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Linsitinib (OSI-906) versus placebo for patients with locally advanced or metastatic adrenocortical carcinoma: a double-blind, randomized, phase 3 study

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Abstract

Background: Adrenocortical carcinoma (ACC) is a rare, aggressive malignancy for which there are few treatment options. Linsitinib (OSI-906) is a potent, oral small molecule inhibitor of both IGF-1R and insulin receptor, which has shown acceptable tolerability and preliminary evidence of antitumor activity. In this phase 3 study, linsitinib was evaluated in patients with advanced ACC.

Methods: This international, double-blind, placebo-controlled phase 3 study investigated linsitinib 150mg orally, twice daily versus placebo, randomized 2:1. The primary endpoint was overall survival (OS) and secondary endpoints included progression-free survival (PFS), disease control rate, best overall response, and duration of response.

Findings: Of 139 patients enrolled, 90 were assigned to linsitinib and 49 to placebo. The trial was unblinded in March 2012 based on data monitoring committee recommendation. There was no difference between linsitinib and placebo in OS (median 323 vs 356 days; $p=0.77$, hazard ratio [HR] 0.94; 95% CI 0.61-1.44) or PFS (median 44 vs 46 days; $p=0.3$, HR 0.83; 95% CI 0.56-1.21). However, 4 patients remained on linsitinib, and treatment led to disease control from 23 to >45 months in these 4 patients. Three of these patients had partial response as best response compared to no objective responses in the placebo group. Linsitinib was well tolerated and pharmacokinetic results showed rapid absorption after first dose and accumulation following continuous twice-daily dosing. Increases in IGF-1 levels were observed in a higher proportion of patients in the linsitinib group versus the placebo group; however, neither drug exposure nor IGF-1 plasma levels correlated with clinical activity.

Interpretation: Although linsitinib did not increase OS and PFS in the overall population, the promising responses seen in individual patients indicate the therapeutic potential of inhibiting IGF-1R in ACC and merits further studies of linsitinib in this disease.

Funding: Astellas

Introduction

Adrenocortical carcinoma (ACC) is a rare aggressive malignancy with an annual incidence of 2 per million worldwide and an estimated 5-year survival rate of 16–44%.^{1,2} Surgical resection is the treatment choice in localized disease and is frequently combined with adjuvant mitotane to increase the chance for cure.^{3–5} For patients with unresectable tumors, available therapeutic options include mitotane (the only drug approved for the treatment of ACC), systemic cytotoxic chemotherapy, and radiation therapy. While several retrospective studies suggest an impact of mitotane on overall survival (OS),^{2,6–9} the observed magnitude of benefit remains unclear. A randomized trial in ACC has recently shown a significantly longer progression-free survival (PFS) with a combination of mitotane/etoposide, doxorubicin and cisplatin as first-line therapy versus mitotane/streptozocin combination, although the difference in OS did not reach significance.¹⁰

Insulin-like growth factor-2 (IGF-2) overexpression is the most common molecular event in ACC and is present in some 90% of tumors.^{11–13} IGF-2 signals through the insulin-like growth factor-1 receptor (IGF-1R) and insulin receptor (IR) to initiate a downstream signaling cascade that drives proliferation, migration, and metastasis of ACC and other cancers.¹⁴ Preclinical and phase 1 studies using a variety of IGF-1R inhibitors have shown promising results, suggesting that antagonizing IGF-1R signaling may be a valuable approach in treating ACC.^{15–17}

Linsitinib (OSI-906) is a potent, oral, small molecule inhibitor of both IGF-1R and IR which has shown preliminary evidence of antitumor activity in a variety of solid tumors, with an acceptable tolerability profile.¹⁸⁻²⁰ Notably, in a dose-finding, phase 1 study, linsitinib resulted in partial responses in two of 15 patients with ACC (79 total study patients).¹⁹

We report here the results of an international phase 3 study evaluating linsitinib in patients with advanced ACC who received at least one but not more than two prior drug regimens.

Methods

Study design and endpoints

This randomized, double-blind, placebo-controlled, phase 3 trial was conducted at clinical sites in nine countries: Australia (1), Canada (3), Germany (3), France (6), Italy (2), the Netherlands (3), Poland (1), the United Kingdom (2), and the United States (14). The study protocol and amendments were reviewed by the Institutional Review Board for each study site. The primary endpoint was OS following administration of linsitinib versus placebo, calculated from date of randomization. Secondary endpoints included PFS, disease control rate (DCR) and duration of disease control, duration of response, and best overall response rate. Disease control rate was calculated as the proportion of patients with a complete response (CR), partial response (PR), or stable disease (SD) at ≥ 6 weeks among all randomized patients. Safety, pharmacokinetics, and pharmacodynamics of linsitinib were also evaluated as secondary endpoints. An independent Data Safety Monitoring Board regularly evaluated the study results including adverse events (AEs).

Patients

Patients were eligible if they had histologically confirmed locally advanced or metastatic ACC not amenable to surgical resection; measurable disease according to RECIST; radiologically confirmed progressive disease in the 6 months prior to randomization; age ≥ 18 ; Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) ≤ 2 ; predicted life expectancy ≥ 12 weeks; fasting glucose ≤ 150 mg/dl; and adequate hematopoietic, hepatic, and renal function.

Patients must have had ≥ 1 but < 3 prior drug regimens for locally advanced/metastatic ACC and were required to have received mitotane as neoadjuvant or adjuvant treatment, or as therapy for advanced/metastatic disease.

Exclusion criteria included: type 1 diabetes mellitus or type 2 diabetes mellitus requiring insulinotropic or insulin therapy, prior IGF-1R inhibitor therapy, malignancy other than ACC within the past 3 years, history of significant cardiovascular disease, QTcF interval > 450 ms, history of cerebrovascular accident within 6 months prior to randomization, and symptomatic brain metastasis.

No other anticancer therapies, including mitotane, or investigational drugs were permitted during the study. Prior use of oral antihyperglycemic agents was allowed if the dose was stable ≥ 4 weeks prior to randomization. All patients received best supportive care for management of symptoms and toxicity and provided written informed consent.

Treatment and randomization

Patients were randomized in a 2:1 ratio to either linsitinib or matching placebo, and were stratified according to the following parameters: prior systemic cytotoxic therapy for ACC (yes or no), ECOG PS (0–1 or 2), and use of ≥ 1 non-insulinotropic oral antihyperglycemic therapy at randomization (yes or no). Unique patient identification numbers were generated via a web-based, centralized randomization system and used to link each patient to the appropriate treatment group.

The identity of the study agent was concealed and patients, investigators, site staff, and sponsor team were blinded to treatment. All patients received study agent (150 mg) twice daily (recommended phase 2 dose of linsitinib¹⁹) with food by continuous dosing schedule for 21-day treatment periods. Treatment was discontinued for disease progression or for unacceptable toxicity. Study agent was withheld for drug-related \geq grade 3 toxicity; at resolution of toxicity to grade 1, study agent was reintroduced at 100 mg twice daily (75 mg twice daily for second AE recurrence). The study agent could be reduced to 100 mg twice daily at the discretion of the investigator for clinically significant grade 1/2 drug-related toxicities or any grade unrelated toxicities, but could not be re-escalated.

Assessments

A physical examination, including ECOG PS assessment and vital signs, was performed at screening, pre-dose on day 1 of every 21-day treatment period, and post-treatment. To assess efficacy, tumor response and progression were evaluated by chest, abdomen, and pelvic CT scan (magnetic resonance imaging for contraindications) after every 2 treatment

periods (6 weeks) according to Response Evaluation In Solid Tumors (RECIST) criteria version 1.1,²¹ utilizing both local (real-time) and central (blinded) review. Safety was assessed by monitoring for any AEs, serious AEs (SAE), clinical laboratory data, vital signs, electrocardiograms, and physical examination. AEs were graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 3.0, and relation to study treatment was judged by the local investigator. Pharmacokinetic data were evaluated from blood samples collected from all patients at pre-dose of day 1 of treatment periods 1, 2, and 3 (a treatment period was a 21-day dose cycle), and from the first 75 randomized patients at pre-dose and 2, 4, and 8 hours post-dose on day 1 of treatment periods 1 and 2. Blood samples were collected for pharmacodynamic assessments at pre-dose and 4 hours post-dose on day 1 of treatment period 1, and at pre-dose on day 1 of treatment periods 2 and 3.

Statistical analysis

Efficacy was assessed in the intent-to-treat population (all randomized patients). Safety was assessed in the safety population, which included all patients who received ≥ 1 dose of study drug and for whom any data were reported after first dose. The pharmacokinetic population included all patients who received active drug and for whom there was ≥ 1 measurable concentration and the pharmacodynamic population included patients who received active drug and for whom there were sufficient data for analysis. OS and PFS were estimated using the Kaplan-Meier method and compared using the unstratified log-rank test. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using a

proportional hazard model. Using a two-sided log-rank test at a significance level of 0.05, and an assumption of 80% power to detect a HR 0.58 for OS (median OS 274 vs 474 days), 112 deaths were required to be observed from 135 enrolled patients. The interim analysis of OS was to be performed when 67 deaths were observed, by an independent statistician not affiliated with the sponsor.

This study is registered with ClinicalTrials.gov, number NCT00924989.

Role of the funding source

As the sponsor of the study, Astellas financially supported the study, provided linsitinib and placebo free of charge, and was responsible for data collection and analysis. Astellas and a Scientific Steering Committee were involved in the study design. The authors had full access to all study data and prepared this report with Astellas, who had the right to review the report before publication. The authors had final responsibility for the decision to submit for publication.

Results

Between December 2, 2009 and July 11, 2011, 139 patients were randomized (figure 1).

One patient in the placebo group did not receive any treatment due to primary investigator-assessed general deterioration, and was excluded from the safety population.

The trial was unblinded in March 2012 based on recommendation of the data monitoring committee. At that point, 6 patients were on study treatment, 2 of whom were receiving placebo. Patients were informed of the risk/benefit of continuing treatment. The 2 patients receiving placebo were not permitted to remain on the study. The 4 other patients chose to continue treatment with linsitinib. The database was locked December 4, 2012 with the analysis cutoff date July 11, 2012. Data from patients who continued with the study drug were available until July 2014.

Overall, baseline demographic and disease characteristics were similar between the two treatment groups (table 1). Approximately 91% of patients had been previously treated with surgery, and 31% with radiotherapy. All patients received prior anticancer drug regimens including mitotane (table 1).

At database lock, median OS was 323 days (95% CI 256–507) in the linsitinib group and 356 days (249–556) in the placebo group (HR 0.94; 95% CI 0.61–1.44; $p=0.771$; figure 2). Based on independent radiologist review, median PFS was 44 days (95% CI 43–61) in the linsitinib group and 46 days (95% CI 43–64) in the placebo group (HR 0.83, 95% CI 0.56–1.21; $p=0.303$; figure 3), giving 17% risk reduction for the entire study population. Complete response was not achieved in any patient; PR was documented in 3 patients in the linsitinib

group (3.3%), but in none of the placebo group. DCR rate (CR+PR+SD) at 6 weeks was 32.2% (95% CI 22.8–42.9) in the linsitinib group vs 34.7% (21.7–49.6) in the placebo group, while it was 15.6% vs 8.2% at 12 weeks and 6.7% vs 0% at 24 weeks. The best change in target lesion size for patients in both arms is illustrated in a waterfall plot (figure 4).

Of the 4 patients who continued on linsitinib after unblinding, 2 patients with a PR as a best response have rolled over to a separate linsitinib study in June and July 2014 following 45 and 38 months on study drug. Another patient with PR as the best response discontinued study drug at 37 months due to an unrelated AE. Interestingly, all 3 responders had relatively low-grade ACC with Ki67 of 3, 10, and 20%. The fourth patient had SD as a best response, and was on study drug for 23 months.

Predefined subgroup analyses of OS and PFS by sex, age, ECOG PS at baseline, smoking history, use of prior systemic and cytotoxic chemotherapy, and use of non-insulinotropic antihyperglycemic drug provided no evidence of differential treatment effect for linsitinib versus placebo.

Mean and median overall drug exposure time was similar between the two groups, with a mean of 100 days and a median of 44.0 days for linsitinib, and a mean of 84.9 days and a median of 47.0 days for placebo. Disease progression was the most common reason for treatment discontinuation for both groups (76.7% for linsitinib and 83.7% for placebo), followed by AEs (13.3% and 4.1%), other medico-ethical reasons (3.3% and 8.2%), and patient-initiated withdrawal (2.2% and 4.1%).

Table 2 summarizes treatment-related AEs in both treatment groups over the entire study period. Treatment-related AEs were reported in 56% in the linsitinib and 44% in the placebo group and were generally low grade (table 2). Treatment-related AEs \geq grade 3 were experienced by 17/90 patients (18.9%) in the linsitinib cohort, and 1/48 patients (2.1%) of the placebo cohort. The most common treatment-related AEs in the linsitinib group included fatigue, nausea, vomiting, and QTc interval prolongation (table 2). Hyperglycemia, one of the main treatment-related toxicities associated with linsitinib in preclinical studies, was observed in 3.3% of the patients in the linsitinib group and in 8.3% in the placebo group. Ten patients died while on treatment or within 30 days from the last dose, 5 (5.6%) in the linsitinib group and 5 (10.4%) in the placebo group, with malignant disease as the most common cause of death. No deaths in the linsitinib group were considered to be treatment-related. Dose reductions and interruptions due to drug-related toxicity were reported for 12 (13.3%) and 11 (12.2%) patients in the linsitinib group, and for 1 (2.1%) and 2 (4.2%) in the placebo group.

Pharmacokinetic and pharmacodynamic profiles of linsitinib were evaluated as secondary endpoints. Pharmacokinetic parameters for linsitinib obtained after single (treatment period 1) and multiple (treatment period 2) doses are summarized in table 3. Linsitinib was absorbed with peak concentration (C_{max}) occurring at a median T_{max} of 2 hours following both single and multiple dose administration. Median exposure (area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; AUC_{last}) was higher in treatment period 2 than in treatment period 1.

IGF-1 plasma levels were measured in 133 patients, 86 in the linsitinib group and 47 in the placebo group. Increases in IGF-1 levels, a surrogate marker of IGF-1R inhibition, were observed in a higher proportion of patients in the linsitinib group versus the placebo group (figure 4). On days 22 and 43 in the linsitinib group, the median changes in IGF-1 concentrations above pre-dose levels were 17.4% and 15.2%, respectively. However, neither drug exposure nor IGF-1 plasma levels correlated with clinical outcome of the patients. In addition, there was no difference in the exposure of linsitinib and plasma IGF-1 levels between patients with a screening mitotane level <1 mg/L vs ≥1 mg/L (limit of quantitation).

Discussion

ACC is a rare and frequently fatal cancer, with limited therapeutic options.^{2,3,9} In this phase 3 study we sought to confirm preliminary evidence of antitumor activity shown by linsitinib in patients with ACC.¹⁹ The results of the present study failed to show a statistically significant beneficial effect of linsitinib as second- or third-line therapy when compared to placebo on OS and PFS in patients with progressing ACC. Nonetheless, linsitinib treatment led to disease control from 23 to >45 months in 4 patients (4.4 %). Although there was no difference in DCR between the two groups at 6 weeks, 8 patients on linsitinib, but none on placebo, had PFS for >100 days. Furthermore, 3 patients achieved a partial response in the linsitinib group while no objective responses were observed in the placebo group. The AE profile in both treatment arms was consistent with the study population. The rate of linsitinib-

attributed toxicity-related dose modifications was low and comparable to the placebo group.

Currently, no demographic, clinical, histopathological, or pharmacokinetic criteria have been identified that might predict response to linsitinib. Ongoing genomic characterization of tumor samples of treatment responders versus non-responders may reveal the basis for the observed sensitivity to linsitinib, and aid in future identification of patients most likely to respond to targeted anticancer agents inhibiting IGF-1R signaling. Of note, all 3 responders had rather low-grade tumors with Ki67 of 3, 10, and 20%. An *in vitro* investigation correlating genetic characteristics of cancer cell lines with antiproliferative activity of figitumumab revealed that components of the IGF pathway play a pivotal role in determining the sensitivity of tumors to this agent.²² No particular signature for response to IGF-1R inhibition has yet been identified in ACC. A possible negative impact on response to platinum-based therapies has been found for high expression levels of the DNA repair gene excision repair complementation group 1 (ERCC1),²³ and high ribonucleotide reductase large subunit (RRM1) gene expression had some association with poor efficacy of adjuvant mitotane therapy.²⁴

As expected, the pharmacokinetic profile of linsitinib was similar to that observed in a dose-determining phase 1 study, with rapid absorption after oral dose and accumulation following continuous twice-daily dosing.¹⁹ In the present study, high variability in PK was observed in treatment period 2, perhaps due to several factors including but not limited to age, weight, and concomitant medications.

While drug interactions may be critical determinants of drug efficacy in ACC treatment regimens, as suggested by the negative impact of mitotane treatment on sunitinib efficacy,²⁵ mitotane blood level at baseline did not significantly influence exposure to linsitinib in the current study. The increase observed in serum IGF-1 levels is consistent with linsitinib inducing a systemic effect on the growth hormone (GH)-IGF axis. Whether such an endocrine effect is indicative of linsitinib-mediated inhibition of the tumoral IGF-1R is unknown. In contrast to the available anti-IGF-1R antibodies, linsitinib not only targets IGF-1R, but also IR. Therefore, it was hypothesized that linsitinib may have a greater activity in ACC, because IGF-2 activates both IGF-1R and IR. However, for the vast majority of patients in this trial, these effects did not translate into better clinical outcome.

Some anticancer drugs can be effective by blocking secondary survival pathways acquired during tumor progression. Evidence gathered from studies with drugs targeting the IGF-1R pathway suggests that combination therapy may provide additional benefits when compared with single-agent therapy. This can be achieved by simultaneously blocking pathways required for tumor growth or by preventing resistance to single pathway agents.²⁶ The IGF-1R pathway is known to synergize with a number of other signaling pathways, including receptor co-signaling involving IGF-1R and epidermal growth factor receptor (EGFR).²⁷ Studies in a number of tumor types have demonstrated synergistic effects by inhibition of both pathways simultaneously,^{27,28} but this could not be confirmed in clinical trials. In a recent phase 1 trial of the anti-IGF-1R antibody cixutumumab in combination with the mTOR inhibitor temsirolimus, disease stabilization in at least 6 months was shown in 42% of patients with ACC.²⁹ Synergy between the Wnt-signaling and

IGF pathway has also been explored in ACC,³⁰ but no clinical data are yet available. Thus, further studies are needed to establish whether the combination of linsitinib with other targeted agents could lead to improved outcomes in patients with ACC.

Treatment with linsitinib was generally very well tolerated. The majority of AEs were manageable according to standard clinical practice. Additionally, 4 patients were treated long term (>23 months) with linsitinib without increase in toxicity. Clinical toxicities of linsitinib reported in this study are consistent with those observed with antibodies targeting IGF-1R in patients with ACC, and included mainly fatigue and gastrointestinal toxicities.^{16,29} Despite inhibition of the IR, the number of patients who experienced serum blood sugar concentrations >160 mg/L was as low as 2 out of 90.

Despite concerns regarding accrual to a phase 3 study in a rare cancer, the trial enrolled subjects rapidly, and was completed ahead of schedule. This should encourage those planning clinical trials to consider rare cancers and other “orphan” indications as a registration pathway.

In conclusion, despite failing to show an effect on OS and PFS in the overall population, the promising responses seen in individual patients in our study indicate the therapeutic potential of inhibiting IGF-1R in ACC. Further studies of linsitinib together with genetic profiling of patients responding to linsitinib, may pave the way for improved therapeutic options in ACC.

Contributions

MF, AB, MJD, DIQ, SP, TF, RR, AWS, and GDH contributed to the conception and design of this study, or study supervision. MF, AB, MJD, HH, and MT were investigators and/or contributed to patient enrollment. Contributions to data collection were made by EB, MJD, HH, MK, DIQ, TKC, SP, and TF; data evaluation, analysis, and interpretation contributions were made by MF, EB, MJD, JG, MK, DIQ, EH, CLR, TKC, SP, TF, RR, JC, AWS, FW, and GDH. MF, EB, JG, HH, MK, DIQ, CLR, TKC, TF, FW, and GDH contributed to writing of the manuscript and EB, MK, and GDH to literature search; all authors reviewed and edited the manuscript.

Declarations of interest

Outside of the sponsorship for the submitted manuscript work, the declared conflicts of interest for the authors are as stated below. SP, TF, RR, and JC are employees of Astellas and AWS was employed by OSI Pharmaceuticals during the time of the study. MF, AB, and DIQ have been on an advisory board for Astellas and MF, MT, and GDH for Atterocor. In addition, GDH has been a consultant for Orphagen and ISIS Pharmaceuticals and holds a pending patent for ATR-101 with Atterocor. HH and MT have received grants from HRA Pharmaceuticals and JG from Boehringer-Ingelheim. EB, MJD, MK, EH, CLR, TKC, and FW have no conflicts to disclose.

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References

- 1 Bilimoria KY, Shen WT, Elaraj D, et al. Adrenocortical carcinoma in the United States: treatment utilization and prognostic factors. *Cancer* 2008; **113**: 3130–6.
- 2 Berruti A, Baudin E, Gelderblom H, et al. Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; **23(Supplement 7)**: vii131–8.
- 3 Else T, Kim AC, Sabolch A, et al. Adrenocortical carcinoma. *Endocr Rev* 2014a; **35**: 282–326.
- 4 Fassnacht M, Kroiss M, Allolio B. Update in adrenocortical carcinoma. *J Clin Endocrinol Metab* 2013; **98**: 4551–64.
- 5 Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. *N Engl J Med* 2007; **356**: 2372–80.
- 6 Hermsen IG, Fassnacht M, Terzolo M, et al. Plasma concentrations of o,p'DDD, o,p'DDA, and o,p'DDE as predictors of tumor response to mitotane in adrenocortical carcinoma: results of a retrospective ENS@T multicenter study. *J Clin Endocrinol Metab* 2011; **96**: 1844–51.
- 7 Malandrino P, Ghuzlan AA, Castaing M, et al. Prognostic markers of survival after combined mitotane- and platinum-based chemotherapy in metastatic adrenocortical carcinoma. *Endocr Relat Cancer* 2010; **17**: 797–807.
- 8 Wangberg B, Khorram-Manesh A, Jansson S, et al. The long-term survival in adrenocortical carcinoma with active surgical management and use of monitored mitotane. *Endocr Relat Cancer* 2010; **17**: 265–72.

- 9 Else T, Williams AR, Sabolch A, Jolly S, Miller BS, Hammer GD. Adjuvant therapies and patient and tumor characteristics associated with survival of adult patients with adrenocortical carcinoma. *J Clin Endocrinol Metab* 2014b; **99**: 455–61.
- 10 Fassnacht M, Terzolo M, Allolio B, et al. Combination chemotherapy in advanced adrenocortical carcinoma. *N Engl J Med* 2012; **366**: 2189–97.
- 11 de Fraipont F, El Atifi M, Cherradi N, et al. Gene expression profiling of human adrenocortical tumors using complementary deoxyribonucleic Acid microarrays identifies several candidate genes as markers of malignancy. *J Clin Endocrinol Metab* 2005; **90**: 1819–29.
- 12 Gicquel C, Bertagna X, Gaston V, et al. Molecular markers and long-term recurrences in a large cohort of patients with sporadic adrenocortical tumors. *Cancer Res* 2001; **61**: 6762–7.
- 13 Giordano TJ, Thomas DG, Kuick R, et al. Distinct transcriptional profiles of adrenocortical tumors uncovered by DNA microarray analysis. *Am J Pathol* 2003; **162**: 521–31.
- 14 Rosenzweig SA, Atreya HS. Defining the pathway to insulin-like growth factor system targeting in cancer. *Biochem Pharmacol* 2010; **80**: 1115–24.
- 15 Barlaskar FM, Spalding AC, Heaton JH, et al. Preclinical targeting of the type I insulin-like growth factor receptor in adrenocortical carcinoma. *J Clin Endocrinol Metab* 2009; **94**: 204–12.

- 16 Haluska P, Worden F, Olmos D, et al. Safety, tolerability, and pharmacokinetics of the anti-IGF-1R monoclonal antibody figitumumab in patients with refractory adrenocortical carcinoma. *Cancer Chemother Pharmacol* 2010; **65**: 765–73.
- 17 Lerario AM, Worden FP, Ramm CA, et al. The combination of insulin-like growth factor receptor 1 (IGF1R) antibody cixutumumab and mitotane as a first-line therapy for patients with recurrent/metastatic adrenocortical carcinoma: a multi-institutional NCI-sponsored trial. *Horm Canc* 2014; **5**: 232–9.
- 18 Ji QS, Mulvihill MJ, Rosenfeld-Franklin M, et al. A novel, potent, and selective insulin-like growth factor-I receptor kinase inhibitor blocks insulin-like growth factor-I receptor signaling in vitro and inhibits insulin-like growth factor-I receptor dependent tumor growth in vivo. *Mol Cancer Ther* 2007; **6**: 2158–67.
- 19 Jones R, Kim E, Nava-Parada P, et al. Phase I study of intermittent oral dosing of the insulin-like growth factor-1 and insulin receptors inhibitor OSI-906 in patients with advanced solid tumors. *Clin Cancer Res* 2014; published online September 10. DOI:10.1158/1078-0432.CCR-14-0265.
- 20 Puzanov I, Lindsay CR, Goff L, et al. Phase I, dose-escalation study of continuous oral dosing of OSI-906, a dual inhibitor of insulin-like growth factor receptor 1 and insulin receptor tyrosine kinases, in patients with advanced solid tumors. *Clin Cancer Res* 2014; published online September 11. DOI:10.1158/1078-0432.CCR-14-0303.
- 21 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.

- 22 Pavlicek A, Lira ME, Lee NV, et al. Molecular Predictors of Sensitivity to the Insulin-like Growth Factor 1 Receptor Inhibitor Figitumumab (CP-751,871). *Mol Cancer Ther* 2013; **12**: 2929–39.
- 23 Ronchi CL, Sbiera S, Kraus L, et al. Expression of excision repair cross complementing group 1 and prognosis in adrenocortical carcinoma patients treated with platinum-based chemotherapy. *Endocr Relat Cancer* 2009; **16**: 907–18.
- 24 Volante M, Terzolo M, Fassnacht M, et al. Ribonucleic reductase large subunit (RRM1) gene expression may predict efficacy of adjuvant mitotane in adrenocortical cancer. *Clin Cancer Res* 2012; **18**: 3452–61.
- 25 Kroiss M, Quinkler M, Johanssen S, et al. Sunitinib in refractory adrenocortical carcinoma: a phase II single-arm, open-label trial. *J Clin Endocrinol Metab* 2012; **97**: 3495–503.
- 26 Sierra JR, Cepero V, Giordano S. Molecular mechanisms of acquired resistance to tyrosine kinase targeted therapy. *Mol Cancer* 2010; **9**: 75.
- 27 Pollak M. The insulin and insulin-like growth factor receptor family in neoplasia: an update. *Nat Rev Cancer* 2012; **12**: 159–69.
- 28 Jin Q, Esteva FJ. Cross-talk between the ErbB/HER family and the type I insulin-like growth factor receptor signaling pathway in breast cancer. *J Mammary Gland Biol Neoplasia* 2008; **13**: 485–98.
- 29 Naing A, Lorusso P, Fu S, et al. Insulin growth factor receptor (IGF-1R) antibody cixutumumab combined with the mTOR inhibitor temsirolimus in patients with metastatic adrenocortical carcinoma. *Br J Cancer* 2013; **108**: 826–30.

- 30 Heaton JH, Wood MA, Kim AC, et al. Progression to adrenocortical tumorigenesis in mice and humans through insulin-like growth factor 2 and β -catenin. *Am J Pathol* 2012; **181**: 1017–33.

| | Linsitinib (n=90) | Placebo (n=49) |
|--|--------------------------|-----------------------|
| Sex, n (%) | | |
| Male | 30 (33·3) | 19 (38·8) |
| Female | 60 (66·7) | 30 (61·2) |
| Age (years; median, range) | 50 (19·0–85·0) | 48 (22·0–78·0) |
| Ethnic origin | | |
| Asian | 1 (1·1) | 1 (2·0) |
| Black | 5 (5·6) | 3 (6·1) |
| White | 81 (90·0) | 44 (89·8) |
| Other | 3 (3·3) | 1 (2·0) |
| ECOG performance Status, n (%) | | |
| 0 | 40 (44·4) | 22 (44·9) |
| 1 | 45 (50·0) | 26 (53·1) |
| 2 | 5 (5·6) | 1 (2·0) |
| Prior disease-related surgery, n (%) | 83 (92·2) | 43 (87·8) |
| Time from initial diagnosis, months | | |
| Mean (SD) | 41·9 (49·7) | 27·9 (28·9) |
| Median (Range) | 26·5 (3·8–276·9) | 14·9 (3·3–129·3) |
| Mitotane concentration, mg/L | | |
| Mean (SD) | 5·7 (5·2) | 5·8 (5·3) |
| Median (Range) | 4·8 (0–23·5) | 3·6 (0·5–23·7) |
| Prior radiotherapy, n (%) | 29 (32·2) | 14 (28·6) |
| Prior anticancer drug regimens, n (%) | 90 (100·0) | 49 (100·0) |
| Prior mitotane | | |
| Neo-adjuvant | 1 (1·1) | 1 (2·0) |
| Adjuvant | 33 (36·7) | 21 (42·9) |
| Advanced/metastatic | 81 (90·0) | 43 (87·8) |
| Prior cisplatin-based chemotherapy | 47 (52·2) | 30 (61·2) |

| | | |
|-----------------------------|-----------|----------|
| Prior streptozotocin | 12 (13·3) | 6 (12·2) |
| Prior other cytotoxic drugs | 10 (11·1) | 4 (8·2) |

Table 1: Demographic and baseline characteristics

| | Linsitinib (n=90) | | | Placebo (n=48) | | |
|------------------------------------|-------------------|-----------|----------|----------------|-----|----------|
| | Any grade | 3 | 4 | Any grade | 3+4 | 5 |
| Any AE n (%) | 50 (55.6) | 16 (17.8) | 1 (1.1)† | 21 (43.8) | 0 | 1 (2.1)‡ |
| Fatigue | 15 (16.7) | 3 (3.3) | 0 | 3 (6.3) | 0 | 0 |
| Nausea | 10 (11.1) | 2 (2.2) | 0 | 4 (8.3) | 0 | 0 |
| QTc prolongation | 9 (10.0) | 0 | 0 | 1 (2.1) | 0 | 0 |
| Vomiting | 7 (7.8) | 1 (1.1) | 0 | 1 (2.1) | 0 | 0 |
| Diarrhea | 4 (4.4) | 1 (1.1) | 0 | 2 (4.2) | 0 | 0 |
| Increased blood creatinine | 4 (4.4) | 0 | 0 | 0 | 0 | 0 |
| Anorexia | 3 (3.3) | 1 (1.1) | 0 | 0 | 0 | 0 |
| Arthralgia | 3 (3.3) | 0 | 0 | 0 | 0 | 0 |
| Asthenia | 3 (3.3) | 0 | 0 | 0 | 0 | 0 |
| Dry Skin | 3 (3.3) | 0 | 0 | 0 | 0 | 0 |
| Alanine aminotransferase increased | 3 (3.3) | 1 (1.1) | 0 | 0 | 0 | 0 |
| Headache | 3 (3.3) | 0 | 0 | 4 (8.3) | 0 | 0 |
| Hyperglycemia | 3 (3.3) | 2 (2.2) | 0 | 4 (8.3) | 0 | 0 |
| Hypokalemia | 3 (3.3) | 1 (1.1) | 0 | 0 | 0 | 0 |

Table 2: Drug-related adverse events reported in three or more patients in either treatment group*

*For each preferred term, each subject was only counted once at maximum grade †Grade 4 AE reported as agitation and confusional state; ‡Grade 5 AE was reported as sepsis and megacolon.

AE = adverse event; QTc = corrected QT interval.

| AUC_{last} (ng*h/mL) | C_{max} (ng/mL) | t_{max} (h) | C_{last} (ng/mL) | t_{last} (h) |
|-------------------------------------|--------------------------------|----------------------------|---------------------------------|-----------------------------|
|-------------------------------------|--------------------------------|----------------------------|---------------------------------|-----------------------------|

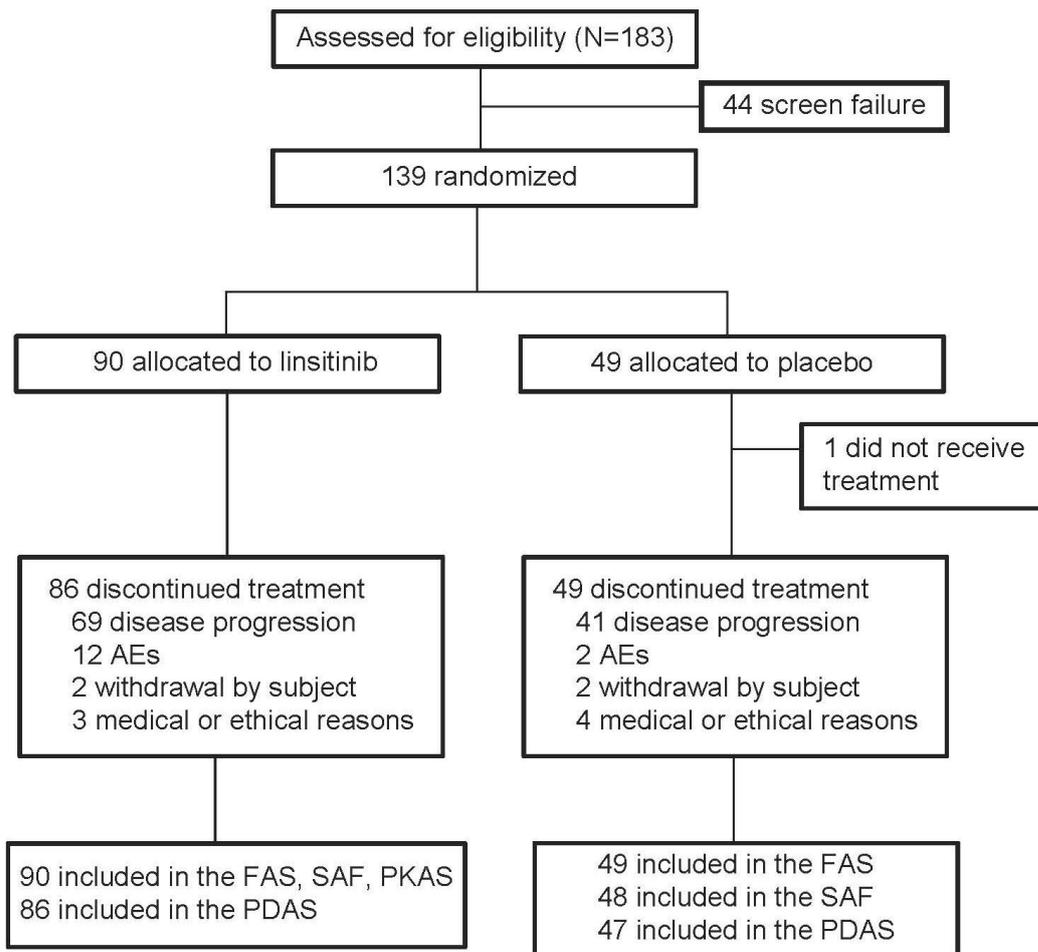
| Treatment period 1, day 1 | | | | | |
|----------------------------------|------------------|----------------|------------|----------------|------------|
| Evaluable, n | 38 | 44 | 44 | 44 | 44 |
| Median | 2571·1 | 782·5 | 2·0 | 130·2 | 7·9 |
| (range) | (317·3, 6188·1) | (85·2, 1883·0) | (1·8, 8·2) | (9·5, 1592·8) | (3·3, 8·3) |
| Treatment period 2, day 1 | | | | | |
| Evaluable, n | 33 | 40 | 40 | 40 | 40 |
| Median | 5580·1 | 1091·1 | 2·0 | 332·4 | 7·9 |
| (range) | (483·0, 26444·0) | (80·9, 4542·8) | (0·7, 4·0) | (18·8, 4542·8) | (0·7, 8·1) |

Table 3: Linsitinib pharmacokinetic parameters after single (treatment period 1) and multiple (treatment period 2) dosing*

*Patients who received active drug, were within the first 75 randomized patients, and for whom the pharmacokineticist determined that there was sufficient data to calculate meaningful pharmacokinetic parameters (Extended Pharmacokinetics Analysis Set).

AUC_{last} = area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; C_{last} = observed concentration at last time point; C_{max} = maximum observed concentration; t_{last} = time of last quantifiable concentration; t_{max} = time to reach maximum observed concentration.

Figure 1: Patient disposition



AE = adverse event; FAS = full analysis set; SAF = safety analysis set; PDAS = pharmacodynamic analysis set; PKAS = pharmacokinetic analysis set.

Figure 2: Overall survival

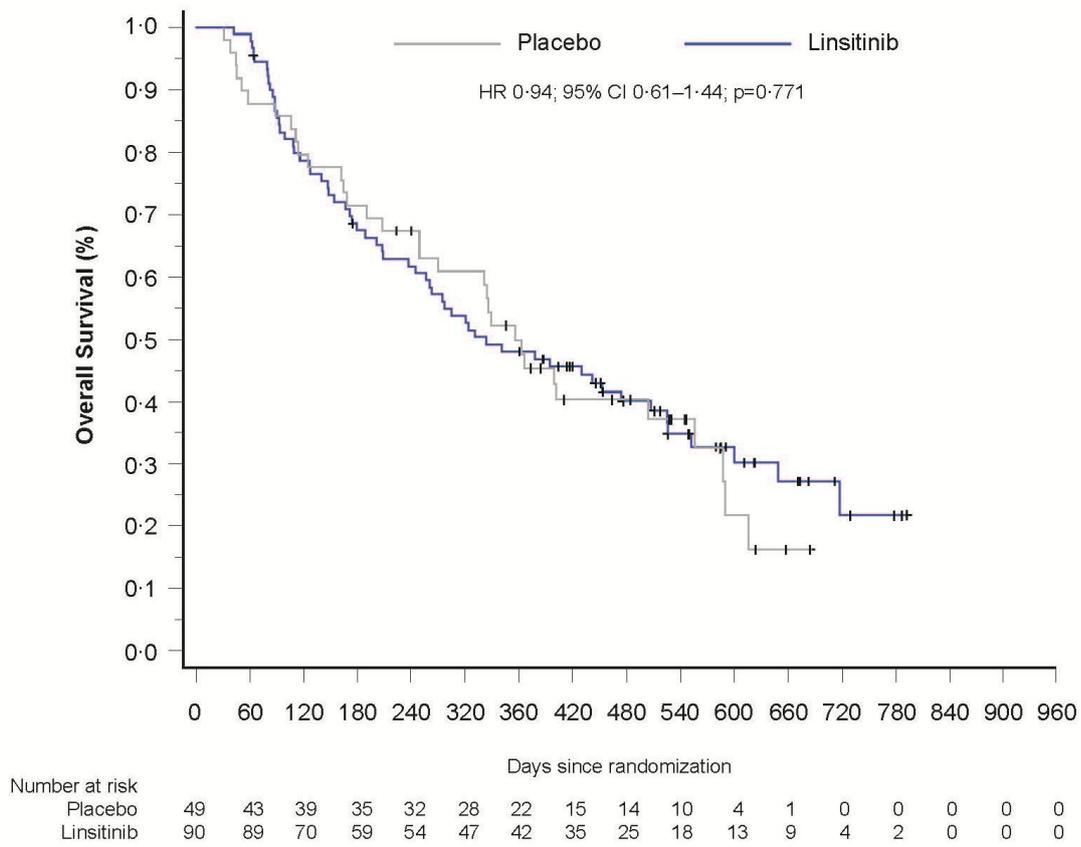
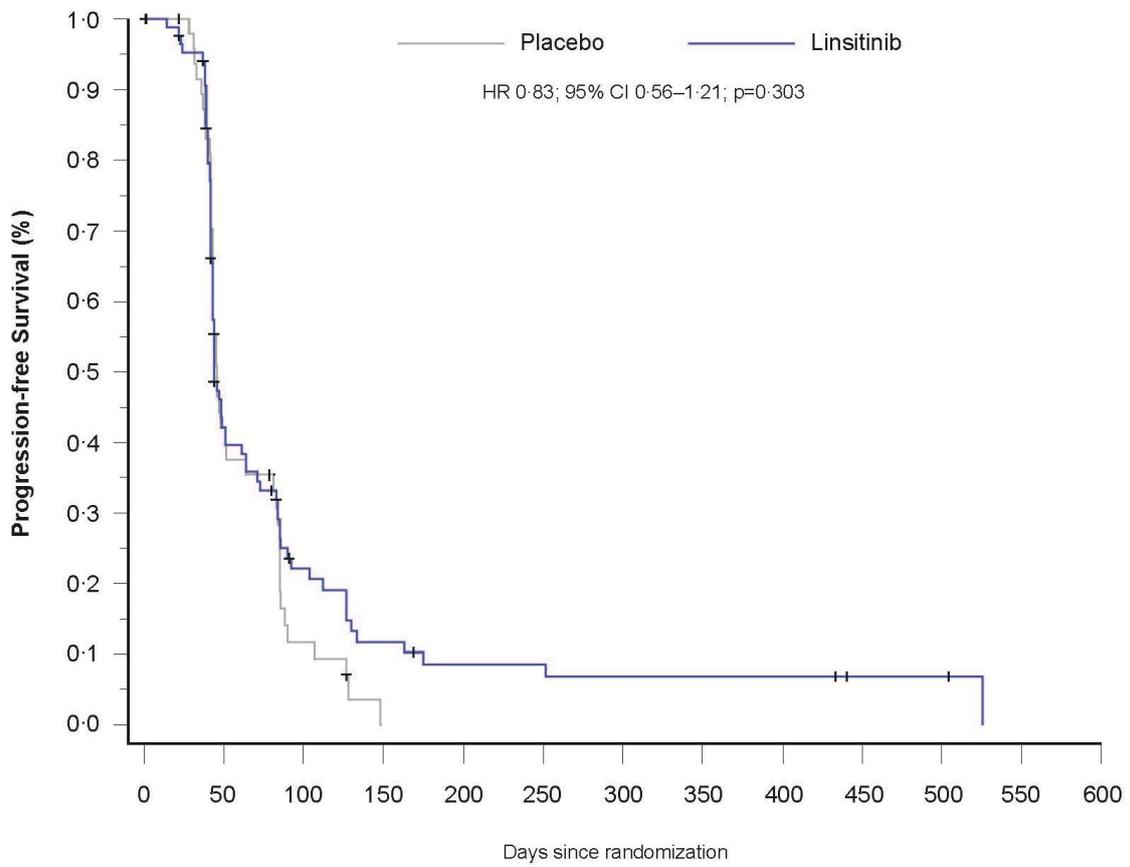


Figure 3: Progression-free survival based on independent radiologist review



| | | Days since randomization | | | | | | | | | | | | |
|----------------|------------|--------------------------|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | 0 | 50 | 100 | 150 | 200 | 250 | 300 | 350 | 400 | 450 | 500 | 550 | 600 |
| Number at risk | Placebo | 49 | 19 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Linsitinib | 90 | 33 | 15 | 8 | 5 | 5 | 4 | 4 | 4 | 2 | 2 | 0 | 0 |

Figure 4: Waterfall plot of best percentage change from baseline in sum of target lesion in linsitinib and placebo arms' central review

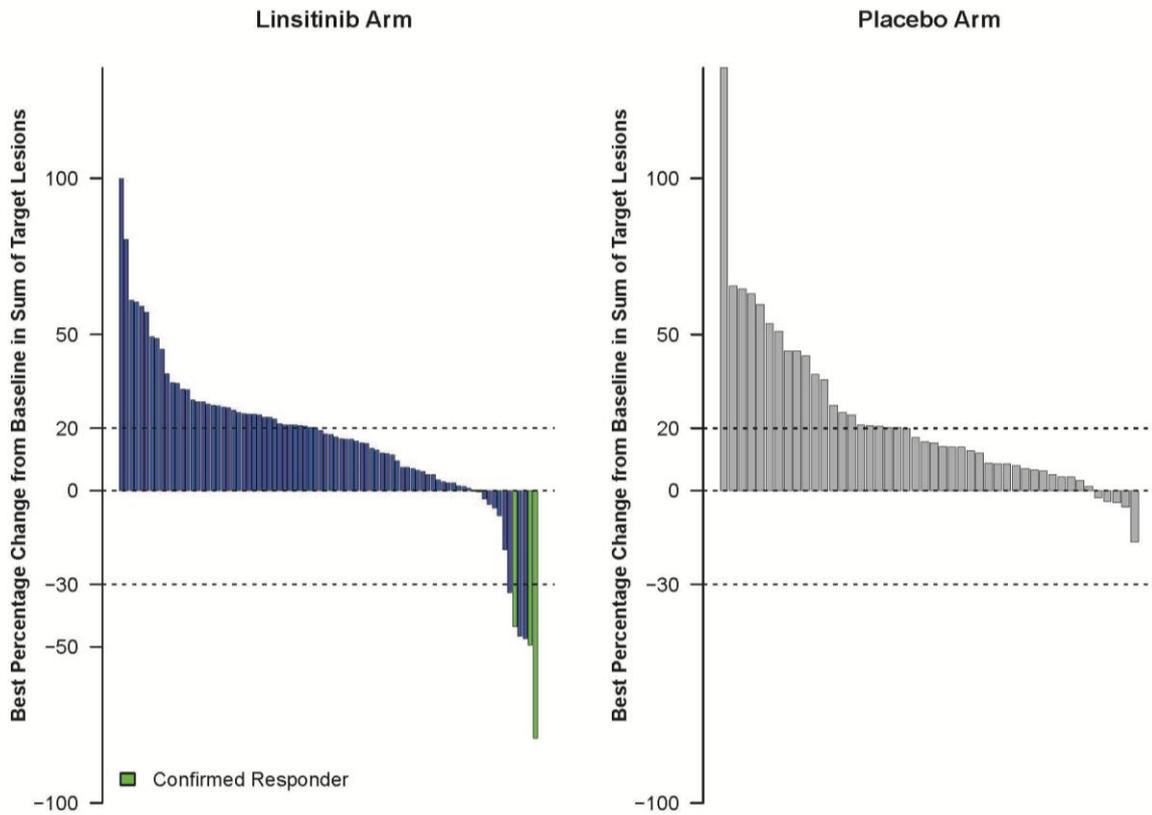
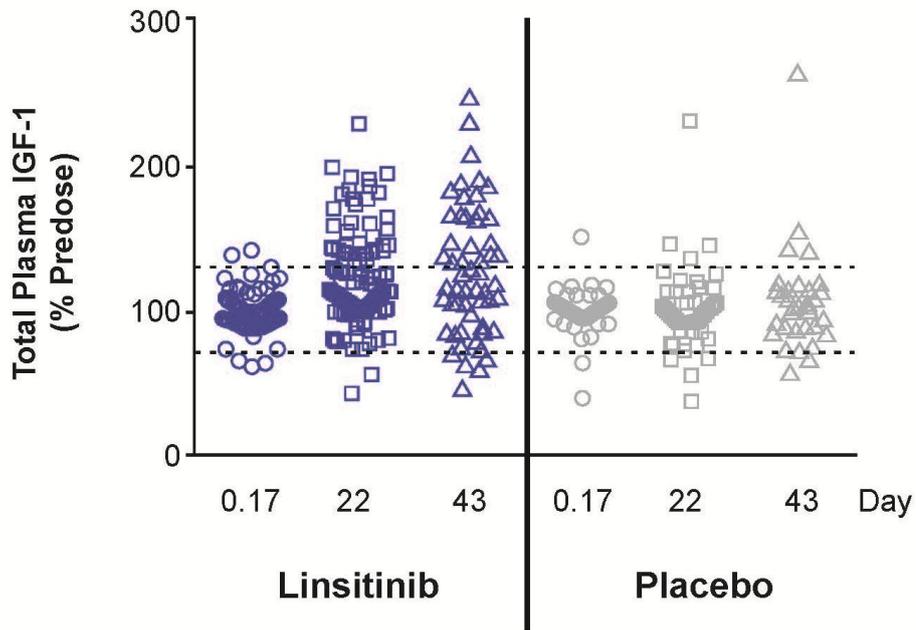


Figure 5: IGF-1 concentrations as a percentage of pre-dose values over time on treatment*



*0.17 is 4 hours post-dose. IGF-1=insulin-like growth factor 1.