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ORIGINAL RESEARCH

Liver Transarterial Chemoembolization and Sunitinib for Unresectable Hepatocellular Carcinoma: results of the PRODIGE 16 study.

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Disclosures: Dr Sefrioui has received honoraria as speaker or/and advisory role from Amgen, Ipsen and Servier. Dr Silvain has received honoraria as a speaker for Bayer. Dr Turpin has received honoraria from Amgen, Servier, Merck-Serono and travel grant from AstraZeneca, Pfizer, Merck-Serono and Sanofi. Sebastien Dharancy has received lecture fees from Novartis, Intercept, Astellas, and Abbvie and serving as a board member of Novartis and Nanobiotix. All other authors have no relevant COI.

Statement of Ethics

All patients provided written informed consent. The trial was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guideline on Good Clinical Practice, and the French laws and regulations. An Independent Data and Safety Monitoring Committee monitored efficacy and safety data.

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List of Abbreviations:

HCC: HepatoCellular Carcinoma

TACE : Trans-Arterial ChemoEmbolization

VEGF: Vascular Endothelial Growth Factor

PFS : Progression-Free Survival

OS: Overall Survival

EASL: European Association for the Study of the Liver

ITT: Intent-To-Treat

mITT: modified Intent-To-Treat

CI: Confidence Interval

Abstract

Background: Trans-arterial chemoembolization (TACE) is one first-line option therapy for patients with hepatocellular carcinoma (HCC) not suitable for surgical resection.

Aims: We evaluated the effects of sunitinib plus doxorubicin-TACE on bleeding or liver failure.

Methods: Seventy-eight patients with HCC were included in this randomized, double-blind study. They received one to three TACE plus either sunitinib or placebo four weeks out of six for one year. The occurrence of severe bleeding or liver failure was assessed during the week after the TACE. The safety and survival outcomes were evaluated.

Results: No bleeding complication was reported. One and two liver failures were respectively observed in sunitinib and placebo patients. Compliance to sunitinib treatment was acceptable.. Sunitinib dose reduction occurred in 37% of patients due to acute toxicity. Main grade 3-4 toxicities were: thrombocytopenia, neutropenia, increased bilirubin, increased ALT and asthenia. In the sunitinib group, the median PFS and OS were 9.05 [5.81 ; 11.63] and 25.0 [13.5 ; 36.8] months, respectively. In the placebo group, the median PFS and OS were 5.51 [4.14 ; 7.79] and 20.5 [15.1 ; 30.6] months, respectively.

Conclusions: TACE plus sunitinib in the first-line therapy for patients with HCC not suitable for surgical resection was feasible.

ClinicalTrials.gov number, NCT0116420

Keywords: Transarterial chemoembolization ; sunitinib ; hepatocellular carcinoma ; liver failure ; bleeding complications

Introduction

Liver cancer is the second leading cause of cancer deaths worldwide with hepatocellular carcinoma (HCC) accounting for 85-90% of all liver cancer [1]. Transarterial chemoembolization (TACE) is the recommended treatment for intermediate stage unresectable HCC [2]. Several randomized trials demonstrated a survival benefit for patients treated with TACE compared to symptomatic treatment [3-5]. Elevated risk of relapse within two years post TACE are frequently observed due to a tumor re-vascularization. Increased serum vascular endothelial growth factor (VEGF) levels during the month following TACE are associated with a higher risk of metastatic relapse [6]. Therefore, the use of neoadjuvant plus adjuvant therapy with angiogenesis inhibitors could potentially reduce the risk of relapse after TACE. Development of new systemic therapies for HCC has evolved since the approval of sorafenib in 2007. First-line therapies such as sorafenib and lenvatinib showed significant effect on overall survival (OS) in randomized clinical trials [7-9]. Favorable results on both median OS and progression-free survival (PFS) were also reported in a randomized trial comparing TACE plus sorafenib with TACE alone [10]. Phase 3 studies comparing TACE plus new systemic molecular targeted agents (brivanib and orantinib) to TACE alone failed to show any significant clinical effect [11].

Sunitinib is a multi-targeted receptor tyrosine kinase inhibitor with known antiangiogenic and antitumor activities targeting VEGF receptors and the platelet-derived growth factor receptor [12,13]. Additionally, sunitinib increased tumor doxorubicin delivery by improving tumoral hemodynamics and blood flow [14]. Sunitinib administered before and after TACE might thus be a suitable therapy strategy in patients with HCC. The results of two phase II studies assessing safety

and efficacy of sunitinib in patients with advanced HCC suggested outstanding antitumor activity. Faivre et al reported a low tumor response rate and a high toxicity profile with sunitinib administered at a dose of 50mg/day [15]. Continuous sunitinib treatment at 37.5 mg administered daily also showed moderate activity in patients with advanced HCC and mild to moderately impaired liver dysfunction [16]. The occurrence of grade 3/4 toxicities was as expected with sunitinib treatment. Similarly, phase II studies in patients with advanced HCC and cirrhosis also demonstrated a good tolerability of bevacizumab, an anti-VEGF monoclonal antibody [17-19]. In a pilot study with patients undergoing TACE, adjuvant treatment with bevacizumab was well tolerated and seemed to increase the disease control duration [20].

As TACE is restricted to patients without portal vein thrombosis and without decompensated cirrhosis, a peri-TACE setting could be appropriate to assess the efficacy and safety of sunitinib in patients with HCC. We evaluated the effect of a non-standard dose of sunitinib (37.5 mg/day) administered for 4 weeks every 6 weeks and started 7 to 15 days before the first doxorubicin beads -TACE session, for a total duration of one year.

Patients and methods

Patients

Patient were eligible if they have an HCC diagnosed by imaging or histology, with Child-Pugh score A, WHO score ≤ 2 , not suitable for surgery resection or radiofrequency ablation, with no extra hepatic disease and portal vein thrombosis. They must have acceptable hematological results and acceptable renal and liver function.

Elective patients were randomized to receive Drug Eluting beads TACE with DC Beads (Biocompatibles UK Ltd) loaded with doxorubicin plus either oral sunitinib or placebo. Stratification factors for randomization based on minimisation techniques were: site, main tumor diameter, uninodular vs multinodular lesion. One to three doxorubicin-TACE were recommended. Patients were hospitalized up to 5 days after each TACE session for routine clinical and biological monitoring.

Treatments

Sunitinib (SUTENT[®], Pfizer) 37.5 mg/d (3 tablets of 12.5 mg per day) treatment or matching placebo treatment (3 tablets per day) were administered orally 7-15 days before first TACE, then 4 weeks over 6 (including 2 weeks with no treatment) during one year (Supplemental Figure 1). DC Bead[®] vials (2 mL of 300-500 μ m; then 2 mL of 500-700 μ m) were loaded with doxorubicin (37.5 mg per mL of DC-Beads, with a maximum dose of 150 mg in 4 ml of beads) in aseptic conditions at the hospital pharmacies prior to administration. An angiography was performed prior to TACE to visualize the tumor vascularisation. A super-selective TACE was performed for patients with 1 to 3 nodules while a sectorial or lobar TACE was done for patients with multinodular disease [21]. Three TACE sessions were scheduled 6 to 8 weeks apart after patient inclusion into the study. Additional TACE were performed according to the tumor response evaluated by CT scan or MRI and the treatment schedule. No further session was recommended in case of complete response according to European Association for the Study of the Liver (EASL) criteria or if progression on tumors occurred already with TACE [22,23]. Dose adjustments and treatment discontinuation were allowed in case of expected toxicities (fatigue, diarrhea, anorexia, vomiting, hand-foot syndrome, skin rash, mucosal inflammation, hypertension, neutropenia, thrombopenia, anaemia and hypothyroidism). In presence

of hypothyroidism symptoms, or for TSH level $> 10\text{mIU/L}$ a hormone replacement therapy was initiated to normalize TSH level. Treatment was interrupted in case of: documented tumor progression, or initiation of other anti-tumor treatment, or unacceptable toxicity, or non-compliance to the treatment schedule, or changes in the patient medical status compromising the patient safety.

Study endpoints and statistical methods

The primary endpoint was the occurrence of severe bleeding or liver failure during the week following each TACE. A severe bleeding was defined as either any bleeding (inguinal, tumoral, gastro-intestinal) requiring a local treatment (other than inguinal compression), or any bleeding requiring a systemic treatment (e.g. blood transfusion), or an inguinal bleeding during more than 24 hours. A severe liver failure was defined as the occurrence of any of the following complications: hepatic encephalopathy, onset of ascites, increase of bilirubin level $> 10\text{mg/L}$, decrease of prothrombin rate $\leq 50\%$. Secondary endpoints were toxicities, PFS (defined as the first progression or first occurring death) and OS.

The expected rate of severe bleeding and/or liver failure in patients undergoing TACE is approximately 10 % to 15% [24]. We thus defined the unacceptable toxicity rate as 30 % in patients undergoing doxorubicin-TACE plus sunitinib treatment. Considering a study power of 85.6% and an alpha type one error of 13.3 % it was anticipated that inclusion of 35 patients would be needed in each treatment arm. The observation of severe bleeding or liver failure 1 week after last TACE-sunitinib session in 7 or less than 7 patients (20 %) would lead to consider the combination treatment as acceptable toxicity.

Population description was performed on the ITT population (all patients randomized). Primary endpoint and TACE treatment were analyzed on mITT (subset of the ITT patients who received at least one TACE). Secondary efficacy criteria and toxicities were analyzed on safety population (subset of the ITT patients who had at least one sunitinib/placebo intake). Results are presented as means (standard deviation), median and range or percentages, and 95% confidence intervals (CI) when applicable. Median treatment follow up is calculated according to the « reverse Kaplan Meier » method. Survival curves were estimated using the Kaplan-Meier methods. Median and time to events at different time-points were done for PFS and OS with their 95% CI. Data analyses were performed using SAS (Version 9.4). The study has been stopped after the Phase II due to new strategy of treatments in HCC.

All authors had access to the study data and had reviewed and approved the final manuscript.

Results

Recruitment and patients' characteristics

From May 2011 to May 2014, 78 patients were randomized in the study, 39 in each group (Figure 1). Eight patients had no TACE and were excluded from the mITT analysis of efficacy. Baseline characteristics were well-balanced between the two groups (Table 1). The median age at inclusion was 66.4 years, 91% were male, 84% were. BLCL B criteria. Liver cirrhosis was present for 92% of sunitinib patients vs. 82% of placebo patients. HCC was bilobar for 67% of sunitinib patients vs. 40% of placebo patients.

Treatment effect on bleeding complications and liver failure

No severe bleeding or liver failure was observed for 97% of patients in the sunitinib group and for 94% of patients in the placebo group (Table 2). One liver failure was observed in the sunitinib group vs. two in the placebo group. In the sunitinib group, one patient had a transient hepatic insufficiency (prothrombin time of 40%, total bilirubin level of 2.60 mg/dL) on Day 3 after the third TACE session. This patient had no additional liver failure event. In the placebo group, one patient had a liver failure (prothrombin time of 42%, total bilirubin level of 5.53 mg/dL) on Day 2 after the second TACE session. This patient experienced an additional liver failure event on Day 2 after the fourth TACE session. One placebo patient had a liver encephalopathy on Day 1 to Day 4 of the first TACE. Ascite was absent in all liver failure events.

Compliance to treatment

The compliance to sunitinib treatment was acceptable. Fifty-seven percent of patients received the planned dose of 37.5 mg/day, and 37% had the dose reduced to 25 mg/day mainly due to acute toxicity. Only 18% of sunitinib patients vs. 26% of placebo patients had the planned 9 treatment sessions (Figure 2A). Twenty, 15 and 18% of sunitinib patients discontinued the treatment after one, two and three sessions, respectively. Treatment discontinuation was mainly due to toxicity (38.5% of sunitinib patients vs. 2.6% placebo patients), and tumor progression (47.4% of placebo patients vs. 28.2% of sunitinib patients).

For TACE compliance, 9% of placebo patients and none of the sunitinib patients had the planned four TACE (Figure 2B).

Maximal toxicity

The time to first occurrence of maximal grade 3-4 toxicities was earlier in sunitinib patients as compared to placebo patients (median time (95%CI): 8.0 (6.0-11.0) vs. 48.5 (10.0-128.0) days respectively; Supplemental Figure 2). Maximal grade 3-4 toxicities were observed for 92.3% of sunitinib patients vs. 71.1% of placebo patients (Table 3). Most frequently reported toxicities with sunitinib were neutropenia and thrombocytopenia, increased bilirubin, increased ALT, asthenia, leukocytosis and hepatic deficiency. Increased AST and increased GGT toxicities were more frequent with placebo.

Efficacy

The median follow-up was 49.1 (95%CI: 35.8-58.3) months in the sunitinib group vs. 52.4 (35.7-60.4) months in the placebo group. The median PFS time was higher in the sunitinib group (9.05 [95%CI: 5.81-11.63] months) than in the placebo group (5.51 [4.14-7.79] months, Figure 3A). The median OS time was also higher with sunitinib (25.0 [13.5-36.8] months) than with placebo (20.5 [15.1-30.6] months, Figure 3B). At 24 months of follow-up, 51.3% of sunitinib patients vs. 44.7% of placebo patients were still alive.

All targeted lesions were treated at first TACE for 64% of sunitinib patients. A complete response of target lesions was reached for 9% of sunitinib patients and 12% of placebo patients at first TACE (Supplemental Figure 3). A partial response and stable disease of target lesions were reached for 17% and 71%, respectively, of sunitinib patients vs. 35.3% and 53%, respectively of placebo patients. Complete response was further achieved for 6% and 8% of patients in the sunitinib and placebo groups, respectively, after a second TACE.

Discussion

We evaluated the effect of oral sunitinib treatment plus doxorubicin TACE on the occurrence of severe bleeding or liver failure complications in HCC patients. Positive results in terms of an absence of severe bleeding or liver failure complications and acceptable compliance to TACE and oral treatments were observed with sunitinib. Higher median PFS and OS were also observed with sunitinib. Sunitinib and TACE combination led to a median PFS of 9.1 months, which was in between of the results obtained in Japan in the TACTICS (median PFS of 25.2 months with TACE plus sorafenib and 13.5 months with TACE alone) and those obtained in the UK in the TACE-2 trial (median 238 days in the TACE plus sorafenib group vs. 235 days in the TACE plus placebo group) [10,24]. Conversely, we did not observe improvement in response rates. Our study population was mainly composed of patients with alcoholic liver cirrhosis, thus differing from the mixed Asian and non-asian population with cirrhosis of viral origin included in the phase III trial (SUN1170) with sunitinib versus sorafenib in first line advanced HCC [25]. In SUN1170, sunitinib treatment failed to show equivalence or superiority on survival outcomes vs. sorafenib treatment. In their study Cheng et al [7] reported a median survival of 7.9 months with sunitinib which was in the same lower range of 8.0 to 9.8 months reported in phase II studies in advanced HCC with higher sunitinib doses and/or different treatment modalities [15,24]. This median survival was even lower than the 9.3 months reported in the SAKK77/06 study of continuous sunitinib treatment at a daily dose of 37.5 mg [16].

Although the survival outcomes reported in our study with sunitinib plus TACE combination were higher than previous outcomes reported with sunitinib treatment alone in phase II studies [15,16], further comparisons with the results of the sorafenib phase III studies would not be appropriate due to differences in study design, sample

size and treatment duration. The lower treatment duration with sunitinib might reflect higher toxicity of sunitinib, the effect of sunitinib treatment interruption or dose reduction on disease progression.

In all studies, including those with TACE interventions, oral sunitinib treatment was associated with more frequent grade 3-4 toxicities and more frequent bleeding events. In our study no severe bleeding event was reported in the sunitinib patient. Hematologic toxicity, fatigue, transaminase elevation, hand-foot syndrome events were common adverse events reported with sunitinib treatment. Faivre et al reported a more severe toxicity profile, several treatment-related deaths and a high number of dose reduction and treatment delays due to adverse events, with a sunitinib dose of 50 mg/day administered to HCC patients [15]. As a consequence a lower dose of 37.5 mg/day was evaluated in subsequent clinical trials leading to the observation of an acceptable safety profile [7].

Although promising, this study was not extended to the phase III design for several reasons. Our study results are limited by the difference of the median follow-up duration between sunitinib and placebo group which was related to the higher treatment discontinuation rate for more frequent acute toxicity with sunitinib. The Prodigé 16 study was initiated several years ago in a different context of different guidelines and clinical development of new molecular targeted agents. The current guidelines do not recommend the use of oral sunitinib as first-line therapy for HCC due to the negative outcomes of the SUN1170 trial [2,24]. Moreover, the failure of several phase III randomized trials evaluating TACE plus new targeted therapies (brivanib or orantinib) were not convincing enough for further development of oral sunitinib plus TACE as a new treatment modality for advanced HCC [26,27]. Regarding the effects of combining TACE with sorafenib, results in the literature are

conflicting. In the TACTICS trial, TACE + sorafenib was associated with improved PFS (HR [95% CI] =0.59 [0.41–0.87]; P=0.006), with better time to unTACEable progression (HR [95% CI] =0.57 [0.36– 0.92]; P=0.02) and also better time to progression (HR [95% CI] =0.54 [0.35–0.83]; P=0.005) in Japanese patients with Hepatitis C virus infection as the most common cause of underlying chronic liver disease [10]. Conversely the addition of sorafenib to TACE showed no significant improvement of PFS vs. placebo in European HCC patients recruited in the TACE 2 trial [24]. Secondly, the repetition of TACE procedures with an aggressive schedule might induce liver failure. The continuation of ineffective TACE can indeed be deleterious by delaying or even preventing the use of systemic treatments to achieve a better tumor response. The decision to switch from TACE to alternative first or second-line systemic therapies should then be made at the earliest time as possible. Currently, the combination of TACE with sorafenib is not recommended in Western guidelines, which limited the opportunity of testing sunitinib, an antiangiogenic showed inferior to sorafenib in the advanced setting, in a phase III trial combining with TACE.

So far five drugs, all with antiangiogenic properties, evaluated in a phase III clinical setting have demonstrated positive outcomes in first-line (sorafenib, lenvatinib) or second line (regorafenib, cabozantinib, ramucirumab) treatment of advanced HCC [8,28]. Recently, positive results of the phase III trial IMbrave150 comparing atezolizumab-bevacizumab with sorafenib were announced. Studies testing the combination with TACE of antiangiogenics with immune checkpoint inhibitors are being launched: The EMERALD-1A study evaluating TACE in combination with durvalumab and bevacizumab therapy is currently recruiting patients with locoregional HCC (ClinicalTrials.gov Identifier: NCT03778957). A study testing the

combination of lenvatinib and pembrolizumab with TACE is also planned. The results of the PRODIGE 16 trial confirm that the combination of an antiangiogenic drugs with TACE is feasible in a multicentric setting, and justify the continuation of research in this field.

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Author Contributions

Contribution: AT contributed to the data aquisition, analysis and interpretation, and the drafting and review of the manuscript. TDB and MH contributed to the study concept and design, study supervision, and critical revision of the manuscript for important intellectual content. KLM contributed to the formal statistical analysis; analysis and interpretation of data, and the drafting and review of the manuscript. AH, IO-H, TL, HP, JV, DS, YR, JE, J-LJ, CS, YB, BD, MB, MD-G, GD, SD, CL contributed to the study investigation and the critical revision of the manuscript for important intellectual content.

Writing Assistance: C. Foucher (freelance medical writer, Dijon, France) provided writing and editing assistance of the manuscript.

References

- [1] Llovet JM, Zucman-Rossi J, Pikarsky E et al. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2016;2:16018. doi: 10.1038/nrdp.2016.18.
- [2] EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018;69:182-236. doi: 10.1016/j.jhep.2019.01.020.
- [3] Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology* 2003;37:429-42. doi: 10.1053/jhep.2003.50047
- [4] Llovet JM, Real MI, Montana X et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;359:1734-39. doi: 10.1016/S0140-6736(02)08649-X
- [5] Lo CM, Ngan H, Tso WK et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35:1164-71.
- [6] Xiong ZP, Yang SR, Liang ZY et al. Association between vascular endothelial growth factor and metastasis after transcatheter arterial chemoembolization in patients with hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int* 2004;3:386-90. doi: 10.1053/jhep.2002.33156
- [7] Cheng AL, Kang YK, Chen Z et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;10:25-34. doi: 10.1016/S1470-2045(08)70285-7.
- [8] Kudo M, Finn RS, Qin S et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391:1163-73. doi: 10.1016/S0140-6736(18)30207-1.
- [9] Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378-90. doi: 10.1056/NEJMoa0708857.
- [10] Kudo M, Ueshima K, Torimura T et al. Randomized, open label, multicenter, phase II trial of transcatheter arterial chemoembolization (TACE) therapy in combination with sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. *J Clin Oncol* 2018;36 suppl:Abstract 4017.

- [11] Kudo M, Arizumi T. Transarterial Chemoembolization in Combination with a Molecular Targeted Agent: Lessons Learned from Negative Trials (Post-TACE, BRISK-TA, SPACE, ORIENTAL, and TACE-2). *Oncology* 2017;93 Suppl 1:127-34. doi: 10.1159/000481243.
- [12] Mendel DB, Laird AD, Xin X et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res* 2003;9:327-37.
- [13] Nassif E, Thibault C, Vano Y et al. Sunitinib in kidney cancer: 10 years of experience and development. *Expert Rev Anticancer Ther* 2017;17:129-42. doi: 10.1080/14737140.2017.1272415.
- [14] Czabanka M, Vinci M, Heppner F et al. Effects of sunitinib on tumor hemodynamics and delivery of chemotherapy. *Int J Cancer* 2009;124:1293-1300. doi: 10.1002/ijc.24019
- [15] Faivre S, Raymond E, Boucher E et al. Safety and efficacy of sunitinib in patients with advanced hepatocellular carcinoma: an open-label, multicentre, phase II study. *Lancet Oncol* 2009;10:794-800. doi: 10.1016/S1470-2045(09)70171-8.
- [16] Koeberle D, Montemurro M, Samaras P et al. Continuous Sunitinib treatment in patients with advanced hepatocellular carcinoma: a Swiss Group for Clinical Cancer Research (SAKK) and Swiss Association for the Study of the Liver (SASL) multicenter phase II trial (SAKK 77/06). *Oncologist* 2010;15:285-92. doi: 10.1634/theoncologist.2009-0316.
- [17] Benatsou B, Lassau N, Chami L et al. Dynamic contrast-enhanced ultrasonography (DCE-US) with quantification for the early evaluation of hepatocellular carcinoma treated by bevacizumab in phase II. *J Clin Oncol* 2008;abstr 4588.
- [18] Siegel AB, Cohen EI, Ocean A et al. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *J Clin Oncol* 2008;26:2992-98. doi: 10.1200/JCO.2007.15.9947
- [19] Zhu AX, Sahani DV, Duda DG et al. Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase II study. *J Clin Oncol* 2009;27:3027-35. doi: 10.1200/JCO.2008.20.9908.
- [20] Britten C, Finn R, Gomes A et al. A pilot study of IV bevacizumab in hepatocellular cancer patients undergoing chemoembolization. *Proc Am Soc Clin Oncol* 2005;abs 4138.
- [21] Vogel A, Cervantes I, Chau B et al. on behalf of the ESMO Guidelines Committee. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; 29 (Suppl 4): iv238–iv255. doi: 10.1093/annonc/mdy308.
- [22] Bruix J, Sherman M, Llovet JM et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. *European*

Association for the Study of the Liver. *J Hepatol* 2001;35:421-30. doi: 10.1016/s0168-8278(01)00130-1

[23] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;30:52-60. doi: 10.1055/s-0030-1247132

[24] Meyer T, Fox R, Ma YT et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. *Lancet Gastroenterol Hepatol* 2017;2:565-75. doi: 10.1016/S2468-1253(17)30156-5.

[25] Cheng AL, Kang YK, Lin DY et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013;31:4067-75. doi: 10.1200/JCO.2012.45.8372.

[26] Kudo M, Han G, Finn RS et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: A randomized phase III trial. *Hepatology* 2014;60:1697-1707. doi: 10.1002/hep.27290.

[27] Kudo M, Cheng AL, Park JW et al. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma (ORIENTAL): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study. *Lancet Gastroenterol Hepatol* 2018;3:37-46. doi: 10.1016/S2468-1253(17)30290-X.

[28] Bruix J, Qin S, Merle P et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;389:56-66. doi: 10.1016/S0140-6736(16)32453-9.

Tables

Table 1. Clinical Characteristics

	Sunitinib	Placebo	All
	(N=39)	(N=39)	(N=78)
Age, yrs*	66.0 (46.0-84.7)	67.4 (43.7-84.7)	66.4 (43.7- 84.7)
Male/Female (N [%])	36 (92) / 3 (8)	35 (90) / 4 (10)	71 (91) / 7 (9)
Presence of liver cirrhosis	36 (92)	32 (82)	68 (87)
Etiology			
Alcohol**	29 (78)	24 (75)	50 (74)
HCV†	4 (11)	4 (12)	8 (12)
HBV	1 (3)	2 (6)	3 (4)
Hemochromatosis§	1 (3)	2 (6)	4 (6)
Others	1 (3)	0	1 (3)
BLCL B criteria	33 (89)	25 (78)	58 (84)
Child-Pugh class (N[%])			
A5	27 (80)	24 (62)	51 (66)
A6	9 (24)	13 (33)	22 (29)
B	2 (5)	2 (5)	4 (5)
Tumor characteristics			
Unilobar disease (N[%])	13 (33)	23 (60)	36 (47)
Bilobar disease (N[%])	26 (67)	15 (40)	41 (53)
Number of nodules*	3 (1-10)	3 (1-15)	3 (1-15)
(median[range])			
Laboratory			

	Sunitinib	Placebo	All
	(N=39)	(N=39)	(N=78)
Alpha-fœtoprotein, ng/ml*	13.10 (3.30-62762)	20.50 (3.10 ; 13728.60)	16.45 (3.10 ; 62762.10)
Thyroid stimulating hormone, mU/L, *	1.60 (0.13 ; 4.13)	1.65 (0.03 ; 3.57)	1.65 (0.03 ; 4.13)

* median (range), ** alcohol + HCV + HBV (n=1 with sunitinib), Alcohol + HCV (n=with sunitinib), Alcohol + hemachromatosis + other (n=1 with sunitinib), Alcohol + other (n=3 with sunitinib, n=4 with placebo) ; † HCV + HBV (n=1 with sunitinib) ; § hemochromatosis + HBV + HCV (n=1 with sunitinib). BLCL: Barcelona-Clinic Liver Cancer, HBV : hepatitis B virus, HCV : hepatitis C virus,

Table 2. Occurrence of Severe Bleeding or Liver Failure

	Sunitinib	Placebo
	(N=36)	(N=34)
Presence of severe bleeding or liver failure N(%)		
No	35 (97.2)	32 (94.1)
[95%CI]	[85.47; 99.93]	[80.32 ; 99.28]
Yes	1 (2.8)	2 (5.9)
[95%CI]	[0.07 ; 14.53]	[0.72 ; 19.68]
Composite of the endpoint (N)		
Severe bleeding	0	0
Liver failure	1	2

Table 3. Maximal Grade 3-4-5 Toxicities[†]

	Sunitinib	Placebo
	(N=39)	(N=38)
	N(%)	N(%)
Maximal Toxicity	36 (92.3)	27 (71.1)
COAGULATION	1 (2.6)	2 (5.3)
Prothrombine time (tp)	1 (2.6)	2 (5.3)
DERMATOLOGY	5 (12.8)	0
Syndrome hand-foot	5 (12.8)	0
PAIN	6 (15.4)	3 (7.9)
Pain	1 (2.6)	0
Abdominal pain	4 (10.3)	3 (7.9)
Hepatic pain	2 (5.1)	0
HEPATIC FUNCTION	20 (51.3)	22 (57.9)
Abnormal Alanine Aminotransferase	8 (20.5)	7 (18.4)
Abnormal Aspartate Aminotransferase	8 (20.5)	17 (44.7)
Increased Gamma-glutamyl	3 (7.7)	6 (15.8)
Abnormal Bilirubin	10 (25.6)	5 (13.2)
Hepatic deficiency	5 (12.8)	4 (10.5)
Abnormal Alkaline Phosphatase	2 (5.1)	3 (7.9)
HEMATOLOGY	18 (46.2)	3 (7.9)
Abnormal Hemoglobin	2 (5.1)	2 (5.3)
Leukocytosis	6 (15.4)	1 (2.6)
Neutropenia	11 (28.2)	0
Thrombocytopenia	12 (30.8)	0
HAEMORRHAGE	2 (5.1)	1 (2.6)
Epitaxis	1 (2.6)	0
Upper gastro-intestinal	1 (2.6)	1 (2.6)
METABOLISM	1 (2.6)	6 (15.8)
Hyperglycaemia	1 (2.6)	3 (7.9)
Hyponatremia	0	1 (2.6)
Hyperlipasemia	0	2 (5.3)
GENERAL DISORDERS	9 (23.1)	2 (5.3)

	Sunitinib	Placebo
	(N=39)	(N=38)
	N(%)	N(%)
Asthenia	9 (23.1)	2 (5.3)
Fever	1 (2.6)	0
CARDIOVASCULAR DISORDERS (GENERAL)	4 (10.3)	4 (10.5)
Thrombo-embolic event	2 (5.1)	0
Arterial Hypertension	2 (5.1)	4 (10.5)
GASTROINTESTINAL DISORDERS	7 (17.9)	2 (5.3)
Anorexia	3 (7.7)	1 (2.6)
Ascitis	2 (5.1)	0
Diarrhea	2 (5.1)	0
Melena	0	1 (2.6)
RENAL DISORDERS	1 (2.6)	0
Acute renal insufficiency	1 (2.6)	0

† NCI-CTC grade, version 4.0.

Figure Legends

Figure 1: Patient Flow Diagram

* documented tumor progression requiring additional treatment, or plus toxicity, or plus general health deterioration. ** general health deterioration, investigator's decision, surgery, hepatic encephalopathy decompensation, portal vein thrombosis, hepatic artery thrombosis, serious adverse event, cirrhosis decompensation, treatment delay >5 weeks

ITT: intent-to-treat, mITT: modified ITT

Figure 2: Compliance to Sunitinib Treatment and TACE

Compliance is expressed A) as numbers of treatment sessions per patient, B) as numbers of TACE sessions per patient

SD: standard deviation.

Figure 3: Kaplan-Meier Curves of (A) Disease Progression-free Survival and (B) Overall Survival in the Sunitinib and Placebo Groups.

N: number of patients at risk. CI: confidence interval, mths: months, OS: overall survival, PFS: progression-free survival.

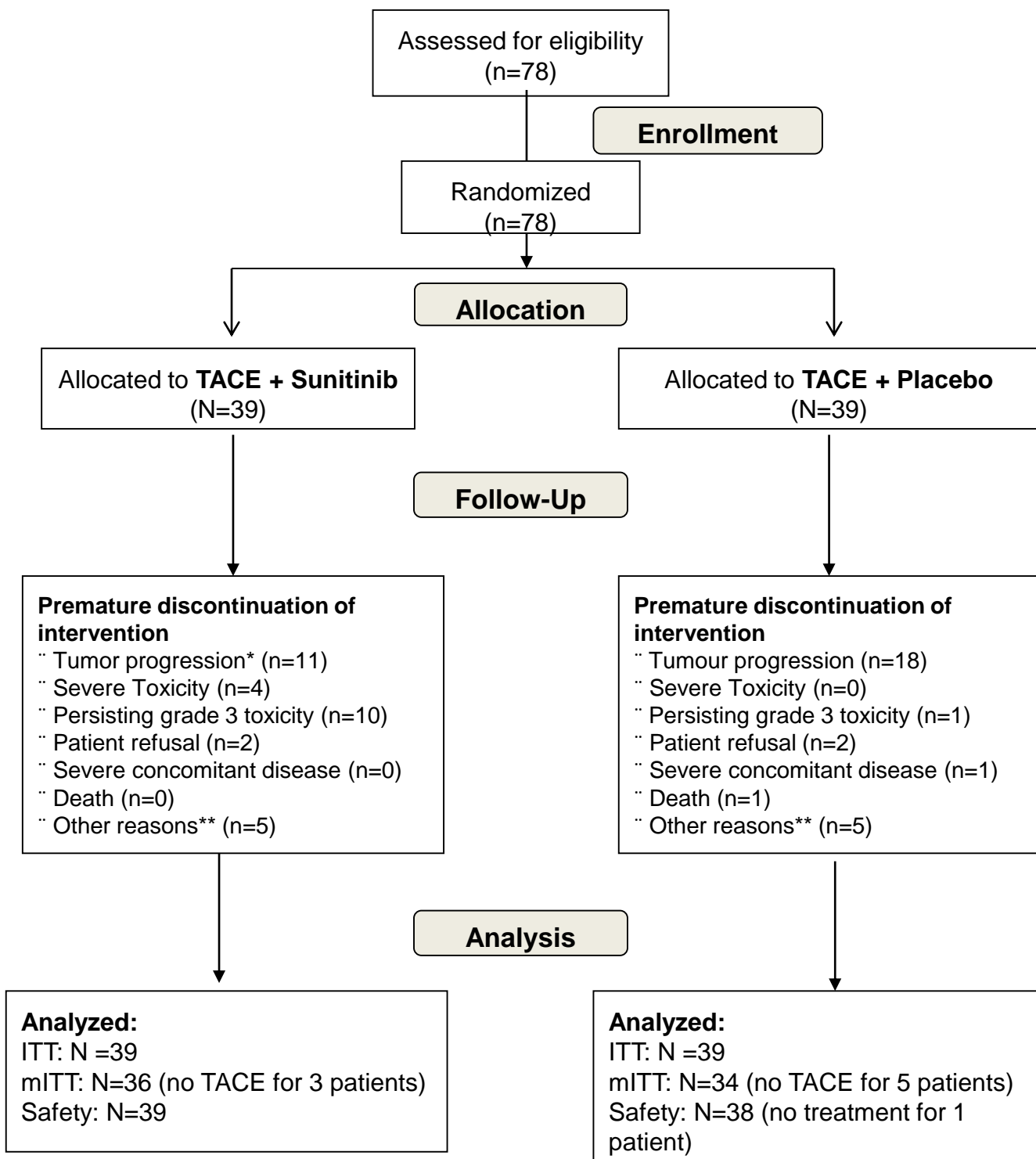


Figure 1.

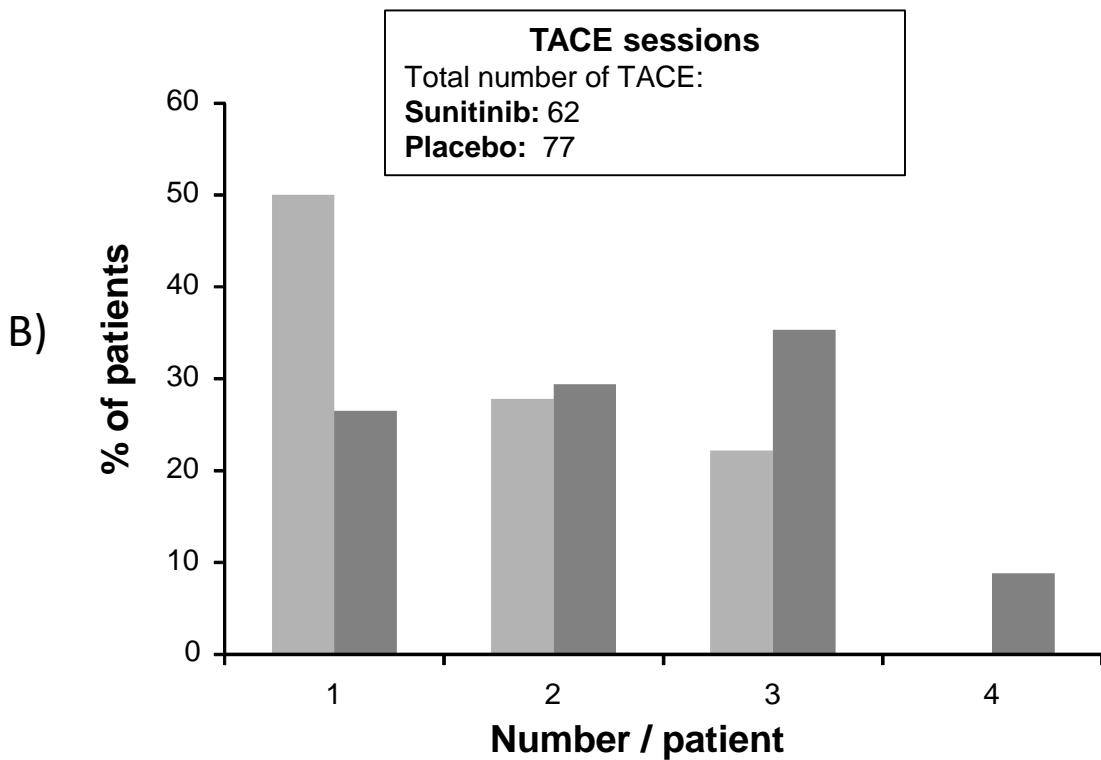
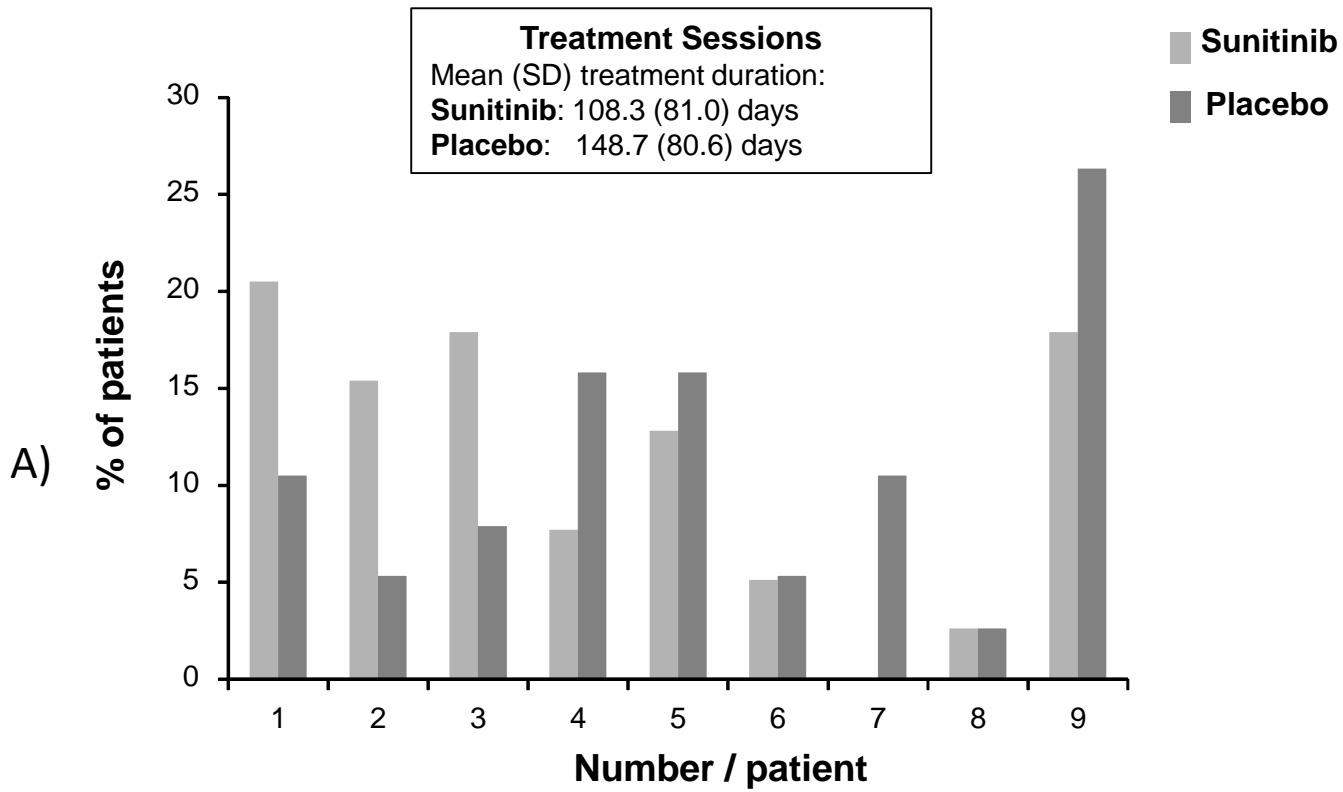
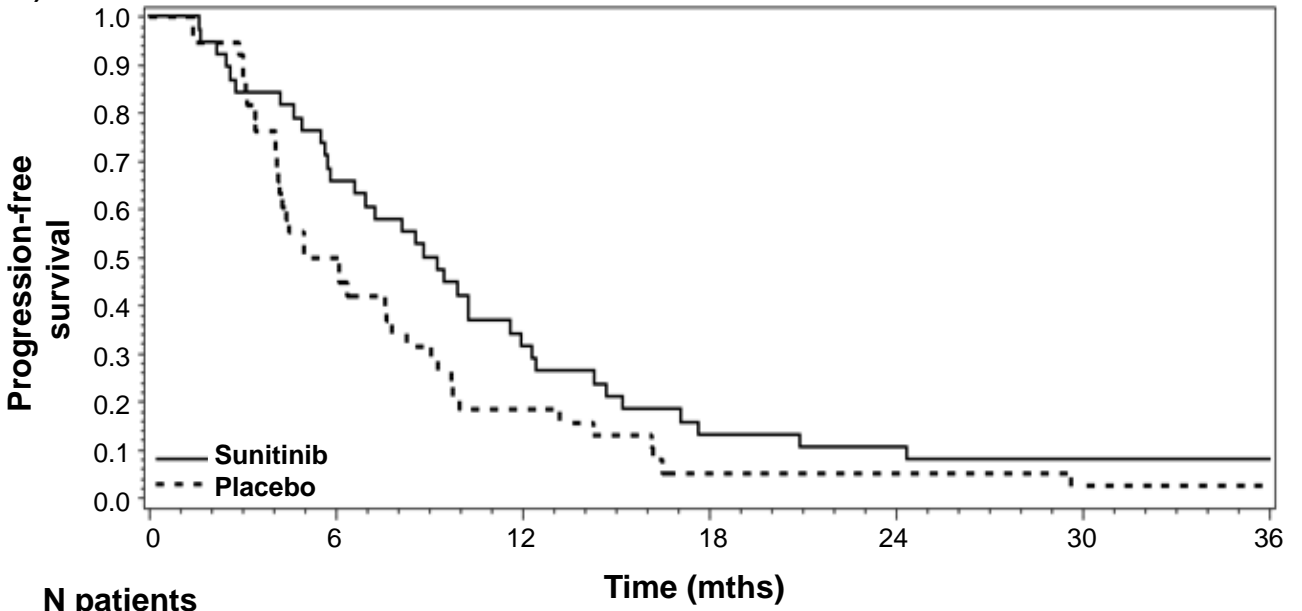


Figure 2.

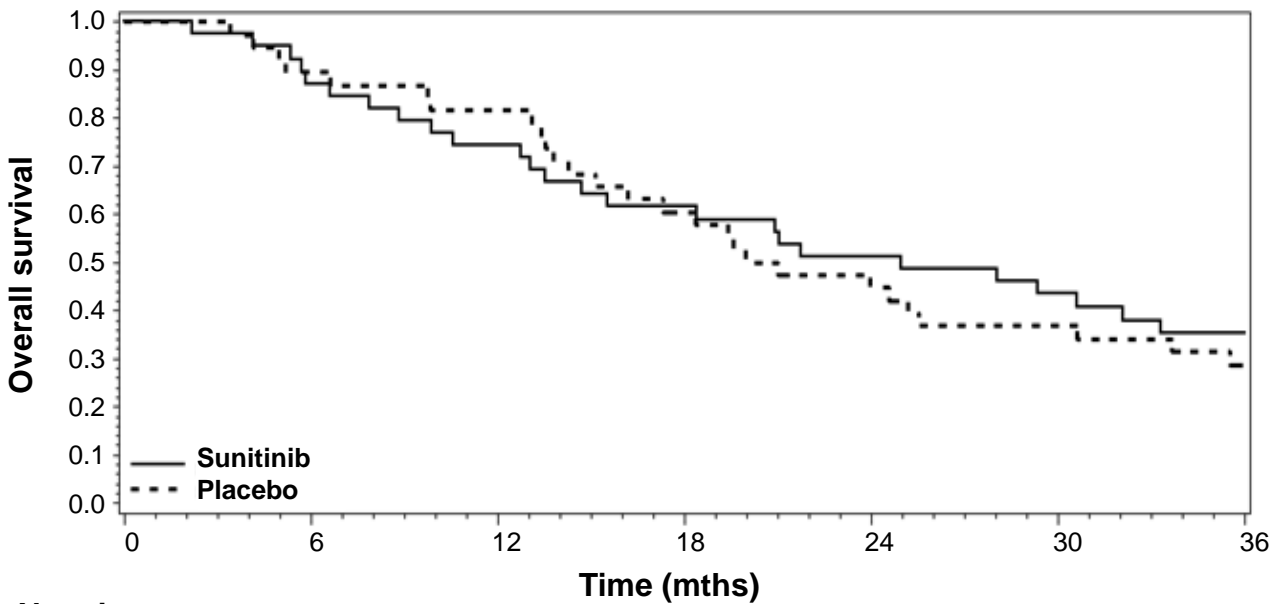
A)



N patients

Sunitinib	38	25	12	5	4	2	2
Placebo	38	19	7	2	2	1	1

B)



N patients

Sunitinib	39	34	29	24	20	16	11
Placebo	38	34	31	23	17	14	9

Figure 3.