IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Tivozanib (renal cell carcinoma) –

Addendum to Commission A17-58[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D	European Quality of Life-5 Dimensions
FACT-G	Functional Assessment of Cancer Therapy-General
FKSI-DRS	Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MID	minimally important difference
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	mechanistic target of rapamycin
PT	Preferred Term
SAE	serious adverse event
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale
VEGFR	vascular endothelial growth factor receptor

1 Background

On 5 March 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-58 (Tivozanib – Benefit assessment according to § 35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") had used results of the TIVO-1 study, among other data, for the assessment of the added benefit of tivozanib in comparison with the appropriate comparator therapy (ACT). The company had presented analyses of a subpopulation of the TIVO-1 study for research question 3 of the benefit assessment (adult patients with advanced renal cell carcinoma who are vascular endothelial growth factor receptor [VEGFR] and mechanistic target of rapamycin [mTOR] pathway inhibitor-naive following disease progression after one prior treatment with cytokine therapy for advanced renal cell carcinoma).

The results of this subpopulation were not used in the dossier assessment because they were not transferable to the population relevant in accordance with research question 3 [1]. With its comment [3], the company presented analyses of a further restricted subpopulation of the TIVO-1 study. The G-BA commissioned IQWiG with the assessment of these analyses presented by the company on patients with documented cytokine pretreatment in the metastatic/unresectable setting.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Research question 3: Assessment of the subpopulation of the TIVO-1 study subsequently submitted

2.1 Relevance of the results for the benefit assessment

According to the Summary of Product Characteristics (SPC) of tivozanib [4], the population relevant for research question 3 of the benefit assessment comprises patients who are VEGFR and mTOR pathway inhibitor-naive following disease progression after one prior treatment with cytokine therapy for advanced renal cell carcinoma.

In its dossier [2], the company presented analyses of a subpopulation of the TIVO-1 study for this research question. Information on the study characteristics can be found in the dossier assessment [1]. The subpopulation of "patients after cytokine pretreatment" presented by the company comprised 154 patients.

The results presented by the company in the dossier were not used for the dossier assessment [1] because, based on the available information, the results of the subpopulation of the TIVO-1 study presented by the company were assessed as not transferable to the population relevant in accordance with research question 3. There were 2 decisive reasons for this: On the one hand, it could be inferred from the study documents that a relevant proportion of patients in the subpopulation received their cytokine therapy not for the advanced renal cell carcinoma. On the other, it was unclear whether the patients had had disease progression after their cytokine therapy and before inclusion in the study.

In its comment [3], the company explained that 11 (7%) patients of the population presented in the dossier had actually received no pretreatment with a cytokine. Of the remaining 143 patients, cytokine therapy in the metastatic stage was documented for 96 (67%) patients. With its comment, the company subsequently submitted the results for this subpopulation of patients with documented cytokine therapy in the metastatic/unresectable stage.

With this subpopulation subsequently submitted, the company addressed only part of the points of criticism described in the dossier assessment, i.e. the fact that cytokine therapy had to be administered in the metastatic stage. It remained unclear whether the patients had progression after their cytokine therapy, however. This was not an inclusion criterion of the TIVO-1 study, and this information was also not recorded in the study. It is therefore possible that patients without disease progression after cytokine therapy were included in the study. Hence the question of transferability of the results to the present research question can still not be answered, and the study can therefore still not be used for the benefit assessment.

Irrespective of this, the subpopulation of the TIVO-1 study subsequently submitted by the company showed no statistically significant difference between tivozanib and sorafenib for any of the patient-relevant outcomes. The results are presented below as additional information.

2.2 Results

Table 1 summarizes the results of the subpopulation of the TIVO-1 study subsequently submitted by the company on the comparison of tivozanib versus sorafenib. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's comments. Kaplan-Meier curves on the event time analyses can be found in Appendix A.

The company presented no information on patient characteristics, treatment durations and observation periods for the subpopulation subsequently submitted.

Table 1: Results (mortality, morbidity, health-related quality of life, side effects – time to event) – RCT, direct comparison: tivozanib vs. sorafenib

Study Outcome category Outcome	Tivozanib N	Tivozanib Median time to event in months [95% CI] Patients with event n (%)	Sorafenib N	Sorafenib Median time to event in months [95% CI] Patients with event n (%)	Tivozanib vs. sorafenib HR [95% CI]; p-value
TIVO-1					
Mortality					
Overall survival	44	31.0 [15.8; NC] 20 (45.5)	52	32.0 [19.5; NC] 25 (48.1)	0.97 [0.54; 1.74]; 0.913
Morbidity					
Symptoms (FKSI-DRS)				No usable data[a]	
Health status (EQ-5D VAS) – time to deterioration by ≥ 7 mm					
	42	3.7 [1.0; NC] 25 (59.5)	52	2.8 [1.1; 4.6] 36 (69.2)	0.75 [0.45; 1.26]; 0.271
Health status (EQ-5D VAS) – time to deterioration by ≥ 10 mm					
	42	4.9 [1.1; NC] 24 (57.1)	52	3.7 [1.8; 5.6] 34 (65.4)	0.75 [0.44; 1.28]; 0.295
Health-related quality of life					
FACT-G – time to deterioration by ≥ 5 points					
Total score	42	1.9 [1.0; 3.8] 34 (81.0)	51	1.9 [1.8; 2.8] 39 (76.5)	0.94 [0.59; 1.52]; 0.809
FACT-G subscales – time to deterioration by ≥ 2 points					
Physical well-being	42	1.9 [1.0; 2.8] 38 (90.5)	52	1.1 [1.0; 1.9] 45 (86.5)	0.83 [0.53; 1.29]; 0.396
Social well-being	43	3.1 [1.8; 10.2] 30 (69.8)	52	2.8 [1.8; 3.7] 36 (69.2)	0.84 [0.51; 1.39]; 0.503
Emotional well-being	42	3.7 [1.9; 6.4] 32 (76.2)	51	3.7 [1.9; NC] 29 (56.9)	1.36 [0.81; 2.26]; 0.241
Functional well-being	43	1.9 [1.0; 3.7] 35 (81.4)	51	1.9 [1.1; 3.7] 36 (70.6)	1.01 [0.63; 1.62]; 0.968
Side effects					
AEs (supplementary information)	43	0.5 [0.3; 0.9] 43 (100.0)	52	0.4 [0.3; 0.5] 51 (98.1)	–
SAEs	43	36.3 [36.3; 39.8] 13 (30.2)	52	NA 13 (25,0)	0.82 [0.36; 1.87]; 0.633
Severe AEs (CTCAE grade ≥ 3)	43	6.5 [3.5; 39.8] 29 (67.4)	52	2.8 [1.1; 9.0] 36 (69.2)	0.72 [0.43; 1.19]; 0.193
Discontinuation due to AEs	43	– 7 (16.3)	52	– 7 (13.5)	RR: 1.21 [0.46; 3.18]; 0.718[b]

(continued)

Table 1: Results (mortality, morbidity, health-related quality of life, side effects – time to event) – RCT, direct comparison: tivozanib vs. sorafenib (continued)

a: Response criterion was not prespecified; no MID can be derived on the basis of the reference cited by the company [5]. Continuous analyses are not available. The results of the analyses presented by the company are shown as supplementary information in Appendix B.
b: Institute's calculation of effect and CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [6]).
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; MID: minimally important difference; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Mortality

Overall survival

There was no statistically significant difference between tivozanib and sorafenib for the outcome "overall survival".

Morbidity

Symptoms (FKSI-DRS)

There were no usable data for the outcome "symptoms" (Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms [FKSI-DRS]). The company presented only analyses of the time to deterioration by 3 points for this outcome. As already described in the dossier assessment, this response criterion was not prespecified in the TIVO-1 study, and no valid minimally important difference (MID) can be derived on the basis of the reference cited by the company [5].

The results of the analyses presented by the company are shown as supplementary information in Appendix B.

Health status (EQ-5D VAS)

No statistically significant difference between tivozanib and sorafenib was shown for the outcome "health status" (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]) for either of the 2 operationalizations (time to deterioration by 7 mm or 10 mm).

Health-related quality of life

FACT-G

There was no statistically significant difference between tivozanib and sorafenib for the outcome "health-related quality of life" (Functional Assessment of Cancer Therapy-General [FACT-G]) for the total score.

Side effects

Serious adverse events, severe adverse events (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), discontinuation due to adverse events

There was no statistically significant difference between tivozanib and sorafenib for the outcomes "serious adverse events (SAEs)", severe adverse events (AEs)", and "discontinuation due to AEs".

Specific adverse events

A choice of specific AEs was not possible. The company only presented selective event time analyses for the following Preferred Terms (PTs): hypertension, fatigue, lipase increased, palmar-plantar erythrodysaesthesia syndrome, and diarrhoea (each CTCAE grade ≥ 3). Frequencies and event time analyses on further System Organ Classes (SOCs) and PTs were missing completely for the subpopulation subsequently submitted.

Subgroups and other effect modifiers

Of the subgroup analyses presented by the company, the following subgroups were considered relevant:

- age (< 65 years; ≥ 65 years)
- sex (female; male)
- geographical region (North America/Western Europe; Central/Eastern Europe)
- number of metastasizing sites/organs involved (1; ≥ 2)
- Memorial Sloan Kettering Cancer Center (MSKCC) score (0; ≥ 1)

The subgroup characteristic of time since diagnosis (< 1 year; ≥ 1 year) considered by the company in the dossier and in the comment was not deemed relevant. The company also provided no content-related reasons for the relevance. Besides, this characteristic is already included in the MSKCC score.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The subgroup analyses on the characteristics of geographical region and number of metastasizing sites did not include at least 10 patients in all subgroups and were therefore not considered. The subgroup analyses for the outcome "health status" (EQ-5D VAS) were also not considered because subgroup analyses were only available for the operationalization of time to deterioration by 7 mm, but not for the time to deterioration by 10 mm.

For the subgroup characteristics considered, relevant effect modifications were not shown for any of the patient-relevant outcomes.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of tivozanib from dossier assessment A17-58.

The following Table 2 shows the result of the benefit assessment of tivozanib under consideration of dossier assessment A17-58 and the present addendum.

Table 2: Tivozanib – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
First-line treatment of patients with favourable or intermediate prognosis (MSKCC score 0–2)	Bevacizumab in combination with interferon alfa-2a *or* monotherapy with pazopanib *or* **sunitinib**	Added benefit not proven
First-line treatment of patients with unfavourable prognosis (MSKCC score ≥ 3)	Temsirolimus	Added benefit not proven
In disease progression in VEGFR and mTOR pathway inhibitor-naive patients after one prior treatment with cytokine therapy	Axitinib *or* **sorafenib**	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MSKCC: Memorial Sloan Kettering Cancer Center; mTOR: mechanistic target of rapamycin; VEGFR: vascular endothelial growth factor receptor		

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Tivozanib (Nierenzellkarzinom): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A17-58 [online]. 29.01.2018 [Accessed: 07.02.2018]. (IQWiG-Berichte; Volume 591). URL: https://www.iqwig.de/download/A17-58_Tivozanib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. EUSA Pharma. Tivozanib (Fotivda): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 21.10.2017 [Accessed: 14.02.2018]. URL: https://www.g-ba.de/informationen/nutzenbewertung/324/.

3. EUSA Pharma. Stellungnahme zum IQWiG-Bericht Nr. 591: Tivozanib (Nierenzellkarzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A17-58. [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/324/ in the document "Zusammenfassende Dokumentation"].

4. EUSA Pharma. Fotivda 890 Mikrogramm/- 1.340 Mikrogramm Hartkapseln: Fachinformation [online]. 08.2017 [Accessed: 20.12.2017]. URL: https://www.fachinfo.de.

5. Cella D, Yount S, Brucker PS, Du H, Bukowski R, Vogelzang N et al. Development and validation of a scale to measure disease-related symptoms of kidney cancer. Value Health 2007; 10(4): 285-293.

6. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

Appendix A – Kaplan-Meier curves on the results of the subpopulation of the TIVO-1 study subsequently submitted by the company

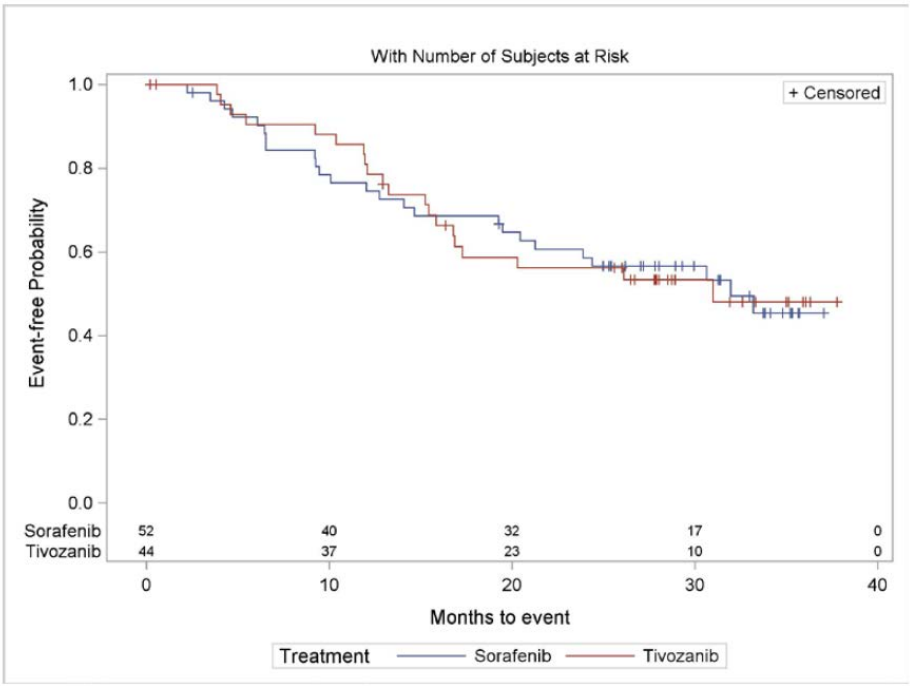

Figure 1: Kaplan-Meier curve for the outcome "overall survival" – RCT, direct comparison: tivozanib vs. sorafenib

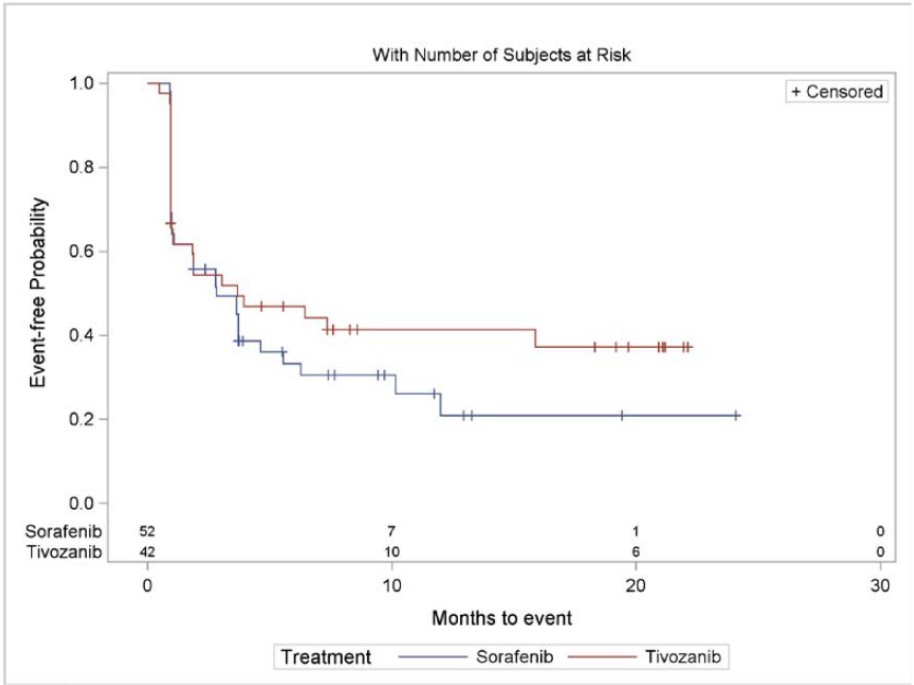

Figure 2: Kaplan-Meier curve for the outcome "EQ-5D VAS – time to deterioration by ≥ 7 mm" – RCT, direct comparison: tivozanib vs. sorafenib

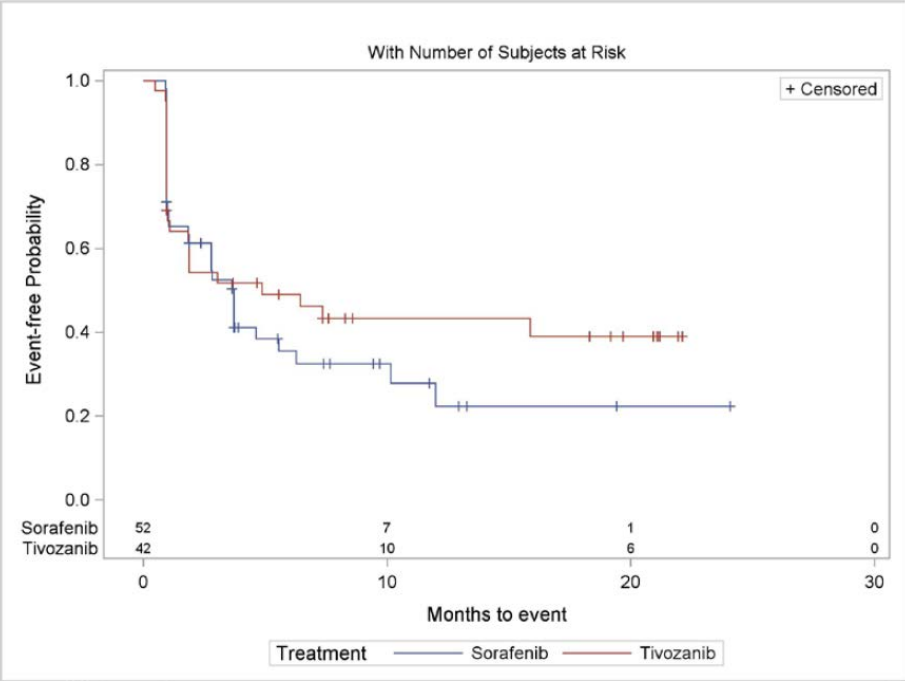

Figure 3: Kaplan-Meier curve for the outcome "EQ-5D VAS – time to deterioration by ≥ 10 mm" – RCT, direct comparison: tivozanib vs. sorafenib

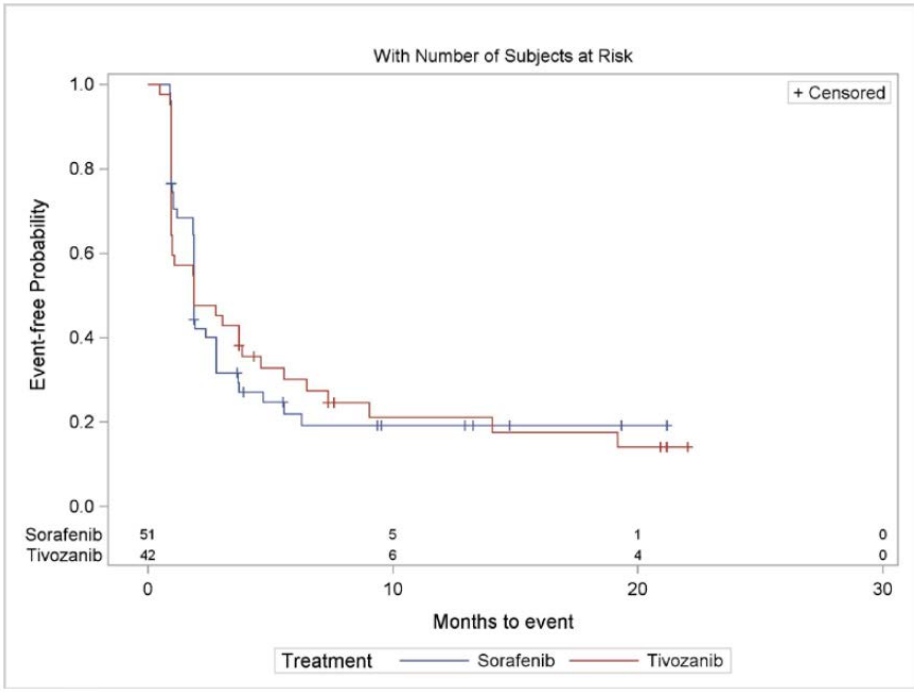

Figure 4: Kaplan-Meier curve for the outcome "FACT-G total score – time to deterioration by ≥ 5 points" – RCT, direct comparison: tivozanib vs. sorafenib

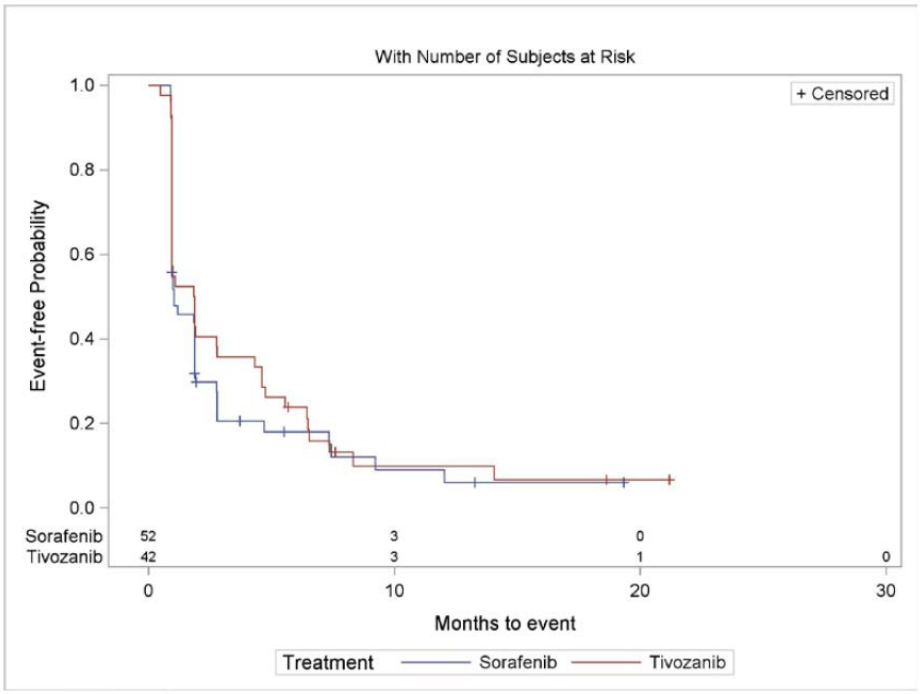

Figure 5: Kaplan-Meier curve for the outcome "FACT-G physical well-being – time to deterioration by ≥ 2 points" – RCT, direct comparison: tivozanib vs. sorafenib

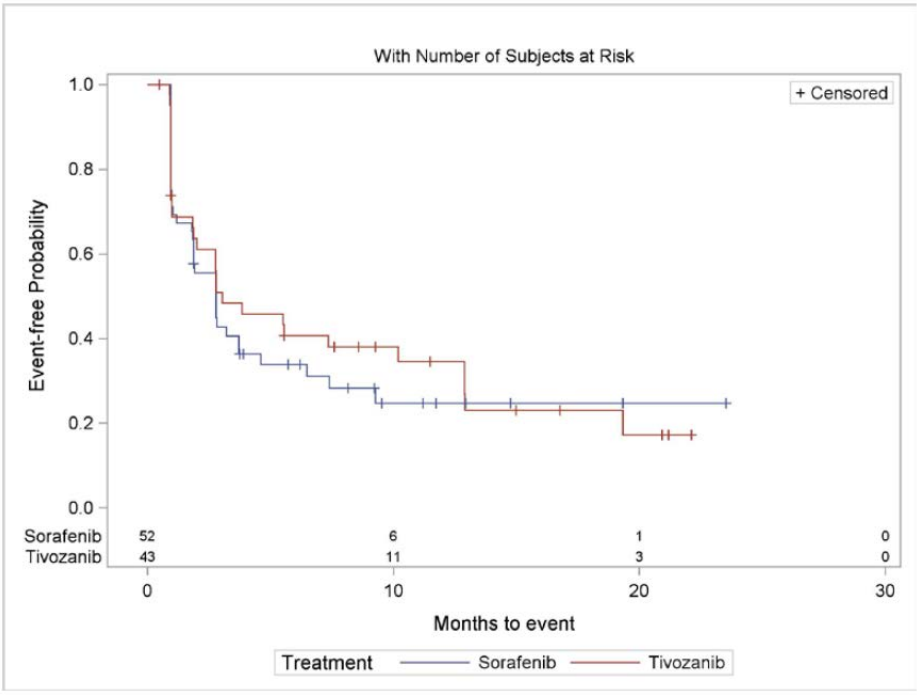

Figure 6: Kaplan-Meier curve for the outcome "FACT-G social well-being – time to deterioration by ≥ 2 points" – RCT, direct comparison: tivozanib vs. sorafenib

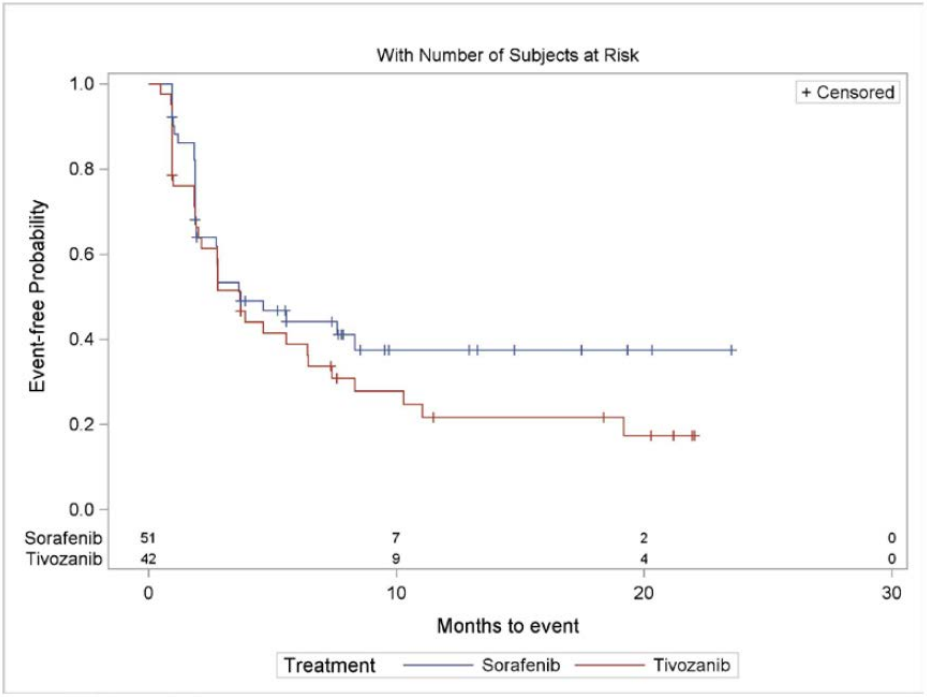

Figure 7: Kaplan-Meier curve for the outcome "FACT-G emotional well-being – time to deterioration by ≥ 2 points" – RCT, direct comparison: tivozanib vs. sorafenib

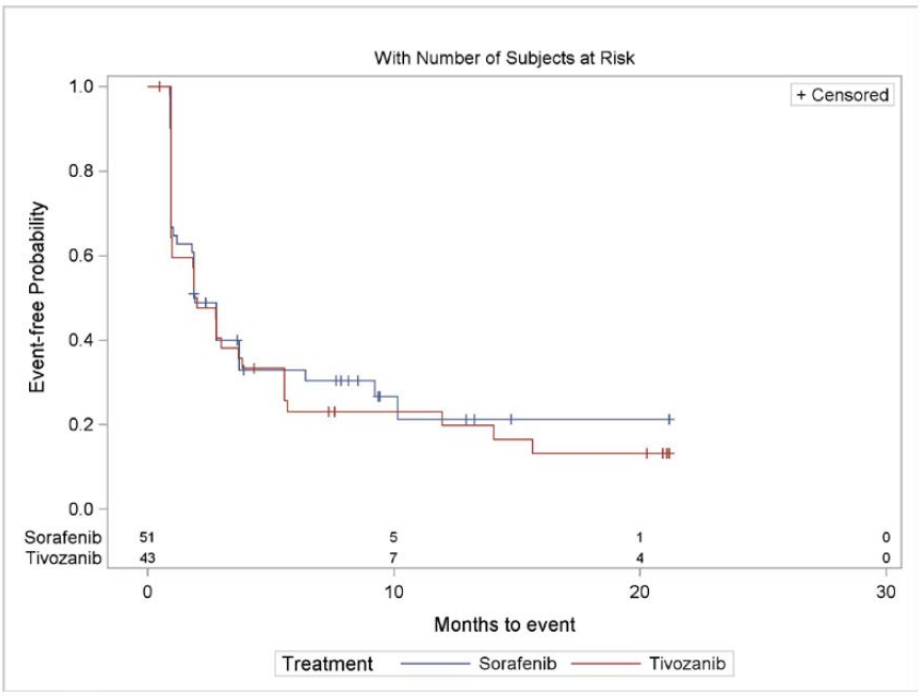

Figure 8: Kaplan-Meier curve for the outcome "FACT-G functional well-being – time to deterioration by ≥ 2 points" – RCT, direct comparison: tivozanib vs. sorafenib

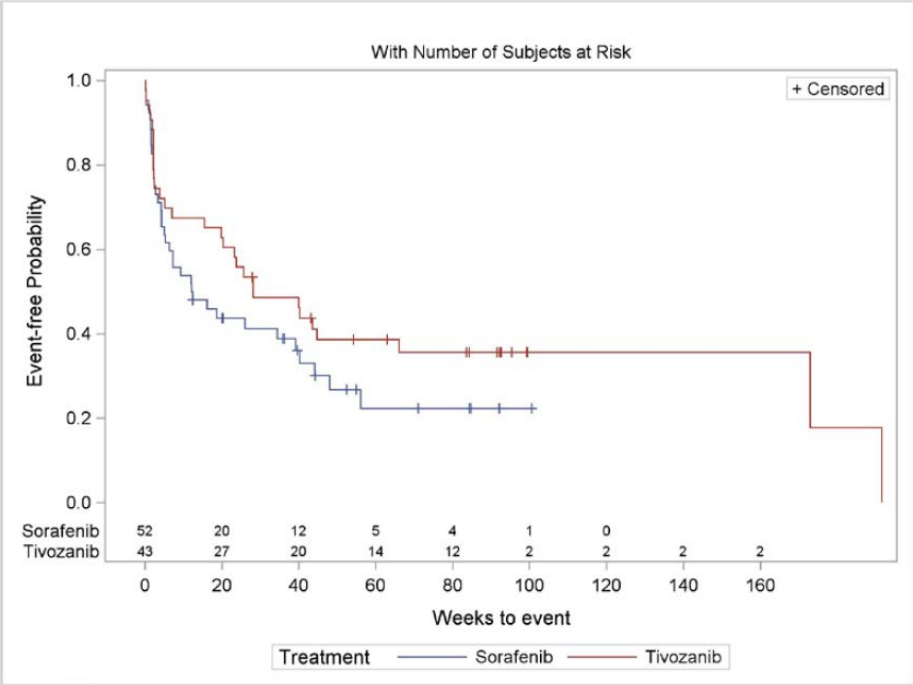

Figure 9: Kaplan-Meier curve for the outcome "severe AEs (CTCAE grade ≥ 3)" – RCT, direct comparison: tivozanib vs. sorafenib

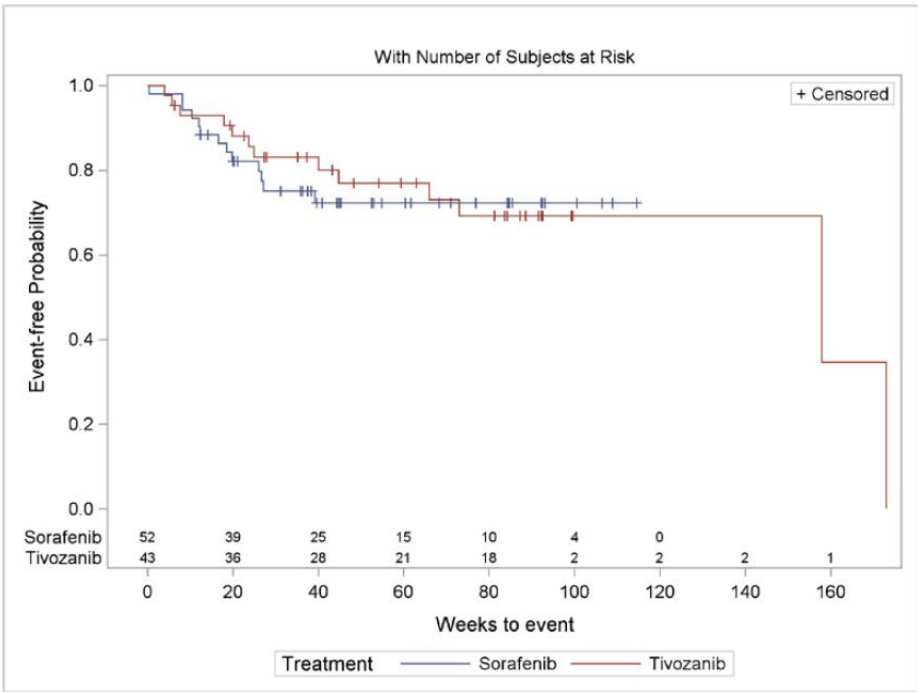

Figure 10: Kaplan-Meier curve for the outcome "SAEs" – RCT, direct comparison: tivozanib vs. sorafenib

Appendix B – Results from the TIVO-1 study presented as supplementary information

Table 3: Results (morbidity) – RCT, direct comparison: tivozanib vs. sorafenib

Study Outcome category Outcome	Tivozanib N	Tivozanib Median time to event in months [95% CI] Patients with event n (%)	Sorafenib N	Sorafenib Median time to event in months [95% CI] Patients with event n (%)	Tivozanib vs. sorafenib HR [95% CI]; p-value
TIVO-1					
Morbidity					
Symptoms (FKSI-DRS) – time to deterioration by 3 points					
	42	4.6 [1.9; 6.4] 32 (76.2)	51	2.8 [1.9; 3.6] 40 (78.4)	0.78 [0.49; 1.25]; 0.300

CI: confidence interval; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus