%, median and 75% survival with confidence intervals incl Kaplan-Meier curve on all patients
2.2-2	Kaplan-Meier estimates for Overall survival by patient risk groups	mRCC	EAS	.1 Physicians prognosis of patients risk .2 Risk groups according to Motzer score .3 Risk groups according to modified Motzer score .4 Risk groups according to Motzer score for pretreated patients .5 by treatment sequence .6 by treatment and treatment line. .7 1st line patients by risk (poor vs. non-poor) .8 by LDH ≤ 300 U/l vs > 300 U/l incl. Log-rank-test and Kaplan-Meier curves

Table No.	Title	Treatment/ Indication	Analysis set	Description
2.2-2	Kaplan-Meier estimates for Overall survival by patient risk groups	MCL	EAS	.1 Risk groups according to MIPI score at time of primary diagnosis .2 Risk groups according to current MIPI score .3 2nd and 3rd line .4 2nd to 4th line .5 4th line and beyond .6 5th line and beyond .7 Patients with OR (CR+PR) .8 Patients with (MR + SD) .9 Patients with clinical benefit (CR+PR+MR+SD) .10 Patients ≤ 65 vs. patients > 65 yrs. including Kaplan-Meier curves .1 OS all patients excluding "not assessable" patients .2 OS patients with OR (CR+PR) vs. (MR+SD) vs. PD .3 OS patients with clinical benefit (CR+PR+MR+SD) vs. PD .4 OS Temsirolimus 2nd to 4th line (1 – 3 prior therapies) vs. 5th line and beyond (≥ 4 prior therapies) .5 OS 2nd to 3rd line Temsirolimus (1 – 2 prior therapies) vs. 4th line and beyond (≥ 3 prior therapies)
2.2-2	Kaplan-Meier estimates for Overall survival by patient risk groups	GIST	EAS	.1 Risk groups according to Fletchers risk table .2 Risk groups according to physician's prognosis
2.2-3	Frequency table of patients status by time window (survival phase)	All	EAS	
2.3	**Progression free survival**			
2.3-1	Kaplan-Meier estimates for Progression free survival	All	EAS Sequence analysis	Time to 25%, median and 75% survival with confidence intervals including Kaplan-Meier curve on all patients

Table No.	Title	Treatment/ Indication	Analysis set	Description
2.3-2	Kaplan-Meier estimates for Progression free survival by patient risk groups	mRCC	EAS	.1 Physicians prognosis of patients risk .2 Risk groups according to Motzer score .3 Risk groups according to modified Motzer score .4 Risk groups according to Motzer score for pretreated patients 5 by treatment sequence .6 1st line patients .7 1st line patients by risk (poor vs. non-poor) .8 2nd line vs. higher lines .9 2nd vs. 3rd line vs. higher lines .10 patients ≤ 65 yrs vs. > 65 yrs .11 by LDH low (≤ 300 U/l) vs high (> 300 U/l) .12 by histology (clear cell vs. other) Kaplan-Meier curves incl Log-Rank-Test .1 PFS 1st line vs. 2nd line and higher .2 PFS 1st line vs. 2nd line vs. 3rd line and higher .3 PFS ≤ 65 yrs vs. > 65 yrs .4 PFS LDH low (≤ 300 U/l) vs high (> 300 U/l) .5 PFS clear cell histology vs. other histology

Table No.	Title	Treatment/ Indication	Analysis set	Description
2.3-2	Kaplan-Meier estimates for Progression free survival by patient risk groups	MCL	EAS	.1 Risk groups according to MIPI score at time of primary diagnosis .2 Risk groups according to current MIPI score .3 2nd and 3rd line .4 2nd to 4th line .5 4th line and beyond .6 5th line and beyond .7 Patients with OR (CR+PR) .8 Patients with MR + SD .9 Patients with clinical benefit (CR+PR+MR+SD) Kaplan-Meier curves incl. Log-Rank-Test .1 PFS all patients excluding "not assessable" patients .2 PFS patients with OR (CR+PR) vs. (MR+SD) .3 PFS patients with clinical benefit (CR+PR+MR+SD) .4 PFS Temsirolimus 2nd to 4th line (1 – 3 prior therapies) vs. 5th line and beyond (≥ 4 prior therapies) .5 PFS 2nd to 3rd line Temsirolimus (1 – 2 prior therapies) vs. 4th line and beyond (≥ 3 prior therapies)
2.3-2	Kaplan-Meier estimates for Progression free survival by patient risk groups	GIST	EAS	.1 Risk groups according to Fletchers risk table .2 Risk groups according to physician's prognosis
2.4	**Physician's global assessment**			
2.4	Physician's global assessment of effectiveness	mRCC	EAS	Frequency table by time windows and for the last documented visit: total and by physician's prognosis of patients risk and by risk groups according to Motzer score, modified Motzer score and Motzer score for pretreated patients.
2.4	Physician's global assessment of effectiveness	MCL	EAS	Frequency table by time windows and for the last documented visit: total and by risk groups according to MIPI score at time of primary diagnosis and according to current MIPI score.

Table No.	Title	Treatment/ Indication	Analysis set	Description
2.4	Physician's global assessment of effectiveness	GIST	EAS	Frequency table by time windows and for the last documented visit: total and by physician's prognosis of patients risk and by risk groups according to Fletchers risk table.
2.5	**Course of Karnofsky performance status scale**			
2.5	Course of Karnofsky performance status scale	mRCC, GIST	EAS Sequence analysis for mRCC	Sample statistics by time windows and for the last documented visit, including absolute and relative differences to baseline (in total and by patient risk groups)
2.5	**Course of ECOG performance status and B-symptoms**			
2.5-1	Course of ECOG performance status	MCL	EAS	Frequency table by time windows and for the last documented visit, shift table for differences to baseline (in total and by patient risk groups)
2.5-2	Course of B-symptoms	MCL	EAS	Frequency table by time windows and for the last documented visit
2.6	**FKSI-15: Course**			
2.6-1	Course of FKSI-15 score	mRCC	EAS Sequence analysis	Sample statistics by time windows and for the last documented visit and absolute and relative change to baseline.
2.6-2	Course of FKSI-DRS score	mRCC	EAS Sequence analysis	Sample statistics by time windows and for the last documented visit and absolute and relative change to baseline.
2.6-3	Course of FKSI domains	mRCC	EAS Sequence analysis	Sample statistics by time windows and for the last documented visit and absolute and relative change to baseline.
2.7	**EQ-5D: Course**			
2.7-1	Course of EQ-5D: domains	mRCC	EAS Sequence analysis	Frequency tables by time window and for the last documented visit and shift tables to baseline
2.7-2	Course of EQ-5D-VAS	mRCC	EAS Sequence analysis	Sample statistics by time windows and for the last documented visit and absolute and relative change to baseline.

Table No.	Title	Treatment/ Indication	Analysis set	Description
2.7-3	Course of EQ-5D: TTO	mRCC	EAS Sequence analysis	Sample statistics by time windows and for the last documented visit and absolute and relative change to baseline.
3	Safety			
3.1	Display of adverse events (AE)			
3.1-1.1	Summary of adverse events	All	Safety	No. / % of patients - at risk - with AE - with drug related AE - with AE related to Pfizer treatment - with AE related to interim treatment – with SAE – with drug related SAE - with SAE related to Pfizer treatment - with SAE related to interim treatment - with AE leading to permanent discontinuation of Torisel®/ Sutent® / Inlyta® - with drug related AE leading to permanent discontinuation of Torisel®/ Sutent® / Inlyta ® - with SAE leading to permanent discontinuation of Torisel®/ Sutent® / Inlyta ® - with drug related SAE leading to permanent discontinuation of Torisel®/ Sutent® / Inlyta ® - Death No. / % of AE - all AE - drug related - related to Pfizer treatment - related to interim treatment - SAE - drug related SAE - SAE related to Pfizer treatment - SAE related to interim treatment

Table No.	Title	Treatment/ Indication	Analysis set	Description
				.1 total .2 by treatment sequence .3 by line
3.1-1.2	Summary of adverse events by concomitant CYP3A4 inducing or inhibiting medications	Torisel® mRCC / MCL	Safety	repeat table 3.1-1.1 by subgroups according to CYP3A4 inducing or inhibiting medication (if number of patients with these medications is sufficiently large
3.1-2	All adverse events (by patients)	All	Safety	Incidence rates overall and for Primary System Organ Classes (PSOC) and preferred terms of MedDRA (non-serious/serious as columns) .1 total .2 by treatment sequence .3 by line
3.1-3	AE by severity (NCI-CTC grade)	All	Safety	Incidence rates overall and for PSOC and preferred terms of MedDRA severity: max. NCI-CTC grade within patient, PSOC, preferred term resp.(non-serious/serious as columns)
3.1-4	AE with relationship to study drug	All	Safety	Incidence rates overall and for PSOC and preferred terms of MedDRA (non-serious/serious as columns)
3.1-5	AE with action taken “Study medication permanently discontinued”	All	Safety	Incidence rates overall and for PSOC and preferred terms of MedDRA (non-serious/serious as columns)
3.1-6	AE by outcome (event basis)	All	Safety	Number of events overall and for PSOC and preferred terms of MedDRA
3.1-7	Treatment emergent AE: action taken (event basis)	All	Safety	Number of events overall and for PSOC and preferred terms of MedDRA
3.2	Deaths, other serious and significant adverse events			
3.2-1.1	Listing of deaths	All	Safety	Sorted by patient
3.2-1.2	Reason for death	All	Safety	Frequency table
3.2-1.3	Listing of serious adverse events (SAE, except deaths)	All	Safety	Sorted by patient

Table No.	Title	Treatment/ Indication	Analysis set	Description
3.2-1.4	Listing of SAE with outcome study treatment permanently discontinued	All	Safety	Sorted by patient
3.3	Laboratory values			
3.3-1	Hematology			
3.3-1	Laboratory values: hematology – study course	All	Safety	.x per parameter Sample statistics by visit, including difference and relative changes to baseline
3.3-2	Clinical chemistry			
3.3-2	Laboratory values: clinical chemistry- study course	All	Safety	.x per parameter Sample statistics by visit, including difference and relative changes to baseline
3.4	Global tolerability assessment			
3.4	Physician's global tolerability assessment	All	Safety	Frequency table by time windows and for the last documented visit
3.5	Vital signs, ECG, echocardiography and pain			
3.5-1	Course of blood pressure	mRCC	Safety	Sample statistics by time windows
3.5-2	Assessment of echocardiography	mRCC	Safety	Frequency table by visit
3.5-3	Course of pain	mRCC	Safety	Sample statistics by time windows
Listing	Listing of AE	All	Safety	
Listing	Data listing for patients included under Amendment VI	mRCC	All	demographic information, previous local and systemic therapy, duration of therapy (by Pfizer therapy, by non-Pfizer treatment), overall survival, progression free survival, course of Karnofsky performance scale, course of FKSI-15 and EQ-5D

10 REFERENCES

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11 APPENDICES

11.1 APPENDIX 1: DATA DERIVATION DETAILS

A1.1 Definition and use of visit windows in reporting

Time points for follow-up visits are not determined by the study protocol. It is only suggested to perform those every 8 to 12 weeks. In order to be able to perform statistical analyses, documented visits will be transferred into corresponding time windows.

The definition of single time windows can be taken from the following table:

	Treatment Phase 1	Treatment Phase 2	Treatment Phase 3	Treatment Phase 4	Treatment Phase 5	Treatment Phase 6
Weeks after Baseline	0 to 15	16 to 25	26 to 35	36 to 45	46 to 55	56 to 65
	Treatment Phase 7	Treatment Phase 8	Treatment Phase 9	Treatment Phase 10	Treatment Phase 11	and so on...
Weeks after Baseline	66 to 75	76 to 85	86 to 95	96 to 105	106 to 115	...
	Survival 1	Survival 2	Survival 3	Survival 4	Survival 5	and so on...
Months after discontinuation	0 to 15	16 to 21	22 to 27	28 to 33	34 to 39	...

In case more than one visit was performed within one time window, than the later one will be used for analyses "by time windows" with the following exceptions:

- Adverse events will be analyzed from all documented visits.
- Duration of PFS will be determined using the first occurrence of a progression of disease.

The study phase while patients are treated with Torisel®/Sutent® is defined as follow-up phase. The follow-up of subjects after discontinuation of Torisel®/Sutent® is defined as survival phase.

A1.2 Definition of Analysis Populations/Sets

Not applicable.

A1.3 Further Definition of Endpoints

Demography

Age (years) = (date of baseline visit – date of birth + 1)/365.25

BMI = body weight (kg) / body height (m)**2

Oncological history

For computation of duration of RCC, MCL and GIST and time since first confirmed metastasis (not for MCL) an arbitrary day 1 will be added and thereafter the SAS function for computing with date values will be used.

Duration of RCC/MCL/GIST (months) = (1/month/year of start of Torisel®/Sutent®/Inlyta® treatment – 1/month/year of date of histological confirmation of RCC/MCL/GIST)*12/365.25

First metastases (months) = (1/month/year of baseline visit – 1/month/year of date of first confirmation of metastasis)*12/365.25

Survival

In case an event (either death or progression) was present and date of event was documented, the following definitions was used:

Overall Survival (OS, months) = (date of death – date of baseline visit +1)/365.25 *12

Progression Free Survival (PFS, months) = (minimum of (date of death, date of progression) – date of baseline visit + 1)/365.25 * 12.

In case information on dates were partly or completely missing or contradictory, the following was done:

- PFS:
    - the presence of a progression was confirmed, but no date was documented: if date of last intake of study medication was given, this date was used as date of progression, otherwise the date of the last visit with a documented "non-progression (e.g. SD)" was used as date of progression.
    - the presence of a progression was confirmed, but dates within a visit and on final documentation were contradictory, the prior date was used.
    - in case a death was documented within a survival follow-up/ within sequence 2 for subjects from sequence 1, but no progression was documented within regular study, the date of last visit + 1 day was used as date of progression.
    - in case no progression was documented, subject was censored with the latest available contact date / assessment date within study/within sequence.
    - in case these rules led to a missing duration or a negative duration, duration was set to "1 day".
- OS:
    - in case a death was documented, but date of death was unknown, the date of death was substituted with the latest available date for the patient (last visit, last contact date, date of assessment)
    - in case no death was documented, subject was censored with the latest available contact date / assessment date within study.
    - in case these rules led to a missing duration or a negative duration, duration was set to maximum of (PFS,"1 day").

Response to therapy (Recist criteria/ Cheson criteria)

Response to therapy according to the Recist/ Cheson criteria will be analyzed using the physician's assessment as documented in the CRF. As neither "size of lesion", "new lesions" or "increase in size" are defined as key fields, contradictory answers will not overvote physicians assessment.

„Best response" will be analyzed using the physician's assessment at final visit. If „Best response" is missing it will be determined from the best response documented during previous follow-up visits.

Treatment

Treatment duration (weeks) = (date of death or date of drop-out or date of end of treatment with Torisel®/ Sutent® - date of first infusion within the registry + 1)/365.25 * 52.

Therapy line

for patients with mRCC:

- Splitted therapy (due to coding) was only counted as one therapy line.
- All medication with an identical start date was counted as one therapy line.
- Interferons, interleukins and immunochemotherapies were summarized as "cytokines".
- Ongoing treatment with the medication documented was not counted as line.
- Bisphosphonates and other supplementary treatment will not be considered.

for patients with MCL:

- Splitted therapy (due to coding) was only counted as one therapy line.
- All medication with an identical start date was counted as one therapy line.
- Rituximab maintenance therapy and stem cell transplantation, both connected with previous immunochemotherapy (ATC L01 Antineoplastic agents and L03 Immunostimulants), were not counted as line.

  Rituximub were counted as maintenance therapy, if
  - physician's comment contained free text / phrases like "Erhaltung", "Erhalt", "Maintenance" or
  - (last therapy prior to Rituximab resulted in remission (CR, PR or MR) and
  - Rituximab was started directly after the last therapy (at most one therapy free month was tolerable).)

FKSI-15

For calculation of the FKSI-15 score documented values for questions 1-6, 8,9, 11, 12 and 14 will be reversed by subtracting the documented value from 4. All original scores (for questions 7, 10, 13 and 15) and all reversed scores will be summed, multiplied by 15 and devided by the number of answered questions resulting in a score within a range from 0 to 60. The FKSI-15 score cannot be determined if more than 7 questions are not answered.

FKSI-DRS score will be calculated like the FKSI-15 score considering only questions 1, 3, 4, 5, 6, 8, 11, 12 and 14 (multiply by 9). FKSI-DRS cannot be determined if more than 4 questions are not answered.

The 4 domains of FKSI-15 will be calculated like the FKSI-15 score. The following tables shows domains and related questions, multiplyer and maximal number of unanswered questions in order to give a valid score.

Domain	Questions	Multiplyer	Maximal number of unanswered questions
Signs and symptoms	1, 2, 3, 4, 5, 6, 12, 13	8	4
Respiratory symptoms	8, 11	2	1
Quality of life	7, 10, 13, 15	4	2
Emotional symptom	9	1	0

EQ-5D (TTO)

EQ-5D-TTO will be calculated from EQ-5D raw values according to the following formula (Greiner, W. et al. 2005):

EQ-5D-TTO = 0.999
- 0.099 * (1*Subject has some problems with walking around + 2 * Subject cannot walk around)
- 0.087 * (1*Subject has some problems with self-care + 2 * Subject has extreme problems with self-care)
– 0.112 * (1*Subject states moderate pain or discomfort + 2 * Subject has extreme pain or discomfort)
– 0.129 * (Subject cannot walk around)
– 0.091 * (Subject has extreme pain or discomfort)
– 0.065 * (Subject is extremely anxious or depressive)
– 0.323 * (Subject states major problems in at least one dimension).

EQ-5D-TTO-values range from –0.205 to 0.999.

Laboratory values

Additional queries were written in the following cases:

- calcium > 10 mmol/L
- albumin > 100 g/L
- hemoglobin > 20 g/dL
- LDH < 80 U/L or > 1000 U/L
- albumin in % of total protein.

Laboratory values were set to "missing" if the documented values were outside the ranges given in the following table:

Laboratory parameter	Lower plausibility range	Upper plausibility range
Neutrophils	6%	100%
Lymphocytes	2.5%	85%
Monocytes	-	26%
Eosinophils	-	16%
Basophils	-	5%
Leukocytes	-	28 G/L
Platelets	-	1000 G/L
Hemoglobin*	-	20 g/dL
Creatinine	-	12 mg/dL
Calcium*	-	10 mmol/L
Sodium	-	320 mmol/L
Potassium	-	15 mmol/L
Phosphate	-	4 mmol/L
Magnesium	-	7 mmol/L
ALT (GPT)	1 U/L	1400 U/L

Laboratory parameter	Lower plausibility range	Upper plausibility range
AST (GOT)	1 U/L	1400 U/L
Gamma-GT	1 U/L	1400 U/L
Alkaline Phosphatase	1 U/L	5100 U/L
Total bilirubin	-	25 mg/dL
Albumin	-	100 g/L
LDH*	80 U/L	1000 U/L
Cholesterol	-	26 mmol/L
Triglycerides	-	35 mmol/L
HbA1c	1%	10%
Glucose	-	-**
TSH	-	21 mU/L
beta-2 Microglobulin	-	-

*: Risk factors according to Motzer score will be set prior to check on plausibility.
**: No plausibility range defined as values do not need to be fasting glucose values.

CYP3A4-inducing and inhibiting substances

A combination of Torisel® and CYP3A4 influencing substances should be handled carefully. Thus documented concomitant medication will be checked manually for CYP3A4 inducing and inhibiting substances by the medical expert.

If the number of patients who received either CYP3A4 inducing or inhibiting substances is sufficiently large, parts of the safety analysis will be repeated for those subgroups.

Comorbidities

In order to analyze data from prior and current version of the CRF regarding comorbidity, the categories presented in the current versions will be MedDRA coded. As the terms “Chron. Magen-Darm-Erkrankungen” and “Andere Krebserkrankung (maligne)” do not have an equivalent, those will be translated to “Chronic gastrointestinal disease” and to “Other malignant neoplasms”. A footnote will be added to state that coding is not completely according to MedDRA.