Title: Phase 2 trial of linifanib (ABT-869) in patients with advanced renal cell cancer after sunitinib failure.


Purpose: The most common kidney cancer in adults is clear-cell renal cell cancer (RCC). It accounts for nearly 85 percent of all RCC and is characterized by overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). The majority of patients with RCC will have metastatic disease at time of diagnosis or go on to develop metastatic disease following nephrectomy. Treatment for patients with advanced RCC is based upon improvement in progression-free survival (PFS) and includes the multitargeted tyrosine kinase inhibitors (TKIs) sunitinib (Sutent) and pazopanib (Votrient), the dual TKI and serine/threonine kinase inhibitor sorafenib (Nexavar) and the selective inhibitor of mammalian target of rapamycin (mTOR), temsirolimus (Torisel). Once a patient has failed primary therapy with a TKI, optimal second-line therapy is still under investigation. Linifanib is a novel adenosine triphosphate competitive inhibitor that is selective for all VEGF receptors and PDGF receptors and has minimal activity against unrelated receptor tyrosine kinases and serine/threonine kinases. As VEGF and PDGF tyrosine kinases mediate tumor progression by multiple mechanisms, their simultaneous inhibition by linifanib may result in greater antitumor activity.
**Methods:** Patients with advanced RCC older than age 18 who had undergone a previous nephrectomy, who had ≥ one unidimensionally measured lesion and who had progressed within 100 days prescreening following at least two cycles or 12 weeks of sunitinib therapy were eligible. Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, life expectancy of at least four months and adequate end-organ function. This was a single-arm, open-label, multicenter phase 2 trial assessing the efficacy and safety of linifanib 0.25 mg/kg (maximum dose 25 mg) administered orally once a day at bedtime. The drug was taken on an empty stomach. Treatment was discontinued if the patient required radiation therapy, surgery or any alternative antineoplastic agent(s) due to tumor progression. The primary end point of the study was objective response rate (ORR), as defined as the percentage of all dosed patients with confirmed complete response (CR) or partial response (PR) based upon Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Secondary end points included PFS, overall survival (OS), time to progression (TTP) and safety.

**Results:** Fifty-three patients, median age of 61 years, were entered in the study. Males made up 79 percent of the treatment group. Clear-cell histology was the most common (81 percent), and most patients had an ECOG performance status of 1 (64 percent). The majority of patients had received prior systemic therapy, most commonly consisting of a cytokine (23 percent), sorafenib (19 percent) and bevacizumab (17 percent). The overall response rate to sunitinib as initial therapy was 13.2 percent. The ORR was 13.2 percent, and all responses were radiographic PRs. Six of the responses occurred in patients who received linifanib as second-line therapy and one as third-line therapy. The median PFS was 5.4 months (95 percent CI 3.6, 6.0), and TTP was similar. The median OS was 14.5 months (95 percent CI 10.8, 24.1). The most common adverse events associated with linifanib were diarrhea (74 percent), fatigue (74 percent) and hypertension (66 percent). The most common treatment-related grade 3/4 adverse event was hypertension (40 percent). Administration of 0.25 mg/kg (maximum 25 mg) was associated with a high rate of dose interruption and dose reduction.

**Conclusion:** Linifanib had clinically meaningful activity in patients with advanced RCC after sunitinib failure. An alternative dose will need to be evaluated to decrease the significant number of patients requiring dose interruption and/or dose reduction.

**Managed Care Implications:** Linifanib is an oral agent with a unique mechanism of action and clinical activity in patients with advanced RCC. If a dose that maintains efficacy but decreases toxicity can be found, it may offer an alternative as second-line therapy in this patient population.

**Title:** Everolimus in metastatic renal cell carcinoma: subgroup analysis of patients with one or two previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase 3 RECORD-1 study.

**Authors:** Calvo E., Escudier B., Motzer R.J., et al.


**Purpose:** Everolimus (Afinitor) is an orally administered inhibitor of mTOR, which regulates cell growth, proliferation, survival and angiogenesis and has activity in patients with metastatic renal cell cancer (mRCC). It is recommended as the standard of care for patients with mRCC who have had disease progression of first-line therapy with a vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKIs). In the phase 3 RECORD-1 clinical trial, everolimus and best supportive care were compared with placebo and best supportive care in patients with mRCC who became refractory to VEGFR-TKI therapy. The median PFS was 4.9 months in patients who received everolimus versus 1.9 months in those receiving placebo. This was a statistically significant finding. This study reports the PFS benefits of everolimus versus placebo in patients with mRCC who experienced disease progression after receiving either one or two previous VEGFR-TKI therapies.

**Methods:** Adult patients at least 18 years of age with measurable clear-cell mRCC who had progressed during or within six months of stopping treatment with sunitinib (Sutent), sorafenib (Nexavar) or both were included.
in the study. Previous treatment with bevacizumab (Avastin), immunotherapy or a combination of the two was also permitted. Patients were required to have a Karnofsky performance status of at least 70 percent and adequate end-organ function. Patients were randomized 2:1 to receive either continuous oral therapy with everolimus 10 mg daily or placebo, both in conjunction with best supportive care. Doses of everolimus were delayed or reduced to 5 mg daily based upon clinically significant adverse events. Treatment continued until disease progression, unacceptable toxicity or discontinuation for any other reason. Patients assigned to the placebo arm who experienced disease progression were permitted to cross over to open-label everolimus.

Results: During the trial, 277 patients were randomly assigned to receive everolimus and 139 patients to placebo. Baseline characteristics of the two groups were similar. When stratified by previous therapy, 74 percent (n = 308) of patients had received one previous VEGFR-TKI and 26 percent had received two previous therapies with the agents. Among those patients treated with one previous VEGFR-TKI, the median PFS was 5.4 months with everolimus and 1.9 months with placebo (hazard ratio [HR], 0.32; 95 percent CI, 0.24-0.43; p < 0.001). In those patients receiving two prior VEGFR-TKI therapies, the median PFS was 4.0 months in the everolimus treatment group and 1.8 months in those patients receiving placebo (HR, 0.32; 95 percent CI, 0.19-0.54; p < 0.001). Many patients treated in the RECORD-1 study who received only one VEGFR-TKI had also received one or more other previous treatments (e.g., immunotherapy). In those patients who had received only sunitinib as their previous therapy (n = 56), median PFS was 4.6 months with everolimus (n = 43) and 1.8 months with placebo (n = 13) (HR, 0.22; 95 percent CI, 0.09-0.55; p < 0.001). The safety profile of everolimus was similar among patients who had received one or two previous VEGFR-TKIs. The most commonly reported grade 3/4 adverse events were anemia (9.3 percent versus 12.5 percent), infection (6.4 percent versus 8.3 percent) and hyperglycemia (5.9 percent versus 6.9 percent).

Conclusion: Everolimus was associated with prolonged PFS relative to placebo in patients who received one or two prior therapies with VEGFR-TKIs. Those receiving only one previous VEGFR-TKI had apparently longer PFS with everolimus in reference to those who received two previous VEGFR-TKIs. This supports the use of everolimus as the standard of care in patients with mRCC who initially fail VEGFR-TKI therapy.
**Managed Care Implications:** Oral everolimus is the standard second-line therapy for patients with relapsed/refractory mRCC who have progressed on a VEGFR-TKI. Its cost versus other intravenous therapy for mRCC, such as bevacizumab and immunotherapy, should be evaluated.

**Title:** A phase 2 study of the efficacy and safety of AMG 102 in patients with metastatic renal cell carcinoma.

**Authors:** Schoffski P., Garcia J.A., Stadler W.M., et al.


**Purpose:** RCC accounts for approximately 2 percent of all new cancers worldwide. Studies have identified VEGF and mTOR pathways as therapeutic targets for patients with metastatic disease. Despite these advances, prognosis for patients with mRCC remains poor, and new molecular pathways need to be identified. Some evidence indicates that the hepatocyte growth factor/scatter factor (HGF/SP) c-Met pathway is such a target, since HGF/SP and its receptor, c-Met, are often overexpressed in mRCC. AMG 102 is an investigational, fully humanized monoclonal antibody to HGF/SP that prevents it from binding to c-Met, thereby blocking a signaling pathway that drives tumor proliferation, migration, invasion and survival. Initial dose-finding studies showed good tolerability of AMG 102 in patients with advanced solid tumors at a dose of 20 mg/kg every two weeks.

**Methods:** Patients who were age 18 or older with histologically confirmed, measurable advanced or mRCC who were unable to receive or who had failed previous therapy with VEGF inhibitors or other multikinase inhibitors were eligible. Up to three previous systemic therapies were allowed. Patients were required to have an ECOG performance status of 0 to 2 and adequate end-organ function. The open-label phase 2 study administered AMG 102 at either a 10 or 20 mg/kg dose intravenously on an every-two-week basis over 30 to 60 minutes. Treatment could be held for toxicity and continued until disease progression, unacceptable toxicity or withdrawal of consent. Tumor response was done at week nine and every eight weeks thereafter. The primary end point of the study was objective best response assessed by an independent central review committee, with a target overall response rate of five confirmed responses among 40 patients at either dose level. Secondary end points included PFS, OS and safety.

**Results:** Sixty-one patients were enrolled, with 40 patients treated with AMG 102 at a dose of 10 mg/kg every two weeks and an additional 21 patients treated at the 20 mg/kg every-two-week dosing schedule. A median of five (range one to 52) doses of AMG 102 were administered per patient. The median duration of treatment for those patients receiving the 10 mg/kg dose was 10.6 weeks (range 2.1 to 101.9) and 9.7 weeks (range 5.4 to 60.9) in the group receiving 20 mg/kg. The overall response rate was 2.5 percent for the group receiving 10 mg/kg (one partial response) and 0 percent for the group receiving 20 mg/kg. Twenty-six patients achieved stable disease as their best response. Ten patients who received the 10 mg/kg dose of AMG 102 had stable disease for ≥ 32 weeks (range 32 to 95.4+). The estimated PFS by investigator review was 3.7 months (95 percent CI, 1.8-7.9) at 10 mg/kg and 2.0 months (95 percent CI, 1.8-3.7) at 20 mg/kg. The median OS was 14.9 months (95 percent CI, 9.4 to not evaluable) and 17.6 months (95 percent CI, 7.1 to not evaluable) in the 10 mg/kg and 20 mg/kg dosing groups, respectively. The most common adverse events were edema (46 percent with 10 percent grade 3/4), fatigue (38 percent with 3 percent grade 3/4) and nausea (28 percent with 0 percent grade 3/4).

**Conclusion:** Single-agent AMG 102 was tolerable, but it is unclear if AMG 102 was growth inhibitory in this patient population with mRCC.

**Managed Care Implications:** While a drug such as AMG 102 lacked efficacy in patients with mRCC, new molecular pathways must be identified to afford improved treatment in patients who have failed VEGF-TKI and mTOR inhibitors.

**Title:** The outcomes and safety of single-agent sorafenib in the treatment of elderly patients with advanced hepatocellular carcinoma (HCC).

**Authors:** Wong H., Tang Y.F., Yao T.-J., et al.

**Reference:** Oncol. 2011;16:1721-1728.

**Purpose:** HCC is the fifth most common malignancy in men and the seventh most common in women worldwide. It is also the third most common cause of cancer mortality. As with most cancers, HCC is age-dependent and is being diagnosed in the elderly population with increased frequency. Medical comorbidities and altered drug kinetics may lead to poor drug tolerance and potential toxicity. Since this population has...
generally been underrepresented in clinical trials, the best management for these patients is unclear. Historically, elderly patients with HCC have been treated more conservatively despite similar tumor stage at diagnosis, leading to significantly worse outcomes. Elderly patients with HCC may have a more favorable tumor biology than younger patients and actually have a better outcome. Treatment outcomes with drugs like sorafenib (Nexavar) in elderly patients are unknown. This study will evaluate the efficacy and tolerability of sorafenib in younger (< 70 years of age) and older (≥ 70 years of age) with advanced HCC not amenable to locoregional therapy or surgical intervention.

Methods: This retrospective study from a single tertiary referral center was conducted in patients with a diagnosis of HCC who were confirmed to be inoperable and/or unsuitable for local ablative therapy or surgical intervention. Patients with underlying liver cirrhosis of Child-Pugh class C or baseline ECOG performance status score of ≥ 3 were excluded. Patients were categorized into one of two groups, older (≥ 70 years of age) and younger (those < 70 years of age). Patients were treated with single-agent sorafenib, 400 mg orally twice a day. Dose reductions were allowed on occurrence of adverse events of ≥ grade 3 by the National Cancer Institute’s (NCI’s) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Treatment continued until disease progression or unacceptable toxicity. Tumor assessments were performed by computed tomography (CT), positron emission tomography-computed tomography (PET-CT) or magnetic resonance imaging at baseline and then every two to three months. End points of the study included PFS, OS, ORR and toxicity.

Results: Of the 172 patients enrolled, 137 (79.7 percent) belonged to the younger group and 35 (20.3 percent) belonged to the older group. The median ages were 55 and 73, respectively. The majority of patients in each group had reasonable liver function prior to treatment; 62.8 percent of patients in the younger group and 62.9 percent of the patients in the older group had Child-Pugh class A disease. Most patients had an ECOG performance status of 1. Disease stage and viral hepatitis C status were also similar between the two groups. At a median follow-up of 25.07 months (95 percent CI, 21.09-25.99) in the younger group and 15.44 months (95 percent CI, 9.66-43.50) in the older group, the median PFS times were 3.09 months (95 percent CI, 2.76-3.4) and 2.99 months (95 percent CI, 2.30-4.53), respectively (p = 0.275). The median OS times were also comparable at 5.16 months (95 percent CI, 4.21-6.05) for the younger group and 5.32 (95 percent CI, 4.44-10.35) for the older group (p = 0.310). Grade 3 or 4 adverse events were observed in 68.6 percent of the older and 62.7 percent of the younger patients (p = 0.560). Older patients experienced more frequent complications with neutropenia (11.4 percent versus 0.7 percent; p = 0.007), malaise (11.4 percent versus 2.2 percent; p = 0.033) and mucositis (5.7 percent versus 0.0 percent; p = 0.041).

Conclusion: The survival benefits and overall treatment adverse events of sorafenib are similar in the elderly and younger patients with advanced HCC. More vigilant monitoring of the elderly patients is warranted since they are more susceptible to developing certain side effects.

Managed Care Implications: Elderly patients should be treated with the same dosing schedule of sorafenib as younger patients to afford them the best chance for response and survival. All patients should be monitored closely for the known toxicities of the drug.

Title: Phase 2 trial of sorafenib combined with concurrent transarterial chemoembolization
with drug-eluting beads for hepatocellular carcinoma.

**Authors:** Pawlik T.M., Reyes D.K., Cosgrove D., et al.


**Purpose:** HCC is a common disease worldwide and treatment includes ablation, resection and transplantation for those with limited disease. Patients with advanced HCC are not candidates for these treatment modalities, and survival with unresectable advanced HCC is poor with one-, three- and five-year survival rates of 29 percent, 8 percent and 0 percent. Sorafenib (Nexavar) inhibits angiogenesis by targeting the vascular endothelial growth factor receptor 2 (VEGFR2) and the platelet-derived growth factor receptor (PDGFR) pathway while also blocking cell proliferation by targeting the Ras/mitogen-activated protein kinase signaling pathway. The drug has shown to increase survival in patients with advanced HCC when compared with placebo, although this is generally less than a one-year advantage. Intraarterial therapy using conventional transarterial chemoembolization (cTACE) can increase survival in selected patients with inoperable, intermediate HCC. Drug-eluting bead (DEB)-TACE has been seen as a method to enhance drug delivery while reducing systemic toxicity. Studies have shown DEB-TACE to yield higher response rates versus cTACE. One limitation of TACE has been the high incidence of recurrence. An increase in plasma VEGF levels following TACE therapy has been documented and may be a potential cause of recurrent disease. The addition of a VEGFR inhibitor may reduce tumor volume and vessel density, leading to longer survival when compared with TACE alone. This phase 2 study evaluated the safety and efficacy of sorafenib combined with DEB-TACE in patients with unresectable HCC.

**Methods:** Patients at least 18 years of age with a diagnosis of unresectable HCC based on histology obtained by a needle biopsy or a hypervascular lesion on cross-sectional imaging and alpha-fetoprotein level of 200 ng/mL or greater were eligible. Patients were required to have an ECOG performance status of 0 or 1, adequate end-organ function (renal, cardiac, bone marrow) and a life expectancy of at least 12 weeks. Eligible patients had Child-Pugh liver function of A to B7 with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < eight times the upper limit of normal, bilirubin < 3 mg/dL and albumin > 2 mg/dL. Patients were treated on a six-week cycle, in which one cycle consisted of sorafenib (400 mg orally twice daily) and DEB-TACE initiated one week after the start of the sorafenib. DEB-TACE was administered with a maximum of 100 mg of doxorubicin (Adriamycin) per procedure loaded onto 100 to 300 \( \mu \)m LC beads. Clinical examination was completed weekly with laboratory assessment in weeks three and five and imaging in week five. The primary end points were safety and toxicity associated with the combined therapy.
Results: Thirty-five patients were enrolled in the study. The population was predominantly male (74 percent) and the majority were Child-Pugh score A (89 percent). The ECOG performance status for stage 0 or 1 was 46 percent and 54 percent, respectively. The mean index tumor size was 7.7 cm (standard deviation +/- 4.2 cm). The patients received a total of 128 cycles of therapy (sorafenib + DEB-TACE, 60 cycles; sorafenib alone, 68 cycles). The median number of cycles was two (range one to five), and the median number of days of sorafenib therapy was 71 (range four to 620). The median number of DEB-TACE treatments per patient was one (range one to five) with the median dose of doxorubicin decreased in each subsequent cycle (cycle one, 75 mg; cycle two, 60 mg; cycle three, 49 mg). The most common toxicities during cycle one were fatigue (94 percent), anorexia (67 percent), alteration in liver enzymes (64 percent) and dermatologic adverse events (48 percent; primarily hand-foot skin reactions). While most patients experienced at least one grade 3 or 4 toxicity (17 percent), most were minor (grade 1 or 2, 83 percent). Toxicity during cycle two was decreased in comparison with cycle one. Over the course of the study, there were 40 sorafenib dose reductions, most commonly for hand-foot skin reactions. Fifty-six targeted lesions among 33 patients were evaluated for treatment response. After one cycle of sorafenib plus DEB-TACE, there was a 4 percent decrease in tumor size (from 6.0 to 5.8 cm; p = 0.05). In contrast, assessment of tumor necrosis revealed a more marked response. After combined therapy, there was a 50 percent decrease in tumor enhancement (from 90 percent to 45 percent; p < 0.001). The disease control rate evaluated per lesion was 92 percent by RECIST criteria; using European Association for the Study of the Liver (EASL) criteria, the objective response rate was 58 percent, and the disease control rate was 100 percent.

Conclusion: The combination of sorafenib and DEB-TACE in patients with unresectable HCC is well-tolerated and safe. Toxicity is manageable with dose adjustment of sorafenib. Preliminary efficacy data are promising.

Managed Care Implications: While not suitable for all patients with advanced HCC, the combination of sorafenib and DEB-TACE offers a unique treatment option for patients who present with adequate hepatic function and more localized disease. Further evaluation is under way.

Title: A randomized phase 2 trial of intra-arterial chemotherapy using SM-11355 (Miriplatin) for hepatocellular carcinoma.

Authors: Okusaka T., Kasugai H., Ishii H., et al.


Purpose: HCC ranks third worldwide behind lung cancer and gastric cancer in number of deaths secondary to a malignancy. The impact of new therapy for advanced HCC, including cTACE using cisplatin (Platinol) or doxorubicin (Adriamycin), is unsatisfactory. New treatments are needed for the management of the disease. SM-11355 is a highly lipophilic platinum derivative that can be delivered suspended in iodized oil and injected into the hepatic artery. Following injection, the iodized oil selectively accumulates in the tumor, allowing a continuous release of active platinum compounds into the tumor tissue. Phase 1 studies identified a recommended dose of 20 mg/mL and an upper limit of injection volume of 6 mL. SM-11355
has shown promising anticancer effect and mild toxicity in early phase 2 studies in patients with advanced HCC. This late phase 2 open-label trial of SM-11355 reevaluates the safety, efficacy and pharmacokinetics of the drug in a larger patient population. To achieve regulatory approval in Japan, a reference study using Zinostatin stimalamer was also done, since it is the only commercially available lipophilic drug approved for advanced HCC.

Methods: Consecutive patients with HCC were eligible if they had no indication for resection or local ablation therapy. Diagnosis was confirmed histologically and/or clinically using angiography and enhanced CT. Each patient had to have at least one measureable intrahepatic lesion that showed tumor staining by CT, tumor stage II or III in the staging system of the Liver Cancer Study Group of Japan, Child-Pugh classification A or B, adequate end-organ function, an ECOG performance status of 0 to 2 and a minimal life expectancy of ≥ three months. Patients were randomly assigned to SM-11355 or Zinostatin stimalamer prior to angiography. Registration was confirmed based on angiographic findings of intrahepatic lesions that showed tumor staining and were fed by an artery with an appropriate structure for catheter insertion. A suspension of SM-11355 (20 mg/mL) suspended in iodized oil in a volume of up to 6 mL depending upon tumor size was injected. Additional patients were injected with Zinostatin stimalamer suspended in iodized oil (1 mg titer/mL) in a volume of up to 6 mL. When iodized oil accumulation in the treated tumor was insufficient and tumor staining was found in diagnostic imaging five weeks (+/- 10 days) after the first injection, a second injection was administered within 12 weeks after the first injection. The primary end points of the study were efficacy and toxicity. Efficacy was evaluated by CT three months after treatment and categorized as therapeutic effect (TE) V to I, where TE V was defined as disappearance or 100 percent necrosis of all treated tumors.

Results: One hundred and thirty-one patients were enrolled and assigned randomly in a 2:1 ratio to receive SM-11355 (n = 85) or Zinostatin stimalamer (n = 41). Of the original 85 patients receiving the investigational therapy, 18 were withdrawn from the study prior to the planned evaluation for efficacy at three months after the first injection. Fifty-six patients received a second injection of SM-11355. The percentage of TE V patients was 26.5 percent (22/83; 95 percent CI, 17.4-37.3 percent) in the SM-11355 group and 17.9 percent (7/39; 95 percent CI, 7.5-33.5 percent) in the Zinostatin stimalamer group. In a RECIST assessment, response rates were 24.1 percent (20/83; 95 percent CI, 15.4-34.7 percent) and 25.6 percent (10/39; 95 percent CI, 13.0-42.1 percent), respectively. The two-year and three-year survival rates were 75.9 percent versus 70.3 percent and 58.4 percent versus 48.7 percent, respectively. Hematologic toxicity was mild and transient in both groups. The incidence of eosinophilis was higher in the SM-11355 group while the incidences of leucopenia and thrombocytopenia were higher in those patients treated with Zinostatin stimalamer. The adverse event with the largest difference between the two groups was hepatic vascular injury (0 percent with SM-11355 versus 48.4 percent with Zinostatin stimalamer).

Conclusion: The results suggest that SM-11355 iodized oil has similar efficacy to Zinostatin stimalamer. Repeated dosing of SM-11355 is possible without hepatic vascular injury in cases of relapse.

Managed Care Implications: New drugs with the ability to be administered intrahepatically may be of benefit to patients with advanced HCC. Additional studies will identify where this type of therapy should be placed.