Published in final edited form as:

Invest New Drugs. 2014 April ; 32(2): 279–286. doi:10.1007/s10637-013-9966-3.

Phase I Clinical Trial of Lenalidomide in Combination with Sorafenib in Patients with Advanced Cancer

Prasanth Ganesan, MD¹, Sarina Piha-Paul, MD¹, Aung Naing, MD¹, Gerald Falchook, MD¹, Jennifer Wheler, MD¹, Siqing Fu, MD, PhD¹, David S. Hong, MD¹, Razelle Kurzrock, M.D¹, Filip Janku, MD, PhD¹, Shell Laday¹, Agop Y. Bedikian, MD², Merrill Kies, MD³, Robert A. Wolff, MD¹, and Apostolia M. Tsimberidou, MD, PhD¹

¹Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center

²Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center

³Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center

Abstract

BACKGROUND—Preclinical data have shown that lenalidomide and sorafenib target endothelial cells, inhibiting growth of ocular melanoma cells in a xenograft model. We conducted a Phase I study of lenalidomide and sorafenib in patients with advanced cancer.

METHODS—During the escalation phase, lenalidomide (days 1–21) and sorafenib (days 1–28) were given orally once daily at the following respective doses: level 1 (10 mg, 200 mg); level 2 (10 mg, 400 mg); level 3 (20 mg, 400 mg); and level 4 (25 mg, 400 mg) (1 cycle = 28 days). A “3+3” study design was used.

RESULTS—Forty-one patients were treated (median age: 50 years). The most common diagnoses were adenoid cystic carcinoma (N=9), ovarian adenocarcinoma (N=7), and melanoma (N=6); 142 cycles (median: 3) were administered. No dose-limiting toxicities were noted. The maximum tested dose (dose level 4) was used in the expansion phase. Grade 3–4 treatment-related toxicities were neutropenia, thrombocytopenia, skin rash, and thromboembolism. Of 38 patients who were evaluable for response, stable disease (SD) was noted in 53% of patients (SD ≥ 6 months: 16%). Tumor types with SD ≥ 6 months were as follows: ocular melanoma, 2/2 (100%); other melanoma, 1/4 (25%); adenoid cystic carcinoma, 2/9 (22%); and ovarian cancer, 1/6 (17%). The median progression-free survival duration was 3.5 months (95% CI, 1.9–5.0), and the median overall survival duration was 12.3 months (95% CI, 10.1–14.5).

Corresponding author: Apostolia Maria Tsimberidou, MD, PhD, The University of Texas MD Anderson Cancer Center, Department of Investigational Cancer Therapeutics, Unit 455, 1515 Holcombe Boulevard, Houston, TX 77030, Phone: 713-792-4259, Fax: 713-794-3249, atsimber@mdanderson.org.

Conflicts of Interest declaration

P. Ganesan: None. S. Piha-Paul: None. A. Naing: None. J. Wheler: None. S. Fu: None. D.S. Hong: None. R. Kurzrock: None. F. Janku: None. S. Laday: None. A.Y. Bedikian: None. M. Kies: None. R. Wolff: None. A.M. Tsimberidou and G. Falchook: Received research funding from Celgene.

CONCLUSIONS—Lenalidomide and sorafenib was well tolerated and associated with disease stabilization for 6 months in patients with melanoma, adenoid cystic carcinoma, and ovarian adenocarcinoma.

Keywords

Lenalidomide; Sorafenib; Phase I trial; advanced cancer

Introduction

Lenalidomide is an immunomodulatory drug with anti-angiogenic properties that is currently approved for use in the treatment of multiple myeloma and 5q-deleted myelodysplastic syndrome.[1–3] Recent studies have demonstrated that lenalidomide has activity in a variety of solid tumors, although its efficacy as a single agent is modest.[4] The activity of lenalidomide against solid tumors could be enhanced by combining it with other anti-cancer agents, including other anti-angiogenic drugs. A few studies have indicated that lenalidomide can be safely combined with cytotoxic chemotherapy, with possible synergistic effects.[5,6]

Sorafenib is an inhibitor of several serine/threonine and receptor tyrosine kinases and a potent anti-angiogenic drug currently approved for use in renal cell carcinoma and hepatocellular carcinoma. Specifically, it inhibits signal transduction involving multiple intracellular kinases (e.g., c-Raf, b-Raf, and mutant b-Raf) and cell surface kinases (e.g., c-Kit, Flt-3, vascular endothelial growth factor receptor [VEGFR]-2, VEGFR-3, platelet-derived growth factor receptor [PDGFR]-b).[7] The combination of sorafenib and lenalidomide is attractive because of the potentially beneficial dual anti-angiogenic effect. Moreover, a preclinical model has demonstrated enhanced antitumor activity with this combination.[8] Therefore, we designed a phase 1 clinical trial of a combination of lenalidomide and sorafenib in patients with advanced cancer. The primary objective was to determine the maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT) of lenalidomide combined with sorafenib. The secondary objective was to assess the antitumor efficacy of this combination, if any.

Patients and Methods

Eligibility criteria

Patients with histologically confirmed advanced or metastatic cancer that was refractory to standard therapy, had recurred after standard therapy, or for which there was no standard therapy available were eligible for the protocol. Participants must have completed their previous anti-cancer therapy (cytotoxic chemotherapy, major surgery or radiation) 3 weeks prior to study entry (or 5 half-lives prior, if they had received targeted or biologic therapy). Participants were also required to have Eastern Cooperative Oncology Group (ECOG) performance status 2 and adequate renal (creatinine clearance 50 ml/min by Cockcroft-Gault formula), hepatic (total bilirubin < 2.0 mg/dL or alanine aminotransferase 5× upper normal reference value), and bone marrow (absolute neutrophil count 1000 cells/μL and platelet count 100,000 cells/μL) function. Female patients of childbearing potential were

eligible if they had a negative urine or human chorionic gonadotropin serum test and agreed to use effective contraception throughout study participation.

Patients were ineligible if they were pregnant or breast feeding or had any of the following: serious uncontrolled medical illness, psychiatric illness that limited their capacity to sign the consent documents, uncontrolled hypertension (systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg on medication), history of deep vein thrombosis or pulmonary embolism, or significant cardiovascular disease (history of myocardial infarction or history of cerebrovascular accident or unstable angina pectoris within the past 6 months). All patients had to sign informed consent forms fully disclosing the investigational nature of the trial prior to enrollment. The protocol was approved by The University of Texas MD Anderson Cancer Center Institutional Review Board.

The sorafenib and lenalidomide arm was one of the four arms of an investigator-initiated clinical trial (www.clinicaltrials.gov, NCT01183663). The other arms were lenalidomide in combination with bevacizumab, temsirolimus, or 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX).

Treatment plan

Lenalidomide was given orally on days 1–21 and sorafenib was given orally on days 1–28 of each 28-day cycle. All treatment was given on an out-patient basis. The starting doses were 10 mg once a day for lenalidomide and 200 mg once a day for sorafenib. New dose cohorts were initiated after a 30-day post-treatment observation period following enrollment of the last patient in each cohort. The dose escalation scheme is shown in Table 1. Patients were to receive prophylactic anticoagulation was to be given at the treating physician's discretion.

Patients received full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics, when appropriate. Hematopoietic growth factors were allowed for grade 3 or 4 neutropenia or for neutropenic fever.

Dose modifications

If grade 3 treatment-related toxicity occurred, treatment was withheld until resolution of toxicity to grade 1 and restarted at the next lower dose. If grade 3 toxicity recurred or grade 4 toxicity occurred, treatment was discontinued.

Patient monitoring

Patients were monitored every 4 weeks by complete clinical evaluation, including assessment for adverse events, complete blood count and blood differential tests, and blood chemistry studies. All patients underwent radiological studies for tumor staging after every two cycles of therapy (1 cycle = 4 weeks).

Endpoints and statistical considerations

The study was conducted with a conventional “3 + 3” study design, followed by an expansion phase. Toxicities were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0.[9] Dose-limiting

toxicities (DLTs) were assessed during the first cycle and defined as follows: any grade 3 or 4 non-hematologic toxicity, as defined in the most current version of the NCI CTCAE, even if expected and believed to be unrelated to the study medications (except nausea and vomiting, electrolyte imbalances responsive to appropriate regimens, or alopecia); any grade 4 hematologic toxicity lasting 7 days or longer (as defined by the NCI CTCAE), despite supportive care or associated with bleeding and/or sepsis; any grade 4 nausea or vomiting lasting more than 5 days despite maximum anti-nausea regimens; any other grade 3 non-hematologic toxicity, including symptoms/signs of vascular leakage or cytokine release syndrome but excluding alopecia; and any severe or life-threatening complication or abnormality not covered in the NCI CTCAE. The maximum tolerated dose was defined by DLTs that occurred in the first cycle. Patients who had response or stable disease were allowed to remain on the study until progression of disease, death, withdrawal of consent, or unacceptable toxicity occurred.

Best response was assessed by an MD Anderson Cancer Center radiologist every 2 cycles of therapy using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.0).[10] These criteria define a partial response as a 30% or greater decrease in the sum of the longest diameters of target lesions, excluding complete disappearance of disease (complete response). Progressive disease was defined as a 20% or greater increase in the sum of the longest diameters of target lesions. Stable disease (SD) was defined as changes not meeting the criteria for a partial response or progressive disease. Waterfall plot analysis was used to illustrate antitumor activity, if any, as previously described.[11] Responses shown in the waterfall plot were grouped according to standard RECIST criteria.

Overall survival was measured from the start of treatment on protocol until death from any cause or until last follow-up. Progression-free survival was measured from the start of treatment on protocol until progression or death due to any cause, whichever occurred first. Failure-free survival was calculated from start of treatment until disease progression. A p-value <0.05 was considered statistically significant. Statistical analyses were carried out using SPSS 19 computer software (SPSS Chicago, IL).

Results

Patient characteristics

From August 2010 to September 2012, 42 patients were registered to be treated on protocol with this combination therapy. One patient did not start therapy due to insurance issues. Forty-one patients were treated. Their median age was 50 years (range, 16–72 years). There were 23 women and 18 men. The most common diagnoses were adenoid cystic carcinoma (n=9), ovarian adenocarcinoma (n=7), and melanoma (n=6). Thirty-three (80%) patients had 2 or more metastatic sites (range, 1–7). The median number of prior therapies was 3 (range, 0–12). The median time from diagnosis to enrollment in the study was 135 months (range, 1–413). Baseline patient characteristics are shown in Table 2.

Dose escalation and dose-limiting toxicity

A total of 142 cycles of therapy were administered. The median number of cycles administered per patient was 3 (range, 1–17). Of the 41 patients who started the study medications, 3 patients withdrew consent and discontinued protocol treatment prior to completion of 1 month of therapy (none had toxicity). Another patient had rapid disease progression within the first month of treatment. These four patients did not complete cycle 1.

The dose escalation schema and the number of patients treated at each dose level are listed in Table 1. No DLT was observed during the dose-escalation portion of the study; therefore, the last dose level (level 4: lenalidomide at 25 mg daily for 21 days and sorafenib at 400 mg daily for 28 days every 4 weeks) was used in the expansion phase. Twenty-two patients were treated in the expansion phase. One of these 22 patients developed a grade 3 skin rash in the first cycle that was considered a DLT. No other patients developed a DLT.

Prophylactic anticoagulation (low molecular weight heparin, coumadin, or aspirin as deemed appropriate) was initially to be given at the treating physician's discretion, but was strongly recommended after 2 patients developed thromboembolism while on the study.

Toxicity

Twenty-four (58%) patients had no toxicity greater than grade 1. The most common non-hematological toxicities were skin rash (n=11), myalgias (n=3), mucositis (n=3), nausea/vomiting (n=2), anorexia (n=2), deep vein thrombosis (n=1), and pulmonary embolism (n=1), tremors (n=1), headache (n=1) and hypertension (n=1) (Table 3). Six patients required treatment with granulocyte colony-stimulating factor (filgrastim) for neutropenia. Dose reduction of lenalidomide (from 25 mg/day to 20 mg/day) was required in three patients because of grade 3 skin rashes (n=2) and respiratory infection (n=1).

Nineteen (46%) of 41 patients received prophylactic anticoagulation therapy. Two patients (one who received anticoagulation prophylaxis and one who did not) developed thromboembolism (1/19 (5%) vs. 1/22 (4.5%); $p=.94$). After these two patients developed thromboembolisms, prophylactic anticoagulation was mandated, and no additional patients developed thromboembolic complications.

The first patient to develop a thromboembolism was a 59-year-old female physician with non-small cell lung carcinoma metastatic to the lung, liver, bones, lymph nodes, and brain who was being treated at dose level 2. She was admitted to the hospital during cycle 2 (day 23) with septic shock and died soon after of multi-organ failure. At the time of admittance, she was found to have bilateral popliteal vein deep vein thrombosis, and no pulmonary embolism was identified on the computed tomography scan of the thorax. Prior to the admission she had reported fever for approximately a week and pain and swelling in her elbow for 3 days. She had refused to visit the emergency center. After being admitted to the hospital, she underwent restaging imaging studies that demonstrated progressive disease, in addition to a pathological fracture of her humerus.

The second patient, a 49-year-old male with squamous cell carcinoma of the urethra metastatic to the lungs and lymph nodes, developed a pulmonary embolism (grade 4

toxicity) while on prophylactic warfarin during cycle 2 of protocol treatment. He presented with dyspnea, and computed tomographic angiography showed a pulmonary embolism. He was treated with low-molecular-weight heparin and recovered. His protocol treatment was subsequently discontinued, however, when progressive disease was found on imaging studies.

Toxicity evaluation at the maximum tolerated dose

Twenty-nine patients were treated at dose level 4 (Table 1). Overall, 100 cycles were administered at this dose level, with a median of four cycles per patient (range, 1–17). The following toxicities were noted: two patients had grade 3 skin rash (one patient during cycle 1 [DLT] and another patient during cycle 2), five patients had grade 3 neutropenia, and one patient developed grade 3 thrombocytopenia. All of these toxicities were fully reversible.

Response evaluation

Response was evaluable for 38 patients. Of these, 3 patients remained on protocol at the time of last follow-up. Thirty-five patients stopped protocol treatment for the following reasons: progression of disease (n=31), consent withdrawal (n=3; 1 due to difficulty in travelling to our center after completing 17 cycles, 2 for taking alternative therapies), and death (n=1). The best response noted was SD in 20/38 (53%) patients, including 6/38 (16%) who had SD for at least 6 months (Tables 4 and 5). Of 6 patients with melanoma, five (83%) had stable disease; of these five patients with stable disease, two had ocular melanoma. Of the six patients who had SD for ≥ 6 months, there were two patients who had very prolonged SD. One was a 30-year-old woman with melanoma metastatic to the lungs and liver who had had four prior therapies. Her best response was a 4% decrease in tumor measurement, and she remained stable on therapy until last follow-up, with minimal toxicity (grade 1 rash), after 14 cycles of treatment. The other patient was a 74-year-old man with adenoid cystic carcinoma metastatic to the lungs that had progressed after two lines of chemotherapy. He had stable disease for 17 cycles (best response, –17%) at the time of protocol discontinuation due to logistic issues. SD ≥ 6 months was noted in ocular melanoma, 2/2 (100%); other melanoma, 1/4 (25%); adenoid cystic carcinoma, 2/9 (22%); and ovarian cancer, 1/6 (17%) (Tables 4 and 5).

Tumor restaging (RECIST) data were available in 33/38 patients who completed at least one cycle of treatment (Figure 1). RECIST measurements were not available for 5 patients owing to the following reasons: rapid clinical progression before radiologic evaluation in 3 patients, disease unmeasurable by RECIST criteria in 2 patients (neural infiltration in 1 and predominant bone disease in 1).

Survival duration

Of the 41 patients enrolled in the protocol, 30 had documented progression of their disease and two patients died. Three patients remain on study, and 6 patients withdrew consent (3 within the first month of treatment without response assessment and with no specific reason; 1 to pursue ipilimumab treatment, which was approved at that time; 1 to pursue anti-interleukin-2 therapy; and 1 because of logistical issues (unable to travel after completing 17 cycles of treatment; the patient had disease and did not experience toxicity).

Progression (30 with documented progression and 2 with death while on therapy) occurred in 32/41 patients yielding a median progression-free survival of 3.5 months (95% CI, 1.9–5.0) (Figure 2a). The failure-free survival duration was estimated to be 3.7 months (95% CI, 2.0–5.3) (Figure 2b).

Fifteen of the 41 patients enrolled had died at last follow-up. The median follow-up duration of surviving patients was 7.6 months. The median overall survival duration was 12.3 months (95% CI, 10.1–14.5; range, 0.1 to 24.9 months) (Figure 2c).

Discussion

This is the first clinical trial to investigate the combination of lenalidomide and sorafenib in patients with advanced cancer. Although the number of patients studied was small, our results appear to support previously published *in vitro* data demonstrating additive to synergistic activity of lenalidomide when combined with sorafenib.[8]

Overall, the combination of lenalidomide and sorafenib was well tolerated. No DLT was noted in the escalation phase (19 patients). One of 22 patients treated in the expansion phase had a DLT (grade 3 skin rash). Two-thirds of patients did not experience adverse effects greater than grade 1. The most common adverse event was skin rash (11 of 38 patients, 29%). Nine patients had grade 1–2 and two patients had grade 3 skin rash. In both patients with grade 3 skin rashes, treatment with sorafenib and lenalidomide was withheld for a week, topical and/or oral corticosteroids were administered, and subsequently, patients continued treatment at a lower dose of lenalidomide as per the protocol. Skin rash is a common adverse event of both sorafenib and lenalidomide. Previously published data demonstrated that the use of lenalidomide is associated with skin rash in 6–11% of patients with solid tumors.[4,12] Single-agent sorafenib is associated with skin rash in 16–40% of patients, although it is more frequent at doses of at least 800 mg/day.[13–15] Although the occurrence of sorafenib-associated skin rash is uncommon at doses of 400 mg/day or less, as used in our study[16], the addition of lenalidomide likely contributed to the skin rash complications that were noted in our study.

Grade 3 neutropenia occurred in seven (18%) of 38 patients. All of these patients were able to continue treatment with granulocyte colony-stimulating factor support. Neutropenia is a well-described adverse effect of single-agent lenalidomide. The reported incidence of grade 3/4 neutropenia in patients with solid tumors varies from as low as 2.7% to as high as 50%. [17–20] Grade 3–4 neutropenia has not been reported in large trials with single-agent sorafenib.[15,14,21] Therefore, neutropenia in our patient population was attributed to lenalidomide.

Thromboembolism is a serious adverse effect of lenalidomide, although it is less common in patients with solid tumors. In two large trials of single-agent lenalidomide in patients with metastatic melanoma, the incidence of thromboembolic complications ranged from 0% to 2.6% (no prophylactic anticoagulation was reported).[18,17] In addition, there were no reports of thromboembolism in some phase 2 and phase 3 studies of single-agent sorafenib in renal and hepatic carcinomas.[14,15] However, a more recent phase 2 study of single-

agent sorafenib in patients with hepatobiliary cancer reported thromboembolism in five of 46 patients.[21] Both lenalidomide and sorafenib are anti-angiogenic agents, and they may be associated with vascular toxicity; therefore, the development of vascular thrombi cannot be ruled out. In our study, prophylactic anticoagulation therapy was left to the discretion of the treating physician until two patients developed thromboembolism during the study (one who did not receive anticoagulation therapy and one who was receiving prophylactic warfarin). After these events, subsequent patients received prophylactic anticoagulation therapy, and there were no additional cases of thromboembolism. These data suggest that patients treated with this combination therapy should receive mandatory prophylactic anticoagulation therapy.

Antitumor activity with this combination was noted in melanoma (including ocular melanoma), ovarian cancer, and adenoid cystic carcinoma. The clinical benefit noted in ocular melanoma correlates in part with preclinical data showing additive to synergistic activity of this combination in ocular melanoma cells.[8] Single-agent lenalidomide has activity in melanoma, but the results of two phase 2/3 trials were disappointing (only 11% of patients with melanoma continued treatment with single-agent lenalidomide 6 months in a double-blind phase 2/3 trial).[18,17] Similarly, sorafenib as a single agent was associated with disease control (SD or greater response) in 11% of patients in a phase 2 study of patients with melanoma.[22] In our study, SD was noted in five (83%) of six patients with melanoma, including two patients with ocular melanoma. We also observed SD 6 months in 25% (1 of 4) of non-ocular melanomas. These results indicate that this combination has a synergistic effect. Disease stabilization was noted in 2 of 9 patients with adenoid cystic carcinoma, which is a rare tumor type with few treatment options. One of these patients had stable disease for 19 months until he finally discontinued participation in the study because he had limited resources to travel to MD Anderson. Although adenoid cystic carcinoma may be associated with an indolent disease course, the patients enrolled in our study had progressive disease at the time of initiation of treatment on protocol and both of them had tumor shrinkage (Table 5).

Although the number of patients was small and no objective responses were noted, 53% of patients had SD, including 16% who had SD 6 months. Keeping in mind that sorafenib, as an anti-vascular endothelial growth factor agent, can lead to disease stabilization without actual tumor shrinkage and that lenalidomide is an immunomodulatory agent, these results are encouraging.[23] Other investigators have reported that a meaningful survival benefit can result even in the absence of measurable “responses,” as indicated by the phase 3 data for sorafenib in hepatocellular carcinoma.[15] Most of the patients who benefited from this protocol received treatment in dose levels 3 or 4, which were the highest dose levels studied. It is possible that the anti-tumor activity is dose related, but the numbers are too small. Another limitation of our study is that molecular profiling was not performed for most of the patients.

In conclusion, our study demonstrated that the combination of lenalidomide and sorafenib was safe and it was associated with antitumor activity in selected patients with melanoma (including ocular melanoma), adenoid cystic carcinoma, and ovarian carcinoma. These

results suggest that further investigation of lenalidomide and sorafenib in these selected tumor types is warranted.

Acknowledgments

Funding Source

This research is supported in part by Celgene (provided free lenalidomide and a research grant to Dr. Tsimberidou).

References

1. Dredge K, Horsfall R, Robinson SP, Zhang LH, Lu L, Tang Y, Shirley MA, Muller G, Schafer P, Stirling D, Dalglish AG, Bartlett JB. Orally administered lenalidomide (CC-5013) is anti-angiogenic in vivo and inhibits endothelial cell migration and Akt phosphorylation in vitro. *Microvasc Res.* 2005; 69(1–2):56–63. [PubMed: 15797261]
2. Corral LG, Haslett PA, Muller GW, Chen R, Wong LM, Ocampo CJ, Patterson RT, Stirling DI, Kaplan G. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. *J Immunol.* 1999; 163(1):380–386. [PubMed: 10384139]
3. Schafer PH, Gandhi AK, Loveland MA, Chen RS, Man HW, Schnetkamp PP, Wolbring G, Govinda S, Corral LG, Payvandi F, Muller GW, Stirling DI. Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs. *J Pharmacol Exp Ther.* 2003; 305(3):1222–1232. [PubMed: 12649301]
4. Segler A, Tsimberidou AM. Lenalidomide in solid tumors. *Cancer Chemother Pharmacol.* 2012; 69(6):1393–1406. [PubMed: 22584909]
5. Petrylak D, Resto-Garces K, Tibyan M, Mohile S. A phase I open-label study using lenalidomide and docetaxel in castration-resistant prostate cancer. *J Clin Oncol.* 2009; 7s(suppl) abstr 5156.
6. Papadopoulos K, Mendelson D, Preston G. A phase I study of lenalidomide and weekly docetaxel in patients with advanced solid tumors. *Clin Cancer Res: Abstracts of the International Conference on Molecular Targets and Cancer Therapeutics.* 2005; 11(24 Pt 2):215.
7. Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, Schwartz B, Simantov R, Kelley S. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nat Rev Drug Discov.* 2006; 5(10):835–844. [PubMed: 17016424]
8. Mangiameli DP, Blansfield JA, Kachala S, Lorang D, Schafer PH, Muller GW, Stirling DI, Libutti SK. Combination therapy targeting the tumor microenvironment is effective in a model of human ocular melanoma. *J Transl Med.* 2007; 5:38. [PubMed: 17640369]
9. Institute NC. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). National Cancer Institute; 2006. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae_v3.pdf [Accessed December 18 2012]
10. Therasse P, Arbus SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000; 92(3):205–216. [PubMed: 10655437]
11. Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner GL, Gore M, Desai AA, Patnaik A, Xiong HQ, Rowinsky E, Abbruzzese JL, Xia C, Simantov R, Schwartz B, O'Dwyer PJ. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2006; 24(16):2505–2512. [PubMed: 16636341]
12. Sharma RA, Steward WP, Daines CA, Knight RD, O'Byrne KJ, Dalglish AG. Toxicity profile of the immunomodulatory thalidomide analogue, lenalidomide: phase I clinical trial of three dosing schedules in patients with solid malignancies. *Eur J Cancer.* 2006; 42(14):2318–2325. [PubMed: 16899362]
13. Strumberg D, Richly H, Hilger RA, Schleucher N, Korfee S, Tewes M, Faghih M, Brendel E, Voliotis D, Haase CG, Schwartz B, Awada A, Voigtman R, Scheulen ME, Seeber S. Phase I

- clinical and pharmacokinetic study of the Novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43–9006 in patients with advanced refractory solid tumors. *J Clin Oncol*. 2005; 23(5):965–972. [PubMed: 15613696]
14. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med*. 2007; 356(2):125–134. [PubMed: 17215530]
15. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Haussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008; 359(4):378–390. [PubMed: 18650514]
16. Strumberg D, Clark JW, Awada A, Moore MJ, Richly H, Hendlitz A, Hirte HW, Eder JP, Lenz HJ, Schwartz B. Safety, pharmacokinetics, and preliminary antitumor activity of sorafenib: a review of four phase I trials in patients with advanced refractory solid tumors. *Oncologist*. 2007; 12(4):426–437. [PubMed: 17470685]
17. Eisen T, Trefzer U, Hamilton A, Hersey P, Millward M, Knight RD, Jungnelius JU, Glaspy J. Results of a multicenter, randomized, double-blind phase 2/3 study of lenalidomide in the treatment of pretreated relapsed or refractory metastatic malignant melanoma. *Cancer*. 2010; 116(1):146–154. [PubMed: 19862820]
18. Glaspy J, Atkins MB, Richards JM, Agarwala SS, O'Day S, Knight RD, Jungnelius JU, Bedikian AY. Results of a multicenter, randomized, double-blind, dose-evaluating phase 2/3 study of lenalidomide in the treatment of metastatic malignant melanoma. *Cancer*. 2009; 115(22):5228–5236. [PubMed: 19728370]
19. Amato RJ, Hernandez-McClain J, Saxena S, Khan M. Lenalidomide therapy for metastatic renal cell carcinoma. *Am J Clin Oncol*. 2008; 31(3):244–249. [PubMed: 18525302]
20. Choueiri TK, Dreicer R, Rini BI, Elson P, Garcia JA, Thakkar SG, Baz RC, Mekhail TM, Jinks HA, Bukowski RM. Phase II study of lenalidomide in patients with metastatic renal cell carcinoma. *Cancer*. 2006; 107(11):2609–2616. [PubMed: 17075879]
21. Bengala C, Bertolini F, Malavasi N, Boni C, Aitini E, Dealis C, Zironi S, Depenni R, Fontana A, Del Giovane C, Luppi G, Conte P. Sorafenib in patients with advanced biliary tract carcinoma: a phase II trial. *Br J Cancer*. 2010; 102(1):68–72. [PubMed: 19935794]
22. Ott PA, Hamilton A, Min C, Safarzadeh-Amiri S, Goldberg L, Yoon J, Yee H, Buckley M, Christos PJ, Wright JJ, Polsky D, Osman I, Liebes L, Pavlick AC. A phase II trial of sorafenib in metastatic melanoma with tissue correlates. *PLoS One*. 2010; 5(12):e15588. [PubMed: 21206909]
23. Figueiras RG, Padhani AR, Goh VJ, Vilanova JC, Gonzalez SB, Martin CV, Caamano AG, Naveira AB, Choyke PL. Novel oncologic drugs: what they do and how they affect images. *Radiographics*. 2011; 31(7):2059–2091. [PubMed: 22084189]
24. Garrido-Laguna I, Janku F, Vaklavas C, Falchook GS, Fu S, Hong DS, Naing A, Tsimberidou AM, Wen S, Kurzrock R. Validation of the Royal Marsden Hospital prognostic score in patients treated in the Phase I Clinical Trials Program at the MD Anderson Cancer Center. *Cancer*. 2012; 118(5):1422–1428. [PubMed: 21823111]

Figure 1.
Waterfall plot depicting the best tumor responses (%) in the treated patients (N=33) by
RECIST

Figure 2.

- a.** Progression-free survival of all patients enrolled in the study (N=41)
- b.** Failure-free survival of all patients enrolled in the study (N=41)
- c.** Overall survival of all patients enrolled in the study (N=41)

Dose escalation scheme of the protocol

Table 1

Dose Level	Lenalidomide PO (mg) daily X 21 days	Sorafenib PO (mg) daily X 28 days	Enrollment (N)	Completed cycle 1 (N)	DLT (N)
1	10	200	3	3	0
2	10	400	6	4	0
3	20	400	3	3	0
4*	25	400	7	6	0
Expansion	25	400	22	21	1
Total			41	37	1

*The defined maximum tolerated dose

Abbreviations: DLT: dose-limiting toxicity PO: orally

Table 2

Patient characteristics

Characteristics	No. of patients (N=41)
Men (%)	18 (44)
Age in years, median (range)	55 (21–78)
Performance status >1	4 (10)
2 metastatic sites	33 (80)
RMH score 2 (poor risk)	7 (17)
Tumor type	
Adenoid cystic carcinoma	9 (22)
Ovarian carcinoma	7 (17)
Melanoma	6 (15)
Non-small cell lung carcinoma	3 (7)
Colorectal carcinoma	2 (5)
Hepatocellular carcinoma	2 (5)
Other *	12(29)

* One patient each had adrenocortical carcinoma, breast adenocarcinoma, cervical squamous cell carcinoma, chondrosarcoma, desmoplastic small round cell tumor, ear canal squamous cell carcinoma, fallopian tube adenocarcinoma, renal cell carcinoma, soft tissue sarcoma, unknown primary adenocarcinoma, urethral squamous cell carcinoma, and uterine leiomyosarcoma.

Abbreviations: RMH: Royal Marsden Hospital score [24]

Table 3

Adverse events

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Total
Nausea/Vomiting		2			2
Fatigue		1			1
Anorexia		1			2
Myalgia/bone pain	2	1			3
Neuropathy	1				1
Neutropenia		1	7		8
Thrombocytopenia		1	2		3
Tremors	1				1
Hypertension		1			1
Headache	1				1
Mucositis	3				3
Rash/Hand-foot syndrome	5	4	2		11
Deep vein thrombus			1		1
Pulmonary embolism				1	1

Table 4

Clinical outcomes by tumor type

Tumor type	N	Evaluable for response, (N) ^a	SD ^b , N (%)	SD 6 months, N (%)
Adenoid cystic carcinoma	9	9	6 (67)	2(22)
Melanoma ^c	6	6	5 (83)	3(50)
Ovarian carcinoma	7	6	5 (83)	1(17)
Colorectal carcinoma	2	2	0 (0)	0
Non-small cell lung carcinoma	3	3	2 (67)	0
Hepatocellular carcinoma	2	2	0	0
Other ^d	12	10	2 (20)	0
Total	41	38	20 (53)	6 (16)

^aThree patients withdrew consent soon after starting 1st cycle of treatment and were not evaluable for response assessment

^bBest response;

^cIncludes 2 patients with ocular melanoma and 1 patient with mucosal melanoma (c-kit wild type);

^dSee Table 2 for other tumor types.

Table 5

Characteristics of patients with stable disease 9 months

Pt. no.	Dose level	Age	Sex	Diagnosis	PS	Disease sites (N)	Prior Rx	Best RECIST response (%)	Cycles (N)	Reason for treatment discontinuation	Life status	PFS (mos)	OS (mos)
33	3	74	M	ACC	2	2	1	-17	17	Logistics-travel issues	Alive	19	19.5
36	4	55	F	Ovary	2	2	10	-5	7	PD	Alive	8	12.1
37	4	67	F	Ocular Melanoma	1	1	1	-6	7	For alternative treatment-Ipilimumab	Alive	8	9.2
49	4	35	F	Ocular melanoma	1	4	5	-4%	14+	Still on study	Alive	13+	13+
54	4	35	F	ACC	0	4	1	-1%	6	PD	Alive	8	10.5
59	4	65	M	Melanoma	1	2	1	-8%	7	PD	Alive	6	7.4

Abbreviations: ACC: Adenoid cystic carcinoma; OS: Overall survival in months; PD: Progressive disease; PFS: Progression free survival in months; Prior Rx: Number of prior lines of therapy; PS: ECOG performance status; RECIST: Response Evaluation Criteria in Solid Tumors