FOLFIRI combined with Sunitinib versus placebo in patients with chemorefractory advanced adenocarcinoma of the stomach or lower esophagus: A randomized, placebo-controlled phase II AIO trial.

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Abstract (250 words)

Background As multi-targeting inhibitor of VEGFR1-3, PDGFR-α-β, and other RTKs, Sunitinib (SUN) is established for renal cancer and gastrointestinal stromal tumors. In advanced refractory esophagogastric cancer, SUN was associated with good tolerability but limited tumor response. Thus, this double-blind, placebo-controlled, multicenter phase II trial evaluated efficacy, safety and tolerability of SUN added to second or third-line FOLFIRI.

Methods Patients were randomized to receive 6-week cycles including FOLFIRI plus sodium folinate (Na-FOLFIRI) every 2-weeks and SUN continuously for 4-weeks or Placebo (PL), followed by 2-week rest. Treatment continued until disease progression or unacceptable toxicity/adverse events (AEs). The primary endpoint was progression-free survival (PFS).

Results: 91 patients were randomized, one withdrawn, leaving 45 in each group. Patient characteristics were well balanced. On average, patients received SUN/PL during 3.7/3.4 cycles, respectively. Median PFS was similar with 3.6 versus 3.9 months (HR 1.02, 95%CI 0.66-1.59, *P*=0.92) for FOLFIRI+SUN vs. FOLFIRI+PL, respectively. There was a trend for longer median overall survival for FOLFIRI+SUN versus PL with 10.3 vs. 9.1 months (HR 0.81, 95%CI 0.51-1.30, *P*=0.39). Objective responses and tumor control were achieved in 20%/29% and 60%/56% for FOLFIRI+SUN/FOLFIRI+PL, respectively. Generally, FOLFIRI+SUN was well tolerated and no unexpected toxicities/AEs occurred. Main Grade ≥3 AE was neutropenia observed in 62%/22% for FOLFIRI+SUN/FOLFIRI+PL, respectively.

Conclusions: SUN added to FOLFIRI had a trend for better overall survival versus FOLFIRI alone and showed a reasonable tolerability. However, there was no

significant improvement of PFS and response rates in chemotherapy-resistant gastric cancer patients. Further combinations with tyrosine kinase inhibitors (TKIs) are warranted.

Key words (5 words) chemorefractory advanced gastric cancer; tyrosine kinase inhibitor; sunitinib; second-line; FOLFIRI

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Introduction

Overall survival (OS) for patients with locally advanced and metastatic gastric cancer (AGC) remains poor with a median of 8-11 months (1-4). Nearly every internationally established first-line palliative chemotherapy contains platin and pyrimidine derivatives, with one frequently used European regimen like epirubicine, cisplatin and fluoropyrimidine (ECF), cisplatin and fluoropyrimidine (CF) in the US and, the common cisplatin and S-1 in Japan (3, 5, 6). Various clinical trials have investigated newer chemotherapeutic combinations with oxaliplatin, capecitabine, irinotecan, and/or docetaxel without clear additional survival benefits in comparison to standard regimens (1, 3, 5-11).

In second-line treatment, irinotecan alone or in combination with 5-FU/leucovorin has proven benefit (12, 13). In several prospective randomized second-line trials, chemotherapy has shown a significant prolonged OS compared to best supportive care (BSC), e.g. for irinotecan, of 4.0 and 2.4 months, respectively, as well as for docetaxel or irinotecan 5.2 or 5.3 vs 3.8 or 3.6 months (14, 15, 16). Since none of the investigated regimens demonstrated significant superiority over the others, the combination of irinotecan, 5-fluorouracil (5-FU) and folinic acid (FOLFIRI) was selected as a safe and efficient combination for patients with AGC including an improvement of quality of life (8).

Tumor angiogenesis, growth, and metastasis can be inhibited by blocking receptor tyrosine kinases (RTKs) overexpressed in human GC, including VEGFRs or PDGFRs (2, 17). Disease progression or poor survival was associated with VEGF, EGFR and PDGF-A expression in the tumor (18,19). Agents such as gefitinib, erlotinib, bevacizumab, and cetuximab specifically target RTKs through a single receptor

pathway and have been investigated in phase II-III studies with AGC patients (20). However, in many tumors, several RTKs are co-expressed (17). SUN malate is an oral, multi-targeted RTK inhibitor of VEGFR-1, -2 and -3, PDGFR-α and -β and several other RTKs (21, 22) and may have additional benefits compared to single receptor targeted inhibition. In patients with gastrointestinal stromal tumors (refractory or intolerant to imatinib) and advanced renal-cell carcinoma, single agent SUN had superior efficacy to standard treatment with acceptable toxicity (23, 24). In *in-vitro* data and in two recent clinical phase II studies in patients with chemorefractory AGC, SUN showed promising preliminary activity and revealed manageable toxicity (25). However, SUN alone may not further improve PFS and OS compared to second-line chemotherapy including docetaxel, paclitaxel, irinotecan, and mitomycin C. This double-blind, placebo-controlled, multicenter phase II clinical trial was conducted to evaluate efficacy, safety and tolerability of SUN versus PL as add-on therapy to second-line FOLFIRI treatment regimen.

Patients and methods

Patient population

Main inclusion criteria: male or female patients aged ≥18 years with histologically proven gastric adenocarcinoma including adenocarcinoma of the esophagogastric junction or lower esophagus; failure of any prior docetaxel and/or platinum-based chemotherapy, locally advanced disease associated with at least one measurable lymph node or measurable metastatic disease according to RECIST 1.1 criteria; Karnofsky index 100-70%; adequate hematological, hepatic and renal function.

Main exclusion criteria: prior treatment with irinotecan, VEGF, VEGFR or RTK inhibitor; any prior palliative radiotherapy of the target lesions; treatment with potent

CYP3A4 inhibitors 7 days prior or inducer 12 days prior of SUN/PL dosing, except dexamethasone for the prevention of chemotherapy-induced emesis; concurrent treatment with anticoagulant medication, except low molecular weight heparin.

Study design and treatment

This randomized, double-blind, placebo-controlled, multicenter phase II trial was conducted at 15 sites in Germany and was performed according to ICH-GCP and the Declaration of Helsinki. Registration was done in the public NCT Clinical Trials Registry (NCT01020630).

Patients were randomized to receive either SUN or PL in addition to backbone two-weekly FOLFIRI plus sodium folinate (Na-FOLFIRI) chemotherapy, given as simultaneous 48 hour infusion of 5-FU combined with sodium folinate.

Patients were treated until occurrence of any of the following: progressive disease (PD), intolerable AEs, any AE that results in a treatment interruption of >14 days within the active treatment cycle or >4 weeks between consecutive active treatment cycles, or withdrawal of consent.

SUN (starting dose: 25 mg) or PL was orally administered once daily for 4 consecutive weeks followed by a 2-week rest to comprise a complete cycle of 6 weeks. In patients experiencing SUN-related toxicity, the dose could be reduced to 12.5 mg daily and/or interruption was allowed. Subsequent dose adjustment was permitted based on outcome.

FOLFIRI was administered in the following regimen: Irinotecan (180 mg/m²) intravenously on Day 1, immediately followed by 5-FU bolus (400 mg/m²) and 46-

hour infusion of sodium folinate (400 mg/m²) and 5-FU (2000 mg/m²) every two weeks, i.e. 3 courses of FOLFIRI in every 6-week SUN/PL cycle (26, 27).

Safety and efficacy assessment

AEs were graded according to National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE), version 4.0. All AEs occurring between the first and up to 28 days after application of the last dose were documented. Baseline tumor-related signs and symptoms were recorded as AEs if they worsened in severity.

Tumor response was measured by CT scan after cycle 1 and 2, then after every 2 cycles and assessed and graded by RECIST 1.1. Screening assessments were carried out within 28 days prior to start of treatment. After the end of treatment (EOT), an EOT visit was performed within 30 days. Patients were followed-up for 1 year.

Trial objectives

The primary endpoint was PFS according to RECIST 1.1. Secondary endpoints were objective response rate, tumor control rate (CR + PR + stable disease (SD)), duration of disease stabilization, 1-year OS, and safety and tolerability of the PL-controlled combination therapy compared to standard second-line therapy.

Statistical analysis

90 patients were to be enrolled to assign 43 patients to each treatment group, taking into account a drop-out rate of 5%. A median PFS of 3 months was assumed for the control group. A total of 86 events had to be observed to show a 50% improvement

(4.5 months median PFS) under SUN versus PL to ensure a power of 80% at a one sided significance level alpha of 15%.

PFS and OS were evaluated by Kaplan-Meier estimates and hazard ratios (HR) resulted from a Cox model including location of the primary tumor (involvement of esophageal junction), number of metastatic sites (≤1/>1) and Karnofsky performance status (PS) at baseline (>80/≤80). The analysis of secondary endpoints and all further data were interpreted descriptively.

The primary analysis population was the intention-to-treat (ITT) set comprising all subjects with at least one available post-baseline assessment of the primary analysis variable. The safety analysis set included all subjects who had received at least one dose of trial medication.

Results

Patient characteristics

91 patients were enrolled. One patient withdrew consent immediately after randomization without having taken any trial medication. Therefore, the ITT set consisted of 90 patients (SUN/PL 45/45).

Demographic and baseline characteristics are provided in Table 1. Nearly all patients had an adenocarcinoma of the stomach or esophageal junction. 76% of patients in both arms had received one palliative treatment line, and 20%/24% of SUN/PL patients had obtained two treatment lines before study recruitment, respectively. Two patients of the SUN group had obtained three and four treatment lines before study entry.

Follow-up was done regularly at 3, 6, 9 and 12 months (+/- 2 weeks) after the EOT visit until progression, which was observed in scheduled staging according to final protocol in 37 and 33 patients of SUN/PL group, respectively. Until end of study, 4/1 of SUN/PL patients had no signs of PD. Therefore, baseline characteristics and conditions of follow-up were equal in both arms.

Treatment

On average, patients started 3.7/3.4 cycles of treatment in SUN/PL group, respectively. Dose was reduced to 12.5 mg in 9/5 patients (SUN/PL). Dose was never increased. 32 and 28 SUN/PL patients terminated treatment due to PD, respectively. Further reasons for ending treatment (SUN/PL) were treatment interruption (4/2), toxicity (1/3), and withdrawal of informed consent (1/2).

Efficacy

Efficacy analysis was carried out on the ITT population. Fig. 2 illustrates the survival distribution per treatment group for PFS and OS by Kaplan-Meier curves. The median PFS was similar in both groups, with 111 and 119 days (3.6 vs. 3.9 months) for SUN and PL patients, respectively (HR 1.02, 95% CI 0.66-1.59, *P*=0.92). OS showed a trend in favor of SUN with 315 vs. 278 days (10.3 vs 9.1 months) in the PL arm. However, the difference was not statistically significant (HR 0.81, 95% CI 0.51-1.30, *P*=0.39). The probability of 1-year survival was 35% and 31% and to live 180 days was 0.66 and 0.59 for SUN and PL, respectively.

Evaluation of response and tumor control was performed in 41/42 patients (SUN/PL see Table 2). Best responses according to RECIST 1.1 were defined in 82 patients. Objective response (CR or PR observed at least once), was seen in 9 and 13 patients of the SUN and the PL group, respectively. Tumor control (CR, PR, or SD observed at least once), was seen in 27 and 25 patients of the SUN and PL group, respectively. Vital state was followed until death in 39 patients in each group. Disease progression was the cause of death in 35 patients with SUN and in 33 PL patients. 6/6 patients (SUN/PL) were not followed until death, 2/0 of them had no signs of PD when withdrawing their consent in further participation.

Safety and tolerability

Frequencies of grade ≥3 AEs are shown in Table 3. All patients experienced at least one AE. 140 and 105 SAEs were reported in 35 SUN and 36 PL patients, respectively. 35 SUN and 34 PL patients had at least one AE CTC Grade ≥3. 21 versus 12 and 6 versus 7 SUN versus PL patients had AEs of CTC Grade 4 or more and Grade 5, respectively.

Most frequent AEs of any grade at least possibly related to trial medication (SUN/PL) included nausea (27/23), neutropenia (31/11), diarrhea (20/19), fatigue (18/15), vomiting (15/14), leukopenia (19/9), stomatitis (12/10), alopecia (11/10), decreased appetite (10/9), mucosal inflammation (9/8), constipation (5/6), asthenia (6/5), pyrexia (4/6), anemia (5/5), and palmar-plantar erythrodysaesthesia syndrome (8/1).

AEs of Grade ≥3 at least possibly related to study medication comprised neutropenia (26/9), leukopenia (13/5), fatigue (1/4), diarrhea (1/4), vomiting (3/1), pulmonary embolism (2/1), mucosal inflammation (1/2), nausea (1/2), thrombocytopenia (1/1), general physical health deterioration (0/2), and increased Gamma-

glutamyltransferase (2/0), and (9/10) other conditions each occurring in one patient only.

Discussion

Patients with chemorefractory AGC have a poor prognosis. After failure of a first-line treatment, various options for a second-line treatment were analyzed in previous studies, but median survival time remained always below 10 months. Best results were achieved with everolimus (10.1 months) (28) FOLFIRI (9.1 months) (29), a combination of docetaxel and oxaliplatin (8.1 months) (30), and paclitaxel (7.8 months) (31). Recent randomized phase III trials of chemotherapy versus best supportive care (BSC) had even lower OS times (14-16) In Europe, FOLFIRI has been considered to be an established option after failure of a platinum-containing first-line therapy (4).

Trials concerning other biologicals are currently ongoing or have shown far worse results than those mentioned above. Cetuximab with 6.1 months OS and 2.8 months PFS was the most effective (32). Some good results with biologicals in first-line-therapy of AGC cause hope for the future (20).

In our study, a beneficial effect of the addition of SUN to FOLFIRI on the endpoints PFS, OS and duration of disease stabilization could not be verified. The primary endpoint PFS could not be reached and median PFS time was similar with 111 vs. 119 days (3.6 vs. 3.9 months) for FOLFIRI+SUN vs. FOLFIRI+PL, respectively. Regarding OS, patients with SUN had a trend for a better OS with median survival time 315 vs. 278 days (SUN/PL). However, the difference was not statistically significant. OS of FOLFIRI+PL patients was highly consistent with one Asian study

investigating the FOLFIRI regimen in second-line therapy that resulted in PFS of 3.2 months and OS of 9.1 months (29).

Two previous second-line studies with SUN monotherapy revealed PFS and OS of 1.3 and 2.3 as well as 5.8 and 6.8 months, respectively (25, 33). Even if cross study comparison has limitations, combination of FOLFIRI with SUN showed an improvement with respect to those endpoints, compared to SUN monotherapy. Concerning OS, the general benefit of second-line therapy was demonstrated by Thuss-Patience and Kang. Park et al. (34) were the first to evaluate subjective Quality of Life in 43 patients using the EORTC QLQ-C30 and HADS questionnaires. Improvements were apparent nearly in all items independently of response to therapy. It might therefore be reasonable to attribute the same importance to toxicities, feasibility and quality of life as to response and survival rates.

Generally, the combination of SUN and FOLFIRI showed a reasonable tolerability. As expected, neutropenia and leukopenia were more frequent in the SUN arm. These data are comparable with a phase I study with 37 patients (35). In our previous study investigating SUN alone for chemorefractory AGC patients, SUN-related hematologic toxicities were mostly lower for thrombocytopenia, neutropenia, and anemia in 21%, 15%, and 13%, respectively. (25)

With respect to non-hematological AEs, diarrhea, vomiting, and lethargy were most frequent in patients being treated with 37.5 mg/d in the study by Starling et al. (35) and were comparable to our study. The frequently observed non-hematological toxicities fatigue, vomiting/nausea, mucosal inflammation, anorexia and diarrhea by SUN alone were indeed higher in the current study and may be contributed to the backbone chemotherapy or the underlying disease (25). In the phase III study of

irinotecan alone by Thuss-Patience et al. diarrhea was the most frequent CTC-grade 3/4 toxicity in 26% of patients (14). In one phase III trial comparing docetaxel, irinotecan and BSC, common grade 3/4 toxicities were neutropenia (15% vs. 18% vs. 2%), anemia (30% vs. 32% vs. 23%), and fatigue (26% vs. 10% vs. 27%), as well as thrombocytopenia, anorexia, nausea, diarrhea, and stomatitis (15). As in our study particularly fatigue occurred in 49% vs. 51% SUN/PL patients, it may also be related to the weaker general condition of second-line AGC patients.

Smaller studies investigating FOLFIRI alone in AGC patients reported neutropenia, anemia, nausea, vomiting, diarrhea, and stomatitis as common toxicities of this regimen (36, 37). These results coincide with the most frequently observed toxicities in our study.

The combination therapy of daily 37.5 mg SUN and FOLFIRI was investigated in patients with metastatic colorectal cancer (mCRC) (38). This phase III study was stopped prematurely due to the occurrence of more Grade ≥3 AEs with SUN than with PL and a higher incidence of toxicity-related deaths. Strikingly, the differences between the treatment groups in our study were less prominent with mCRC patients compared to this study. Since toxicity related deaths were also less frequent, the lower daily dose of 25 mg SUN may be more attractive to be combined with FOLFIRI.

In summary, although combination therapy of SUN and FOLFIRI in the present study demonstrated positive trends in survival times and showed a reasonable tolerability, the addition of SUN did not meet its primary end point. Currently, molecular biomarkers are under investigation to further define potential subgroups of patients who may benefit from the addition of SUN to FOLFIRI.

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Conflicts of interest

Educational and research funding was provided by Pfizer, Berlin to MM and PRG.

Table and Figure Legends

Table 1

Demographic and baseline characteristics in the ITT population

Table 2

Response and tumor control. ITT population (N=90)

Table 3

Frequency of adverse events Grade ≥3, reported in ≥2 (4%) of patients of either group regardless of causality

Figure 1

Disposition of patients

Figure 2

Kaplan-Meier curves for progression-free survival and overall survival in the primary analysis Population. (mITT). Hazard ratios estimated by Cox proportional hazards model; PFS, progression-free survival; HR, hazard ratio; mITT, modified intention-to-treat

Table 1: Demographic and baseline characteristics in the ITT population

Characteristic	Sunitinib		Placebo	
	N	n (%)	N	n (%)
Number of patients	45	100	45	100
Age (years)				
Mean (SD)	59 (11)		57 (11)	
Median (Range)	62 (37-76)		57 (28-84)	
Gender				
Male	33	73	30	67
Female	12	27	15	33
Karnofsky Performance Status				
90-100%	27	60	26	58
70-80%	16	36	18	40
Histology: Adenocarcinoma of				
Stomach	22	49	24	53
Cardia	23	51	21	47
Treatment lines before study entry				
1	34	76	34	76
2	9	20	11	24
3 or 4	2	4	-	-
Screening pT-stadium				
0	-	-	1	2
1	1	2	1	2
2	5	11	7	16
3	22	49	18	40
4	7	16	10	22
X	10	24	8	18
Screening pN-stadium				
0	2	4	7	16
1	16	36	11	24
2	9	20	9	18
3	8	18	7	13
X	10	22	11	24
Screening pM-stadium				
0	9	20	4	8
1	32	71	39	87
X	4	9	2	4

Table 2: Response and tumor control. ITT population (N=90)

	Sunitinib		Placebo	
	N=45	**100%**	**N=45**	**100%**
Best response				
Complete response (CR)	-	-	5	11
Partial response (PR)	9	20	8	18
Stable disease (SD)	18	38	12	27
Progressive disease (PD)	14	29	16	36
Not evaluable*	4	13	4	11
Objective response (CR + PR)	9	20	13	29
Tumor control rate (CR + PR + SD)	27	58	25	56

* Of 4+4 patients non evaluable for best response 2+3 the likely best response is PD, because progression or death occurred within 45 days, for 2+1 patients progression was seen not before day 114.

Table 3: Frequency of adverse events of Grade ≥3,

	Sunitinib plus FOLFIRI*		Placebo plus FOLFIRI*	
Adverse events	**N = 45**	**100%**	**N = 45**	**100%**
Neutropenia	28	62	10	22
Leukopenia	13	29	7	16
Diarrhoea	1	2	7	16
Vomiting	4	9	3	7
Disease progression	4	9	3	7
Nausea	3	7	3	7
General physical health deterioration	2	4	4	9
Gamma-glutamyltransferase increased	5	11	1	2
Fatigue	1	2	4	9
Cholangitis	1	2	3	7
Pulmonary embolism	2	4	2	4
Subileus	.	.	4	9
Mucosal inflammation	2	4	2	4
Back pain	.	.	3	7
Dehydration	2	4	1	2
Abdominal pain	1	2	2	4
Blood alkaline phosphatase increased	2	4	1	2
Pneumonia	.	.	3	7
Pain	.	.	3	7
Dysphagia	2	4	1	2
Ileus	1	2	1	2
Paraesthesia	1	2	1	2
Abdominal pain upper	1	2	1	2
Renal failure	2	4	.	.
Decreased appetite	1	2	1	2
Anaemia	2	4	.	.
Blood bilirubin increased	2	4	.	.
Infection	2	4	.	.
Thrombosis	1	2	1	2
Oesophageal stenosis	1	2	1	2
Sepsis	1	2	1	2
Device related infection	2	4	.	.
Thrombocytopenia	1	2	1	2
Dyspnoea	1	2	1	2
Ascites	2	4	.	.
Alanine aminotransferase increased	1	2	1	2
Aspartate aminotransferase increased	1	2	1	2

Abbreviation: FOLFIRI: 5-fluorouracil, leucovorin and irinotecan
*Schedule: 4/2, 4 weeks on treatment, followed by 2 weeks off; dosage: starting dose 25 mg/day

Figure 1: Disposition of patients

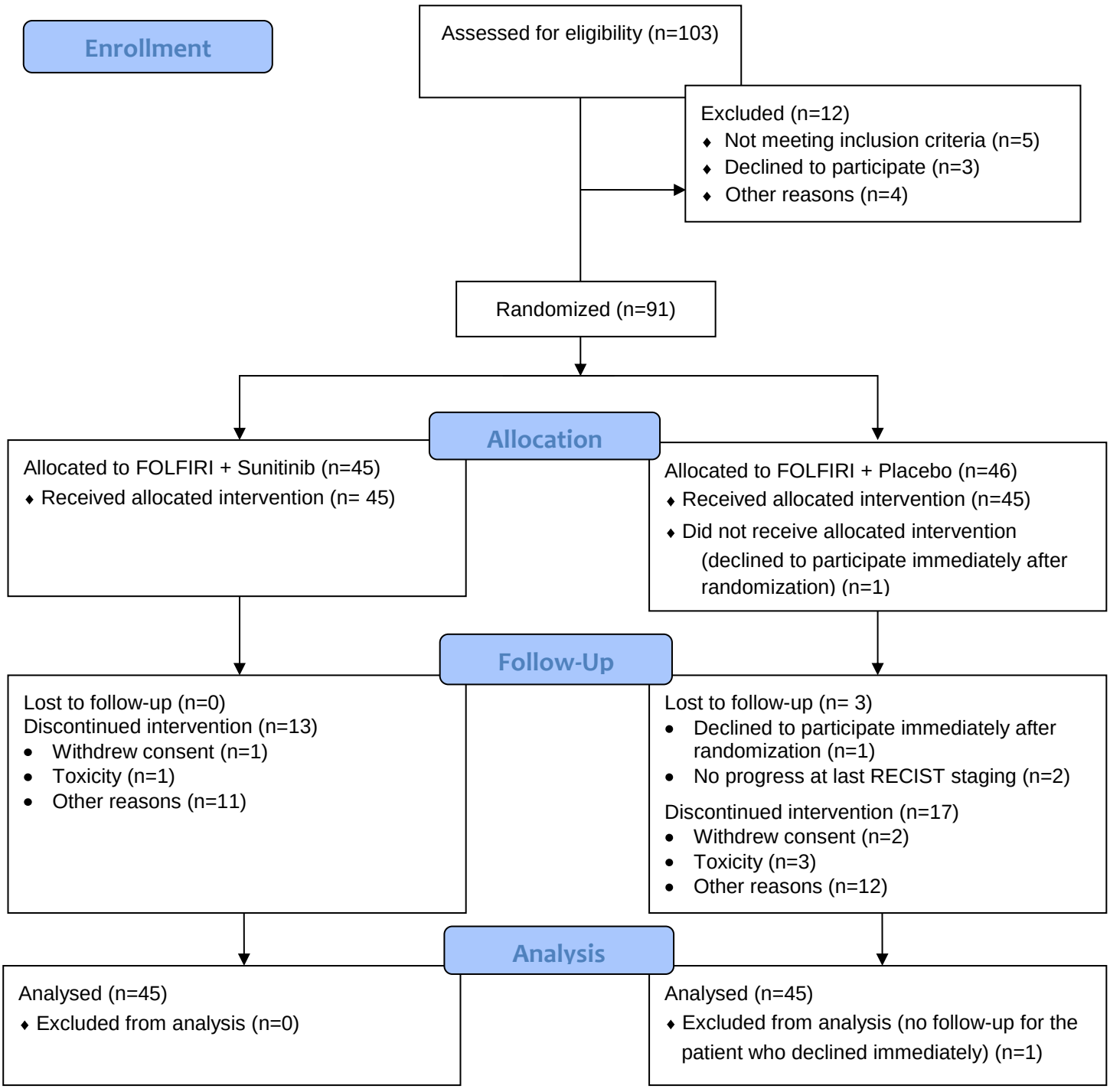
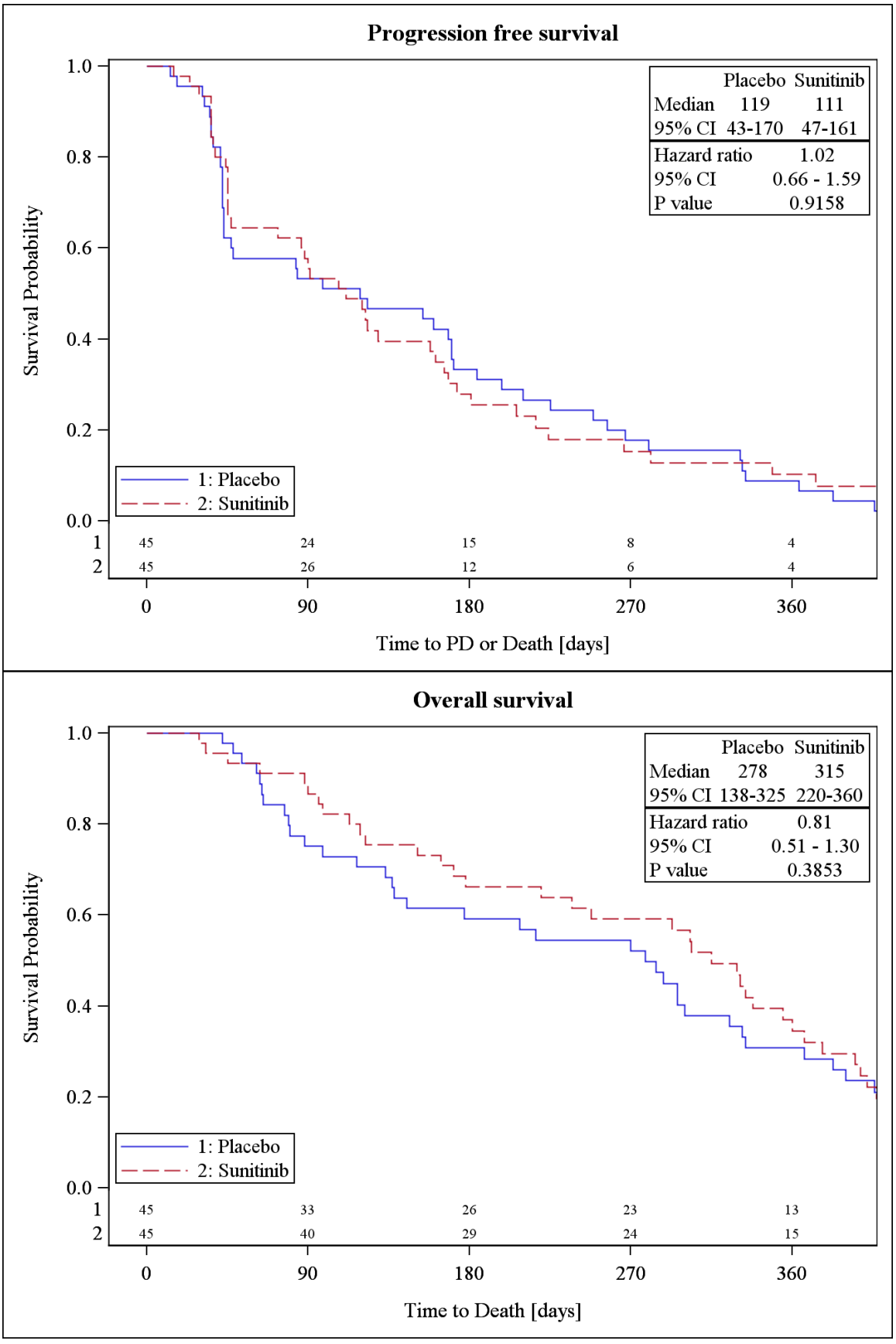


Figure 2: Kaplan-Meier estimates of progression-free survival and overall survival. Analysis set ITT, N = 90



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