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Highlights in Renal Cell Carcinoma From the 2012 American Society of Clinical Oncology Annual Meeting

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PLUS Meeting Abstract Summaries

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Cardiac Safety Analysis for a Phase III Trial of Sunitinib (SU) or Sorafenib (SO) or Placebo (PLC) in Patients (pts) With Resected Renal Cell Carcinoma (RCC)

Cardiac dysfunction is a well-known risk of tyrosine kinase inhibitor therapy. The mechanism of action is thought to be myocyte metabolic dysfunction. Sunitinib is the best-characterized tyrosine kinase inhibitor, and most analyses of cardiac dysfunction relating to its use are retrospective. Naomi B. Haas, MD, presented cardiac safety data[1] from the phase III Eastern Cooperative Oncology Group (ECOG) 2805/ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma) trial of adjuvant sorafenib versus sunitinib for patients with completely resected renal cell carcinoma (RCC).[2] Eligible patients were required to have a normal left ventricular ejection fraction (LVEF) by multigated acquisition (MUGA) scan, controlled blood pressure or hypertension, and no clinically significant recent cardiac arrhythmias or cardiovascular disease. Patients received either 1 year of sunitinib daily for 4 of every 6 weeks, 1 year of daily sorafenib, or 1 year of daily placebo. Accrual ended in September 2010, and the primary endpoint has not yet been met.

The primary endpoint of the cardiac substudy is to determine whether clinically significant decreases in LVEF—defined as an LVEF below the institutional lower limit of normal, where the drop was at least 16% from baseline—occurred within 6 months of treatment initiation. A planned interim analysis was undertaken when 200 patients had accrued in each arm, although data collection continued for the remainder of the study. Secondary cardiac objectives included determining the frequency of clinically significant congestive heart failure, exploring the association between congestive heart failure and LVEF changes, determining optimal timing of scans for assessing clinically significant changes of LVEF, describing relationships between blood pressure changes and changes in LVEF, and assessing reversibility of any changes in LVEF. Results of MUGA scans were obtained from institutional reporting; there was no central review. Due to a nationwide shortage of technetium 99 that occurred during the study, a small number of patients underwent monitoring by echocardiogram.

Asymptomatic left ventricular decline was managed by evaluating the absolute decline in LVEF and compar-

ABSTRACT SUMMARY Phase III Randomized Sequential Open-Label Study to Evaluate Efficacy and Safety of Sorafenib (SO) Followed by Sunitinib (SU) Versus Sunitinib Followed by Sorafenib in Patients With Advanced/Metastatic Renal Cell Carcinoma Without Prior Systemic Therapy (SWITCH Study): Safety Interim Analysis Results

Sequencing of sorafenib and sunitinib in RCC patients has been examined retrospectively, but the preferred sequence has not been established. A phase III clinical trial is in progress comparing sorafenib followed by sunitinib versus sunitinib followed by sorafenib in patients with metastatic RCC unsuitable for cytokine treatment and no prior systemic therapy (Abstract 4539). Patients have ECOG performance status of 0 or 1, MSKCC score of low or intermediate, and at least 1 measurable lesion. The primary endpoint is PFS. Monitoring includes echocardiography and measurement of N-terminal pro-B-type natriuretic peptide. At the time of the presentation, 361 patients had been randomized to treatment, 116 patients had completed treatment, and safety data were available for 333 patients. In patients receiving sorafenib first versus sunitinib first, adverse events occurred in 93.4% and 92.8% of patients, grade 3/4 adverse events occurred in 59.9% and 50.0% of patients, and serious adverse events occurred in 46.7% and 42.2% of patients, respectively. For both arms, patients experienced a greater frequency of adverse events during the first treatment compared with the second treatment. Available data suggested that the frequency of LVEF was similar between the 2 treatment arms at screening and on the day of stopping first-line treatment, with an approximate range of 62–64%.

Table 1. Cardiac Safety Analysis of the ASSURE Trial

	Sunitinib	Sorafenib	Placebo
Patients Assessed	397	394	502
Events	9	7	5
Rate	2.3%	1.8%	1.0%
90% CI	1.2–3.9%	0.8–3.3%	0.4–2.1%

ASSURE=Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; CI=confidence interval. Data from Haas NB et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 4500.

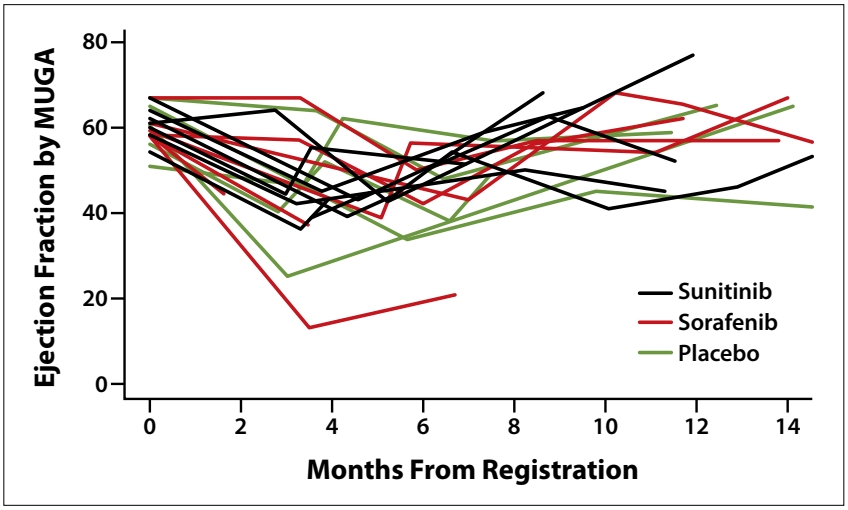

Figure 1. LVEF declines in the ASSURE trial. Declines were reversible regardless of the treatment arm. ASSURE=Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; LVEF=left ventricular ejection fraction; MUGA=multigated acquisition. Data from Haas NB et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 4500.

ing it to the institutional lower limit of normal. For example, if a patient showed an LVEF decline of 16%, and the LVEF was at least 6% below the institutional lower limit of normal, then drugs were held and a repeat MUGA scan was repeated 2–4 weeks later. If the patient's LVEF returned to the institutional lower limit of normal, then treatment with study agents was resumed. If the patient's LVEF was within 1–5% of the institutional lower limit of normal, then study treatment was resumed with a dose reduction.

The trial randomized 1,943 patients, of whom 1,867 were assessed at baseline by MUGA scan and 59 were assessed by echocardiogram. From the patients with a baseline MUGA, 1,589 had at least 1 follow-up MUGA scan, and of these patients, 1,293 had a 6-month follow-up MUGA scan or experienced an event and thus could be assessed for the primary endpoint.

There were 9 (2.3%), 7 (1.8%), and 5 (1.0%) events in the sunitinib (n=397), sorafenib (n=384), and placebo (n=502) arms, respectively (Table 1). A similar proportion of patients in each arm experienced an LVEF decline of at least 16% shown cumulatively over 12 months. The group of patients who met the primary endpoint showed patient characteristics similar to those of the overall population. However, in comparison to the general study population, the 21 patients who had a primary cardiac event were more likely to have a very high risk of RCC recurrence, their performance status was worse, they were more likely to be male, they tended to be older, and they tended to have a history of cardiovascular events. Examination of individual changes in LVEF showed that in most patients, a decline in LVEF appeared to be reversible regardless of the treatment arm (Figure 1), and treatment was held and then resumed in most cases.

Other LVEF events were defined as LVEF declines of at least 16% below the institutional lower limit of normal occurring after 6 months, and grade 2 or 3 left ventricular systolic or diastolic dysfunction. Other events were reported by means of the Adverse Event Expedited Reporting System or case reports. These events occurred at a low rate and were evenly distributed among the 3 treatment arms, with 12 events recorded in the sunitinib arm and 11 events in each of the other 2 arms. Similarly, the combined cardiac events in each of the 3 arms show a low rate and even distribution across the arms, with combined rates of 4.3%, 5.3%, and 3.7% combined cardiac events in the sunitinib, sorafenib, and placebo arms, respectively. The analysis of hypertension was incomplete at the time of the presentation. Five events of cardiac ischemia occurred in each of the 3 arms, and these events were reported as possibly related or unrelated to study treatment. One event was reported as definitely related for a patient who was receiving placebo.

ECOG 2805 is the largest prospective study ever conducted to determine the cardiac effects of tyrosine kinase inhibitors. Its findings show that adjuvant sunitinib and sorafenib are not associated with significant cardiac dysfunction in the study population. Further prospective studies are needed to examine the effects of tyrosine kinase inhibitors on patients with pre-existing cardiac dysfunction. There are no significant cardiac contraindications against the use of sunitinib and sorafenib in the adjuvant setting.

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Tivozanib Versus Sorafenib as Initial Targeted Therapy for Patients With Advanced Renal Cell Carcinoma: Results From a Phase III Randomized, Open-Label, Multicenter Trial

Robert J. Motzer, MD, reported initial results from a randomized, multicenter, international, open-label, phase III trial comparing the anti-angiogenic agents tivozanib and sorafenib in patients with advanced RCC.[1] Tivozanib is a potent and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3. The drug's half-life of 3.7–4.7 days is designed to optimize blockade while minimizing off-target toxicity. Its pharmacokinetic profile allows once-daily dosing. A phase II trial conducted in 272 patients with advanced RCC yielded a median progression-free survival (PFS) of 11.7 months; hypertension was the predominant toxicity, and there was a low incidence of "off-target" adverse events.[2] The primary endpoint of the phase III trial was to demonstrate PFS superiority in patients with metastatic RCC receiving tivozanib versus sorafenib as first-line therapy. Objective response rate (ORR) and safety were secondary endpoints.

Key eligibility criteria included advanced RCC, clear cell histology, measurable disease, a prior nephrectomy, no more than 1 prior therapy for metastatic disease, no prior VEGF-directed or mammalian target of rapamycin (mTOR)-directed therapy, and ECOG performance status of 0 or 1. Patients were equally randomized to receive either tivozanib (1.5 mg/day) on a schedule of 3 weeks on and 1 week off or sorafenib (400 mg/day). Patients with progressive disease on the sorafenib arm were offered open-label tivozanib on a separate protocol.

Safety data were collected from the day of patient consent until 30 days after the patient's final dose. Response assessment occurred every 8 weeks. Treatment continued until disease progression or intolerance. Blinded, real-time, third-party review was used to confirm investigator-determined disease progression, and radiographic progression was required for patients to cross over from sorafenib to tivozanib. In addition, independent, blinded review of all study scans was performed by a core imaging laboratory for primary endpoint assessment.

The statistical test for the primary endpoint of independently-assessed PFS was a stratified log-rank test with 2-sided significance and an alpha level of 5%. The planned trial size was 500 and required 310 events. The trial had 90% power to detect a 45% or greater improvement in median PFS from 6.7 months for sorafenib to 9.7 months for tivozanib.

The trial enrolled 517 patients between February and August of 2010 at 76 sites in 15 countries in North America, Europe, South America, and Asia. Approximately 90% of patients were enrolled in Europe. Patients were randomized to receive tivozanib (n=260) or sorafenib (n=257). The 2 arms were generally well balanced with respect to patient characteristics; however, the sorafenib arm had a slightly higher proportion of patients with ECOG performance status of 0 compared to the tivozanib arm (54% vs 45%, respectively). The majority of patients in both arms were of intermediate risk based on the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic criteria; however, 27% of patients in the tivozanib arm and 34% of patients in the sorafenib

ABSTRACT SUMMARY Overall Survival (OS) in Metastatic Renal Cell Carcinoma (mRCC) Sequentially Treated With Different Targeted Therapies (TTs): Results From a Large Cohort of Patients

A retrospective study is examining the characteristics and outcomes of RCC patients who received targeted therapies (Abstract 4629). Data from 336 patients were available from the database of the Istituto Nazionale Tumori of Milan. Patient characteristics included ECOG performance status of 0 or 1 (94%), clear cell histology (87%), and prior nephrectomy (87%). Risk as assessed by MSKCC classification was low (32%), medium (48%), or poor (20%). Fifty percent of patients had received 2 or more targeted therapies. Prior targeted therapies included sorafenib (73% of patients), sunitinib (63%), a bevacizumab-containing regimen (10%), and other targeted therapies (22%), including everolimus, temsirolimus, and axitinib. After a median follow-up of 43 months, 199 patients (57%) had died. Median OS was 24 months (95% CI, 20.0–27.0 months). Five-year OS was 24.6% (95% CI, 18.7–30.8). Univariate analyses uncovered no differences in HR values for sorafenib followed by sunitinib compared with either sunitinib followed by sorafenib or with other therapies. Multivariate analysis failed to show a significant difference between the 2 sunitinib/sorafenib sequences or for bevacizumab-containing regimens compared with either sequence of sunitinib and sorafenib. In univariate and multivariate analyses, independent predictors of outcome included ECOG performance status, prior nephrectomy, Fuhrman grade, and number of disease sites (all $P<.01$). The authors concluded that targeted therapies improve OS in metastatic RCC patients without any statistically significant difference among different sequences.

Table 2. Progression-Free Survival With Tivozanib According to Blood Pressure Levels*

	Diastolic Blood Pressure	Systolic Blood Pressure		
	>90 mmHg	≤90 mmHg	>140 mmHg	≤140 mmHg
Patient Number	101	158	115	144
Median PFS (months)	18.3	9.1	16.7	9.0
Hazard Ratio (95% CI)	0.553 (0.391–0.781)	0.543 (0.390–0.756)		
P Value	.001	<.001		

*Based on independent assessment. PFS=progression-free survival.

Data from Motzer RJ et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 4501.

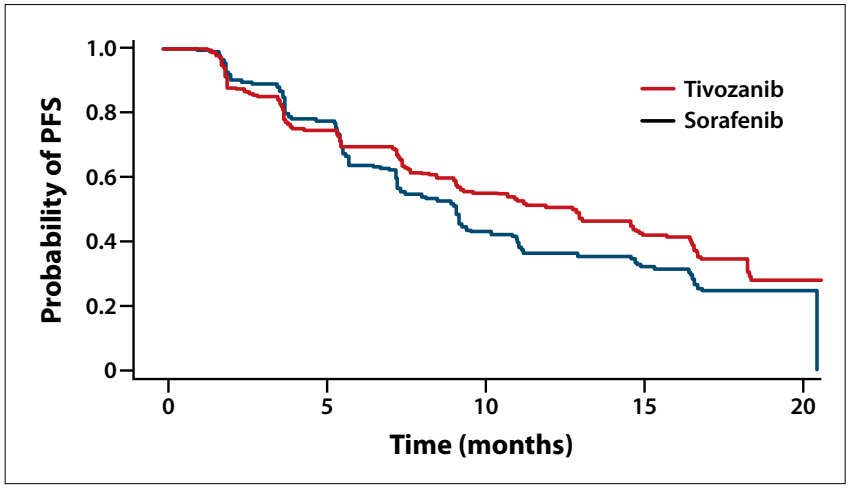

Figure 2. Progression-free survival (PFS) in a randomized, multicenter, international, open-label, phase III trial comparing the anti-angiogenic agents tivozanib and sorafenib in patients with advanced renal cell carcinoma. Data from Motzer RJ et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 4501.

arm had favorable risk classification. In both arms, 70% of patients had received no prior therapy for their metastatic disease and were therefore considered treatment-naïve. Of the remaining 30% of patients, more than 95% had received interferon alpha as their prior therapy.

The median PFS was 11.9 months for patients who received tivozanib versus 9.1 months for those who received sorafenib (hazard ratio [HR], 0.797; *P*=.042; Figure 2), thus demonstrating superior efficacy for tivozanib over sorafenib and reaching the primary endpoint. The median PFS based on investigator assessment was 14.7 months for tivozanib versus 9.6 months for sorafenib (HR, 0.722; *P*=.003).

Prespecified subset analysis of the treatment-naïve patients yielded a PFS of 12.7 months with tivozanib treatment versus 9.1 months with sorafenib (HR, 0.756; *P*=.037). Other prespecified subset analyses, including those based on MSKCC prognostic group, geographic region, and prior systemic therapy, also favored tivozanib.

Based on independent review, complete and partial responses occurred in both arms and yielded an ORR of 33% for tivozanib versus 23% for sorafenib (*P*=.014). Dose adjustments due to adverse events were more frequent overall in the sorafenib arm. Dose interruptions occurred in 18% of patients receiving tivozanib versus 35% of patients receiving sorafenib. Dose reductions occurred in 12% of patients in the tivozanib arm and 43% of patients in the sorafenib arm. Treatment was discontinued in both arms at 4–5%.

Clinical laboratory abnormalities were generally similar between the 2 treatment arms, although liver function test abnormalities and hypophosphatemia occurred with a higher frequency in the sorafenib arm. Neutropenia of any grade was reported in 10% of the tivozanib arm and 9% of the sorafenib arm. Thrombocytopenia of any grade was reported in 17% and 11% of patients, respectively. Grade 3/4 myelosuppression was infrequent in both arms.

Treatment-emergent adverse events occurred in more than 90% of patients in both arms. The most common adverse event of any grade was hypertension, occurring in 44% of patients in the tivozanib arm and 34% of patients in the sorafenib arm. Grade 3/4 events of note included hypertension, occurring in 24% of patients treated with tivozanib and 17% of patients treated with sorafenib, and palmar-plantar erythrodysesthesia, occurring in 2% of patients receiving tivozanib and 17% of patients receiving sorafenib.

Important safety differences were observed for the 2 drugs. Patients on the tivozanib arm experienced higher rates of hypertension, dysphonia, and back pain, while patients on the sorafenib arm experienced higher rates of diarrhea, hand-foot skin reaction, and alopecia. Hypertension, which has been highlighted as an important adverse event associated with tivozanib, was controlled with medication in most patients receiving the drug, resulting in tivozanib dose

reductions in 2% of patients and drug discontinuations in 1% of patients.

Based on this study and others, development of hypertension appears to be associated with tivozanib efficacy. In the current trial, patients with a diastolic blood pressure of greater than 90 mmHg had a median progression-free survival of 18.3 months compared to 9.1 months for patients without hypertension (Table 2). A similar relationship was found for systolic blood pressure and efficacy, and the findings are likely directly related to tivozanib's mechanism of action. Dr. Motzer concluded that tivozanib achieved superior efficacy and decreased off-target toxicity in comparison to sorafenib in patients with metastatic RCC.

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Axitinib for First-Line Metastatic Renal Cell Carcinoma (mRCC): Overall Efficacy and Pharmacokinetic (PK) Analyses From a Randomized Phase II Study

Axitinib is a potent and selective, second-generation tyrosine kinase inhibitor of VEGF receptors 1, 2, and 3.[1] It has shown efficacy as second-line treatment for RCC.[2] Variable levels of drug exposure have been observed in patients receiving the starting dose of 5 mg twice daily.[3] Based on population pharmacokinetic analyses from phase II trials of axitinib in RCC patients, higher drug exposure is associated with better clinical outcome.[4] It was hypothesized that upward dose titration of axitinib in patients who tolerate the 5 mg twice daily regimen could optimize drug exposure and thus improve therapeutic efficiency.

Retrospective analyses of phase II studies of axitinib in metastatic RCC show variable levels of exposure to axitinib based on the area under the curve (AUC). Not only does the level of exposure vary among different patients, many patients' exposure is below the proposed therapeutic threshold of AUC at 12 hours (AUC_{12}) of 150 ng·h/mL. Patients without drug titration are largely above the target threshold, with an average value of AUC_{12} 231 ng·h/mL. For many patients who tolerate the initial dose of axitinib 5 mg twice daily, dose titration to either 7 mg or 10 mg twice daily can increase their drug exposure from below the therapeutic threshold to therapeutic drug levels.

Improved efficacy outcomes appear to correlate positively with therapeutic axitinib exposure defined as AUC 150 ng·h/mL, as evidenced by an approximate doubling of PFS in patients with at least a therapeutic level of axitinib versus patients who cannot achieve the

ABSTRACT SUMMARY Sunitinib Objective Response (OR) in Metastatic Renal Cell Carcinoma (mRCC): Analysis of 1,059 Patients Treated on Clinical Trials

In light of the robust objective responses and improved PFS demonstrated by sunitinib in metastatic RCC patients, a retrospective analysis was performed to assess the ORR and survival rates with sunitinib treatment and to discern patient features associated with a response (Abstract 4542). Data from 6 phase II or III trials were pooled representing 1,059 patients who received sunitinib either on the approved schedule of 50 mg/day for 4 weeks on, 2 weeks off (n=689), or at 37.5 mg/day. The analysis included patients receiving sunitinib as first-line (n=783) or second-line (n=376) treatment. Median PFS and OS were estimated by the Brookmeyer and Crowley method. The log-rank test was used to compare results in responders versus nonresponders and in early responders (patients with a response at 12 weeks of treatment or earlier) versus late responders (those with a response after 12 weeks). Confirmed, investigator-assessed responses by RECIST occurred in 398 (38%) of patients. Median time to tumor response in all patients was 10.6 weeks (range, 2.7–94.4 weeks) and was similar in the first- and second-line settings. Characteristics of responders included better baseline ECOG performance status, more favorable MSKCC risk classification, longer interval since initial diagnosis, increased likelihood of prior nephrectomy, and reduced presence of baseline bone metastases (all $P<.05$). Early responders had more lung metastases than late responders ($P<.01$). Significant improvements were observed for responders versus nonresponders in PFS (16.3 months vs 5.3 months, respectively; $P<.001$) and OS (40.1 months vs 14.5 months, respectively; $P<.001$). Results were similar for first- and second-line treatment, and median OS was similar for early and late responders ($P=.1438$).

Table 3. Clinical Outcome According to Axitinib Exposure

	AUC_{12} on Cycle 1 Day 15	
	≥150 ng·h/mL (n=27*)	<150 ng·h/mL (n=25)
mPFS (months)	13.9	11.0
Best RECIST Response		
Partial Response	59%	40%
Stable Disease	26%	36%
Progressive Disease	11%	24%

*Response for 1 patient was indeterminate.

AUC=area under the curve; mPFS=median progression-free survival; RECIST=Response Evaluation Criteria In Solid Tumors (RECIST). Data from Rini BI et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 4503.

therapeutic level either with or without dose titration (52 weeks vs 32 weeks, respectively; HR, 0.56; 95% confidence interval [CI], 0.359–0.874).

Based on these retrospective findings, a prospective trial was designed to determine whether axitinib drug titration could improve efficacy.[5] Key eligibility requirements included metastatic RCC with clear cell histology, no prior systemic therapy for metastatic disease, measurable disease based on Response Evaluation Criteria In Solid Tumors (RECIST) criteria, ECOG performance status of 0 or 1, adequate organ function, and blood pressure controlled to less than or equal to 140/90 mmHg with the use of up to 2 antihypertensive medications.

All patients received axitinib at a starting dose of 5 mg twice daily during a lead-in period of 4 weeks. During cycle 1, a subset of approximately 60 patients underwent 24-hour ambulatory blood pressure monitoring on days 1 and 15. On day 15 of the same cycle, the same subset of patients underwent 6-hour pharmacokinetic sampling. At the end of the 4-week lead-in period, all patients were assessed for randomization criteria comprising blood pressure below 150/90 mmHg, no more than 2 concurrent antihypertensive medications, no grade 3 or greater axitinib-related toxicities, and no need for a dose reduction during the first cycle. Patients who met all 4 randomization criteria were then randomized 1:1 to receive either axitinib 5 mg twice daily with dose titration up to either 7 or 10 mg twice daily as tolerated (Arm A) or axitinib 5 mg twice daily plus placebo titration (Arm B). Patients who did not meet all 4 randomization criteria received axitinib 5 mg twice daily or a lower dosage as determined by tolerance (Arm C).

Brian I. Rini, MD, reported pooled efficacy data from all 3 trial arms and from arms A and B combined.[5] Unblinding and comparison of arms A and B will occur after the specified number of events has occurred. The study's primary objective was to compare the ORR of patients receiving axitinib plus dose titration versus axitinib plus placebo dose titration. The trial had an 80% power to detect an improvement of at least 25% in ORR. The presented findings pertain to the secondary objectives, including PFS, axitinib plasma pharmacokinetics, blood pressure measurements, and safety.

Tumor assessments were performed at screening and at 8, 16, and 24 weeks of therapy and every 12 weeks thereafter. Safety was assessed and adverse events graded based on the Common Terminology Criteria for Adverse Events version 3.0. In the subset of approximately 60 patients, serial 6-hour pharmacokinetic sampling was performed on day 15 of cycle 1, prior to making the decision for dose titration. In the same subset of patients, ambulatory blood pressure monitoring was performed at baseline and on days 4 and 15 of cycle 1, also prior to the decision for dose titration.

The trial enrolled 213 metastatic RCC patients with a median age of 61 years, of whom 82% had undergone prior nephrectomy and approximately 60% were diagnosed within 1 year of study registration. At the time of reporting, slightly more than half of the patients had progressed or died while on the study, and median follow-up was 644 days.

Analysis of the entire study population yielded a median PFS of 14.5 months and ORR of 48%. Arm C enrolled 91 patients and yielded a median PFS of 16.4 months and an ORR of 59%. Pooled data from the 112 patients in Arms A and B combined showed a PFS of 14.5 months and an ORR of 43%.

Comparison of pharmacokinetic parameters assessed on day 15 of cycle 1 showed that the patients in Arm C—many of whom were ineligible for dose titration due to blood pressure elevation—had a median AUC_{12} of 234 ng·h/mL versus 99 ng·h/mL for patients in Arms A and B (P<.0001). Analysis of clinical outcome based on axitinib exposure on day 15 of cycle 1 showed a median PFS of 13.9 months in patients with AUC_{12} of at least 150 ng·h/mL (n=27) versus 11.0 months for patients with AUC_{12} less than AUC_{12} 150 ng·h/mL (n=25; Table 3). Partial response rates were 59% versus 40%, respectively.

In the subset of patients who underwent ambulatory blood pressure monitoring, PFS and ORR were improved in patients who exhibited greater increases in diastolic blood pressure as measured on day 15 of cycle 1. For example, PFS was 16.7 months versus 8.3 months for patients with a change in diastolic blood pressure of at least 10 mmHg (n=39) versus less than 10 mmHg (n=22), respectively, with ORRs of 59% versus 45%, respectively, and median AUC_{12} of 176 ng·h/mL versus 63 ng·h/mL, respectively. Improved outcomes were also observed

for patients with changes in diastolic blood pressure of at least 15 mmHg versus those with a change of less than 15 mmHg. Finally, analysis of patients based on blood pressure of at least 90 mmHg versus less than 90 mmHg also showed improved outcomes and a higher plasma concentration of axitinib for the former group. Unblinding of Arms A and B and hence comparison of patients who received dose titration of axitinib versus those who remained at the starting dose will be forthcoming.

Consistent with previous reports, hypertension was the most common adverse event of any grade, reported in 63% of patients, and grade 3 hypertension was reported in 29% of patients. Other common adverse events of any grade occurring in at least 40% of the population included diarrhea (58%), fatigue (48%), and dysphonia (40%). Laboratory adverse events of any grade occurring in at least 5% of the study population included thrombocytopenia (9%) and anemia (7%). There were very few grade 3/4 laboratory adverse events.

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Patient Preference Between Pazopanib (Paz) and Sunitinib (Sun): Results of a Randomized Double-Blind, Placebo-Controlled, Cross-Over Study in Patients With Metastatic Renal Cell Carcinoma (mRCC)—PISCES Study, NCT 01064310

Bernard J. Escudier, MD, presented results from the PISCES (Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer) trial.[1] This randomized, double-blind, placebo-controlled, crossover study was designed to evaluate whether sunitinib and pazopanib result in clinically meaningful differences in tolerability for patients. Both pazopanib and sunitinib are approved for first-line treatment of metastatic RCC. Indirect comparison suggests that the 2 drugs have comparable efficacy and different safety profiles. Given the relationship between adverse events and quality of life, plus the increasing emphasis on health-related quality of life, patient preference was explored as an endpoint.

In the PISCES study, 169 patients were stratified based on ECOG performance status (0 vs 1) and number of metastatic sites (1 vs >1). They were then randomized 1:1 to receive 10 weeks of treatment with either pazopanib (800 mg daily) or sunitinib (50 mg daily). After a 2-week washout period, patients were crossed over to the other drug for another treatment period of 10 weeks. At the end of these 22 weeks, patient preference was assessed by means of a questionnaire.

Computed tomography (CT) scans were performed at baseline, after the 10-week treatment with the first drug, and at the study's end. Questionnaires included EQ-5D, Functional Assessment of Chronic Illness Therapy-Fatigue, and Seville Quality of Life Questionnaire. The primary endpoint of the study was patient preference for sunitinib or pazopanib. The patients received the questionnaire at the end of the second 10-week treatment period, while they were still blinded regarding treatment and before the results of the final study imaging scan were available. The questionnaire was completed by patients who had received at least 1 dose in both treatment periods.

The primary question asked for the patient's drug preference, and possible answers included the first treatment, the second treatment, or no preference. Patients were also asked to describe the reasons that influenced their drug choice and to select the most important reason. Endpoints in addition to drug preference included quality of life, safety, and dose modification. Further analyses assessed physician preference, pharmacokinetics, and biomarkers.

The trial design was based on the hypothesis that a difference of greater than 20% in patient preference would be clinically relevant. The design also assumed that 20% of patients would state no drug preference, resulting in a study requirement of 160 patients.

Eligible patients had previously untreated metastatic RCC, any renal cancer cell histology, measurable or non-measurable disease, ECOG performance status of 0 or 1, good

ABSTRACT SUMMARY Safety and Efficacy of MET Inhibitor Tivantinib (ARQ 197) Combined With Sorafenib in Patients (pts) With Renal Cell Carcinoma (RCC) From a Phase I Study

This phase I study examined tivantinib plus sorafenib in patients with advanced solid tumors (Abstract 4545). Endpoints were safety, the recommended phase II dose of the combination, and antitumor activity. Dose escalation had previously established the recommended phase II dose as tivantinib 360 mg twice daily plus sorafenib 400 mg twice daily. Extension cohorts enrolled at least 20 patients each with RCC or other tumors. Twenty RCC patients received treatment at the recommended phase II dose (n=19) or a dose of tivantinib 360 mg twice daily plus sorafenib 200 mg twice daily (n=1). Four patients remain on study. Sixteen patients, including 13 with clear cell RCC, received 1 or more prior systemic therapies. The most common adverse events were rash (65%), diarrhea (45%), alopecia (40%), and hypophosphatemia (35%). Fatigue, stomatitis, palmar-plantar erythrodysesthesia syndrome, and pruritus each occurred in 25% of patients. Three patients with clear cell RCC exhibited a partial response, and 15 patients experienced stable disease, including 11 clear cell, 3 papillary, and 1 clear cell/chromophobe RCC patient. Seven patients with stable disease had a tumor size reduction of at least 10%. The ORR and disease control rate (PR plus stable disease) were 15% and 90%, respectively. Median PFS was 1.27 months (95% CI, 7.1–14.5 months). In the 14 patients treated previously with a VEGF inhibitor, the ORR and disease control rate were 14% and 86%, respectively, and median PFS was 12.7 months (95% CI, 5.3 months–not yet reached).

Table 4. Reasons for Patient Withdrawal Prior to the Second Treatment Period in the PISCES Trial

Reason for Withdrawal After Treatment Period 1	Period 1: Pazopanib	Period 1: Sunitinib
Adverse event	9	7
Disease progression	6	3
Consent withdrawn	2	2
Investigator discretion	1	2
Total withdrawn	18	14
Reason for Withdrawal After Treatment Period 2	**Period 1: Pazopanib**	**Period 1: Sunitinib**
Adverse event	1	1
Disease progression	5	2
Other	0	1

PISCES=Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer.

Data from Escudier BJ et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract CRA4502.

or intermediate prognosis based on the MSKCC prognostic criteria, no brain metastases, and adequate cardiac and renal function. Baseline characteristics were well balanced between the 2 arms. Patients had a median age of 63 years, and 67% were male. Nephrectomy had been performed in 89% of patients. Twenty-six percent of patients had only 1 metastatic site; 92% had measurable disease; and 90% had clear cell carcinoma. The median time since diagnosis was 7.7 months.

The trial initially randomized 86 patients to receive pazopanib and 82 patients to receive sunitinib during the first treatment period. Because patients withdrew for various reasons (Table 4), 68 patients entered into the second treatment period in both arms.

At the end of treatment period 1, best responses included 1% complete response (CR), 20% partial response (PR), 53% stable disease, and 11% progressive disease for the 80 patients who had received sunitinib. Fifteen percent of patients were not evaluable. In the group of 85 patients who had received pazopanib, best responses included 1% CR, 18% PR, 42% stable disease, and 20% progressive disease. Twenty percent of patients were not evaluable.

Several patients withdrew from the study during treatment period 2. In addition, patients who experienced disease progression during the first treatment period were excluded from the primary analysis of health-related quality of life, resulting in completed questionnaires from 54 patients who received pazopanib followed by sunitinib and 60 patients who received sunitinib followed by pazopanib. These remaining 114 patients who had at least 1 drug dose from each treatment period, did not have progressive disease, and completed the questionnaire, thus constituted the primary analysis population.

The primary endpoint showed that 70% of patients preferred pazopanib, 22% preferred sunitinib, and 8% expressed no preference (Figure 3). The difference of pazopanib versus sunitinib preference was 49.3% (90% CI, 37.0–69.5; $P<.001$). Several preplanned analyses were undertaken to further explore the data. For the subset of 80 patients who completed full study treatment, preference for pazopanib over sunitinib was significant ($P<.001$). For all patients in the study, including patients with progressive

ABSTRACT SUMMARY An In-Depth Multicentered Population-Based Analysis of Outcomes of Patients With Metastatic Renal Cell Carcinoma (mRCC) That Do Not Meet Eligibility Criteria for Clinical Trials

Many patients with metastatic RCC are ineligible for enrollment in clinical trials due to factors such as Karnofsky Performance Status (KPS) less than 70%, brain metastases, non–clear cell histology, hemoglobin at or less than 9 g/dL, creatinine exceeding 2 times the upper limit of normal, platelet count less than 100 10^3/uL, neutrophil count less than 1,500/mm^3, and corrected calcium at or greater than 12 mg/dL. Although such patients are excluded from clinical trials, the data generated from these trials often play a role in their management. This study compared outcome in patients included (n=894) and excluded (n=2,076) from clinical trials (Abstract 4536). Response rate, median PFS, and median OS were all significantly lower in patients excluded from trials. Ineligible patients had a response rate of 21%, a median PFS of 5.2 months, and an OS of 14.5 months, whereas eligible patients had a response rate of 29%, a median PFS of 8.8 months, and an OS of 28.8 months (*P*<.001 for all differences). Second-line PFS was 3.2 months in excluded patients and 4.4 months in included patients (*P*=.0074). Among ineligible patients, the HR of death varied according to the exclusionary criteria, with an HR of 2.8 (95% CI, 2.4–3.4) for patients with KPS less than 70, HR of 1.8 (95% CI, 1.4–2.2) for patients with hemoglobin at or less than 9 g/dL, HR of 1.8 (95% CI, 1.2–2.7) for patients with calcium at or greater than 12 mg/dL, HR of 1.4 (95% CI, 1.1–1.8) for brain metastases, and HR of 1.4 (95% CI, 1.1–1.7) for non–clear cell histology (*P*<.01 for all differences). When adjusted by the Heng prognostic criteria, the HR for death between ineligible patients and eligible patients was 1.511 (95% CI, 1.335–1.710; *P*<.0001).

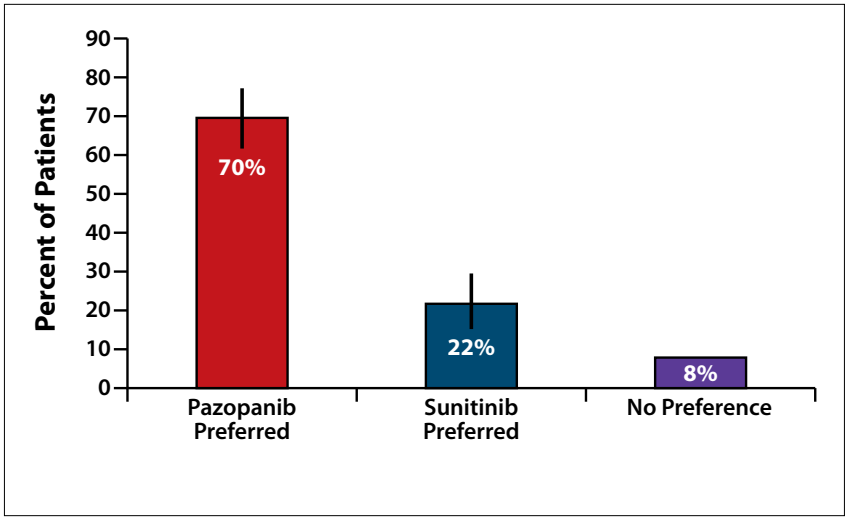

Figure 3. Patient preference in the PISCES trial. PISCES=Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer. Data from Escudier BJ et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract CRA4502.

disease in the first treatment period, the preference for pazopanib was again significant (*P*<.001). Physician drug preference was remarkably similar to that of the patients, with 61% of physicians preferring pazopanib, 22% preferring sunitinib, and 17% expressing no preference. After the investigators postulated a preference for sunitinib for all patients who withdrew from the study, the trend toward pazopanib persisted but was not significant (*P*<.065).

The reasons for drug preference included better quality of life, less fatigue, fewer changes in food tastes, less soreness in the mouth and throat, reduced nausea and vomiting, reduced soreness in hands and feet, and reduced loss of appetite. Most patients reported that their drug preference was not determined by a single reason, although many patients who preferred pazopanib cited less fatigue as the single reason.

A preliminary examination of health-related quality of life data based on 13 questions from the Functional Assessment of Chronic Illness Therapy-Fatigue questionnaire showed a strong preference for pazopanib (*P*=.002). In a supplementary questionnaire, patients also showed a preference for pazopanib based on soreness of the mouth, throat, hand, or foot, as well as limitations based on these conditions.

Dose reductions occurred in 20% of patients in the sunitinib arm and 13% of patients in the pazopanib arm. Treatment was prematurely discontinued in treatment period 1 due to adverse events in 18% versus 14% of patients, respectively. In period 2, treatment was prematurely discontinued due to an adverse event in 31% versus 15% of patients, respectively.

Adverse events reported for both pazopanib and sunitinib were consistent with reports from phase III trials, although diarrhea of any grade was slightly more common with pazopanib (42% vs 32%). Dysgeusia, mucositis, stomatitis, and hand and foot syndrome showed numerically greater frequency with sunitinib. Liver toxicity appeared more common with pazopanib treatment, as reflected in a slightly higher incidence of increased liver enzymes and total bilirubin. By contrast, sunitinib was associated with a higher incidence of myelosuppression, including thrombocytopenia

(47% vs 15%) and neutropenia (45% vs 13%) of any grade.

The authors concluded that, despite the modest differences in reported adverse events, patients showed a clear preference for pazopanib over sunitinib. Efficacy of the 2 drugs is being examined in the COMPARZ (Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma) trial.[2]

References

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Updated Results on Long Term Overall Survival (OS) of the French Randomized Phase II Trial TORAVA in Metastatic Renal Cell Carcinoma (mRCC) Patients

The randomized, phase II TORAVA (Combination of Temsirolimus and Bevacizumab in Patient With Metastatic Renal Cell Carcinoma) trial investigated the safety and efficacy of combining temsirolimus and bevacizumab in previously untreated patients with metastatic RCC.[1] The study showed that the combination of temsirolimus plus bevacizumab failed to increase PFS over standard treatment. Moreover, adding temsirolimus to bevacizumab caused unexpectedly high toxicity. Extending these initial results, Jacques-Olivier Bay, MD, PhD, presented long-term results on OS and information on second-line therapy after failure from the TORAVA trial.[2]

Patients were randomly assigned in a 2:1:1 ratio to treatment with bevacizumab (10 mg/kg every 2 weeks) plus temsirolimus (25 mg weekly; Arm A [n=88]), or sunitinib (50 mg/day for 4 weeks followed by 2 weeks off; Arm B [n=42]), or interferon alfa (9 MIU 3 times per week) plus bevacizumab (10 mg/kg every 2 weeks; Arm C [n=41]). Patients were treated until disease progression or unacceptable toxicity. The primary endpoint was PFS at 48 weeks. Secondary endpoints included toxicity, ORR, and survival. Key eligibility requirements included metastatic RCC, ECOG performance status of 0 or 1, measurable disease by RECIST criteria, and no brain metastases.

Table 5. Patient Characteristics in the TORAVA Study

Characteristic	Arm A (n=88) (%)	Arm B (n=42) (%)	Arm C (n=41) (%)
Male	74	76	66
>1 Metastatic site	55	52	49
Nephrectomy	83	98	85
Fuhrman grade 1–2	26	32	38
Metastasis-free interval >12 months	38	29	39
Liver metastases	6	19	15
High LDH	15	17	8
MSKCC prognosis			
Good risk	33	31	39
Intermediate risk	53	59	44
Poor risk	14	10	17

LDH=lactate dehydrogenase; MSKCC=Memorial Sloan-Kettering Cancer Center; TORAVA=Combination of Temsirolimus and Bevacizumab in Patient With Metastatic Renal Cell Carcinoma.

Data from Bay J-O et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 4625.

PFS at 48 weeks was 29.5% in Arm A, 35.7% in Arm B, and 61.0% in Arm C. Median PFS was 8.2 months in Arm A, 8.2 months in Arm B, and 16.8 months in Arm C.[1] Fifty-one percent of patients in Arm A stopped treatment for reasons other than progression compared with 12% in Arm B and 38% in Arm C. Thus, the combination of temsirolimus plus bevacizumab showed low activity and unexpectedly high toxicity.

In the analysis presented by Dr. Bay, median follow-up was 35.1 months (range, 24.2–44.7 months).[2] Data were available in 65 patients from Arm A, 32 patients from Arm B, and 27 patients from Arm C. Patient characteristics were somewhat unevenly distributed across the 3 treatment groups (Table 5).

In the intent-to-treat population, 35-month OS rates were 37% (95% CI, 27–48%), 55% (95% CI, 40–69%), and 62% (95% CI, 47–76%) in Arms A, B, and C, respectively. OS was not significantly lower for Arm A relative to Arm B, but was significantly lower for Arm A relative to Arm C (HR, 0.48 [95% CI, 0.27–0.86]). In Arms A, B, and C, tyrosine kinase inhibitors were administered in 79.7%, 79.2%, and 63.9% of patients, respectively (*P*=.20). The authors concluded that the OS rates confirmed the absence of synergistic or additive effects of combined temsirolimus plus bevacizumab and that patients treated with bevacizumab plus interferon alfa showed a prolonged survival.

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Efficacy of Cabozantinib (XL184) in Patients (pts) With Metastatic, Refractory Renal Cell Carcinoma (RCC)

Toni K. Choueiri, MD, presented data from a multi-institutional trial of patients with metastatic RCC who failed prior therapy.[1] Cabozantinib (XL184) is a potent dual inhibitor of the MET and VEGF receptor 2 pathways. Loss of the von Hippel–Lindau (VHL) tumor suppressor gene, a frequent occurrence in clear cell RCC, leads to upregulation of both VEGF and MET, which ultimately fuels metastasis.[2] Inhibition of MET can overcome acquired resistance to agents that target pathways regulated by VEGF.[3] MET knockdown has been shown to reduce the viability of RCC VHL-negative cells, while cabozantinib has resulted in the resolution of metastatic bone lesions and the regression of soft tissue lesions in multiple tumor types.

Despite major advances with VEGF-targeted therapy in RCC, several unmet medical needs remain. Primary disease that is refractory to anti-VEGF therapy is evidenced by progressive disease as the best response to anti-VEGF therapy in 26% out of 1,056 consecutive patients with clear cell metastatic RCC in the International Metastatic RCC Database Consortium. In the same study, the median OS of patients with best response of progressive disease was 6.8 months versus 29 months for patients without progressive disease.[4] Bone metastases, a negative prognostic factor, occur in up to 30% of RCC patients and are generally resistant to existing therapies.[5,6]

The current study, designed to investigate drug-drug interaction,

ABSTRACT SUMMARY The Use of Tumor Growth Rate (TGR) in Evaluating Sorafenib and Everolimus Treatment in mRCC patients: An Integrated Analysis of the TARGET and RECORD Phase III Trials Data

RECIST criteria have been used in clinical trials to evaluate targeted therapies in patients with metastatic RCC. Measurement of tumor growth rate (TGR) may provide additional important data. This study (Abstract 4540) prospectively examined patients at the Institut Gustave Roussy (IGR) treated with sorafenib, everolimus, or placebo in 2 phase III trials: TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial) and RECORD (Renal Cell Cancer Treatment With Oral RAD 001 Given Daily). TGR was assessed at several points: before treatment (wash-out), during treatment (in the first cycle), at progression (in patients still receiving the drug), and after treatment interruption (wash-out). Results were subsequently validated in the entire TARGET cohort (n=902). Compared with placebo, TGR was significantly decreased during the first cycles of sorafenib and everolimus. In most patients who received sorafenib or everolimus, TGR was decreased during treatment versus before treatment, regardless of the RECIST evaluation. TGR after sorafenib or everolimus interruption was significantly higher than TGR at progression. There was no significant difference in TGR after treatment interruption as compared with before treatment in both sorafenib and everolimus patients. High TGR during first-cycle treatment was associated with poor PFS and overall survival in sorafenib-treated patients and with poor OS in everolimus-treated patients. The authors concluded that the addition of TGR assessment may provide better evaluation of the tumor response, regardless of RECIST criteria. TGR may have independent prognosis value. This study also suggests that continuation of treatment with sorafenib or everolimus after disease progression might be beneficial.

the incidence of Grade 3 or 4 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients receiving IFL alone (14%). In Study 4, the incidence of Grade 4 neutropenia was increased in NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26.2%) compared with patients receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs. 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious infections including pneumonia, febrile neutropenia, catheter infections and wound infections was increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm [29 patients (6.6%)].

In Study 5, one fatal event of neutropenic infection occurred in a patient with previously treated glioblastoma receiving Avastin alone. The incidence of any grade of infection in patients receiving Avastin alone was 55% and the incidence of Grade 3-5 infection was 10%.

Proteinuria

Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4 and 7. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 7, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 7). [See *Warnings and Precautions (5.8).*]

Congestive Heart Failure (CHF)

The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in patients receiving Avastin compared to 0.6% in the control arm across indications. In patients with metastatic breast cancer (MBC), an indication for which Avastin is not approved, the incidence of Grade 3–4 CHF was increased in patients in the Avastin plus paclitaxel arm (2.2%) as compared to the control arm (0.3%). Among patients receiving prior anthracyclines for MBC, the rate of CHF was 3.8% for patients receiving Avastin as compared to 0.6% for patients receiving paclitaxel alone. The safety of continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

In previously untreated patients with diffuse large B-cell lymphoma (DLBCL), an indication for which Avastin is not approved, the incidence of CHF and decline in left-ventricular ejection fraction (LVEF) were signficantly increased in the Avastin plus R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) arm (n=403) compared to the placebo plus R-CHOP arm (n=379); both regimens were given for 6 to 8 cycles. At the completion of R-CHOP therapy, the incidence of CHF was 10.9% in the Avastin plus R-CHOP arm compared to 5.0% in the R-CHOP alone arm [relative risk (95% CI) of 2.2 (1.3, 3.7)]. The incidence of a LVEF event, defined as a decline from baseline of 20% or more in LVEF or a decline from baseline of 10% or more to a LVEF value of less than 50%, was also increased in the Avastin plus R-CHOP arm (10.4%) compared to the R-CHOP alone arm (5.0%). Time to onset of left-ventricular dysfunction or CHF was 1-6 months after initiation of therapy in at least 85% of the patients and was resolved in 62% of the patients experiencing CHF in the Avastin arm compared to 82% in the control arm.

Ovarian Failure

The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months, FSH level ≥ 30 mIU/mL and a negative serum β-HCG pregnancy test) was prospectively evaluated in a subset of 179 women receiving mFOLFOX chemotherapy alone (n = 84) or with Avastin (n = 95). New cases of ovarian failure were identified in 34% (32/95) of women receiving Avastin in combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone [relative risk of 14 (95% CI 4, 53)]. After discontinuation of Avastin treatment, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the Avastin-treated women. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Long term effects of Avastin exposure on fertility are unknown. [See *Warnings and Precautions (5.10), Use in Specific Populations (8.6).*]

Metastatic Colorectal Cancer (mCRC)

The data in Table 1 and Table 2 were obtained in Study 1, a randomized, double-blind, controlled trial comparing chemotherapy plus Avastin with chemotherapy plus placebo. Avastin was administered at 5 mg/kg every 2 weeks.

All Grade 3–4 adverse events and selected Grade 1–2 adverse events (hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Severe and life-threatening (Grade 3–4) adverse events, which occurred at a higher incidence (≥ 2%) in patients receiving bolus-IFL plus Avastin as compared to bolus-IFL plus placebo, are presented in Table 1.

Table 1
NCI-CTC Grade 3–4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥ 2 %] Avastin vs. Control))

	Arm 1 IFL+ + Placebo (n = 396)	Arm 2 IFL+ + Avastin (n = 392)
NCI-CTC Grade 3-4 Events	74%	87%
Body as a Whole		
Asthenia	7%	10%
Abdominal Pain	5%	8%
Pain	5%	8%
Cardiovascular		
Hypertension	2%	12%
Deep Vein Thrombosis	5%	9%
Intra-Abdominal Thrombosis	1%	3%
Syncope	1%	3%
Digestive		
Diarrhea	25%	34%
Constipation	2%	4%
Hemic/Lymphatic		
Leukopenia	31%	37%
Neutropenia[a]	14%	21%

[a]Central laboratories were collected on Days 1 and 21 of each cycle. Neutrophil counts are available in 303 patients in Arm 1 and 276 in Arm 2.

AVASTIN® (bevacizumab)

Grade 1–4 adverse events which occurred at a higher incidence (≥ 5%) in patients receiving bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm are presented in Table 2. Grade 1–4 adverse events were collected for the first approximately 100 patients in each of the three treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + Avastin) was discontinued.

Table 2
NCI-CTC Grade 1-4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥ 5%] in IFL + Avastin vs. IFL)

	Arm 1 IFL + Placebo (n = 98)	Arm 2 IFL + Avastin (n = 102)	Arm 3 5-FU/LV + Avastin (n = 109)
Body as a Whole			
Pain	55%	61%	62%
Abdominal Pain	55%	61%	50%
Headache	19%	26%	26%
Cardiovascular			
Hypertension	14%	23%	34%
Hypotension	7%	15%	7%
Deep Vein Thrombosis	3%	9%	6%
Digestive			
Vomiting	47%	52%	47%
Anorexia	30%	43%	35%
Constipation	29%	40%	29%
Stomatitis	18%	32%	30%
Dyspepsia	15%	24%	17%
GI Hemorrhage	6%	24%	19%
Weight Loss	10%	15%	16%
Dry Mouth	2%	7%	4%
Colitis	1%	6%	1%
Hemic/Lymphatic			
Thrombocytopenia	0%	5%	5%
Nervous			
Dizziness	20%	26%	19%
Respiratory			
Upper Respiratory Infection	39%	47%	40%
Epistaxis	10%	35%	32%
Dyspnea	15%	26%	25%
Voice Alteration	2%	9%	6%
Skin/Appendages			
Alopecia	26%	32%	6%
Skin Ulcer	1%	6%	6%
Special Senses			
Taste Disorder	9%	14%	21%
Urogenital			
Proteinuria	24%	36%	36%

Avastin in Combination with FOLFOX4 in Second-line mCRC

Only Grade 3-5 non-hematologic and Grade 4–5 hematologic adverse events related to treatment were collected in Study 2. The most frequent adverse events (selected Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events) occurring at a higher incidence (≥2%) in 287 patients receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting mechanisms used in Study 2.

Unresectable Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in Study 4. Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events (occurring at a higher incidence (≥2%) in 427 patients receiving PC plus Avastin compared with 441 patients receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs. 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3% vs. 0%).

Glioblastoma

All adverse events were collected in 163 patients enrolled in Study 5 who either received Avastin alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide. Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan. Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

In patients receiving Avastin alone (N = 84), the most frequently reported adverse events of any grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%) and diarrhea (21%). Of these, the incidence of Grade ≥ 3 adverse events was infection (10%), fatigue (4%), headache (4%), hypertension (8%) and diarrhea (1%). Two deaths on study were possibly related to Avastin: one retroperitoneal hemorrhage and one neutropenic infection.

In patients receiving Avastin alone or Avastin plus irinotecan (N = 163), the incidence of Avastin-related adverse events (Grade 1–4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%), and RPLS (1%). The incidence of Grade 3–5 events in these 163 patients were bleeding/hemorrhage (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and gastrointestinal perforation (2%).

Metastatic Renal Cell Carcinoma (mRCC)

All grade adverse events were collected in Study 7. Grade 3–5 adverse events occurring at a higher incidence (≥ 2%) in 337 patients receiving interferon alfa (IFN-α) plus Avastin compared to 304 patients receiving IFN-α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

Grade 1–5 adverse events occurring at a higher incidence (≥ 5%) in patients receiving IFN-α plus Avastin compared to the IFN-α plus placebo arm are presented in Table 3.

AVASTIN® (bevacizumab)

Table 3
NCI-CTC Grades 1–5 Adverse Events in Study 7
(Occurring at Higher Incidence [≥ 5%] in IFN-α + Avastin vs. IFN-α + Placebo)

System Organ Class/ Preferred term[a]	IFN-α + Placebo (n = 304)	IFN-α + Avastin (n = 337)
Gastrointestinal disorders		
Diarrhea	16%	21%
General disorders and administration site conditions		
Fatigue	27%	33%
Investigations		
Weight decreased	15%	20%
Metabolism and nutrition disorders		
Anorexia	31%	36%
Musculoskeletal and connective tissue disorders		
Myalgia	14%	19%
Back pain	6%	12%
Nervous system disorders		
Headache	16%	24%
Renal and urinary disorders		
Proteinuria	3%	20%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	4%	27%
Dysphonia	0%	5%
Vascular disorders		
Hypertension	9%	28%

[a]Adverse events were encoded using MedDRA, Version 10.1.

The following adverse events were reported at a 5-fold greater incidence in the IFN-α plus Avastin arm compared to IFN-α alone and not represented in Table 3: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs.0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs.1); tinnitus (7 vs. 1); tooth abscess (7 vs.0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Avastin has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with Avastin, primarily in combination with chemotherapy. High titer human anti-Avastin antibodies were not detected.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Avastin with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Avastin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Polyserositis

Cardiovascular: Pulmonary hypertension, RPLS, Mesenteric venous occlusion

Eye disorders (from unapproved intravitreal use for treatment of various ocular disorders): Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort

Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration

Hemic and lymphatic: Pancytopenia

Hepatobiliary disorders: Gallbladder perforation

Musculoskeletal: Osteonecrosis of the jaw

Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)

Respiratory: Nasal septum perforation, dysphonia

Systemic Events (from unapproved intravitreal use for treatment of various ocular disorders): Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

7 DRUG INTERACTIONS

A drug interaction study was performed in which irinotecan was administered as part of the FOLFIRI regimen with or without Avastin. The results demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan or its active metabolite SN38.

In a randomized study in 99 patients with NSCLC, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with Avastin. However, 3 of the 8 patients receiving Avastin plus paclitaxel/carboplatin had substantially lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel/carboplatin without Avastin had a greater paclitaxel exposure at Day 63 than at Day 0.

In Study 7, there was no difference in the mean exposure of interferon alfa administered in combination with Avastin when compared to interferon alfa alone.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate or well controlled studies of bevacizumab in pregnant women. While it is not known if bevacizumab crosses the placenta, human IgG is known to cross the placenta Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab demonstrated teratogenicity, including an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Other observed effects included decreases in maternal and fetal body weights and an increased number of fetal resorptions. [See *Nonclinical Toxicology (13.3).*

Because of the observed teratogenic effects of bevacizumab in animals and of other inhibitors of angiogenesis in humans, bevacizumab should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether Avastin is secreted in human milk. Human IgG is excreted in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from bevacizumab, a decision should be made whether to discontinue nursing or discontinue drug, taking into account the half-life of the bevacizumab (approximately 20 days [range 11–50 days]) and the importance of the drug to the mother. [See *Clinical Pharmacology (12.3).*]

8.4 Pediatric Use

The safety, effectiveness and pharmacokinetic profile of Avastin in pediatric patients have not been established.

Antitumor activity was not observed among eight children with relapsed glioblastoma treated with bevacizumab and irinotecan. There is insufficient information to determine the safety and efficacy of Avastin in children with glioblastoma.

Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

8.5 Geriatric Use

In Study 1, severe adverse events that occurred at a higher incidence (≥ 2%) in patients aged ≥65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of Avastin on overall survival was similar in elderly patients as compared to younger patients.

In Study 2, patients aged ≥65 years receiving Avastin plus FOLFOX4 had a greater relative risk as compared to younger patients for the following adverse events: nausea, emesis, ileus, and fatigue.

In Study 4, patients aged ≥65 years receiving carboplatin, paclitaxel, and Avastin had a greater relative risk for proteinuria as compared to younger patients. [See *Warnings and Precautions (5.8).*]

Of the 742 patients enrolled in Genentech-sponsored clinical studies in which all adverse events were captured, 212 (29%) were age 65 or older and 43 (6%) were age 75 or older. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients, in addition to those described above, were dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients aged ≥65 years and 1127 patients <65 years of age. The overall incidence of arterial thromboembolic events was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the increase in arterial thromboembolic events incidence was greater in patients aged ≥65 years (8.5% vs. 2.9%) as compared to those <65 years (2.1% vs. 1.4%). [See *Warnings and Precautions (5.5).*]

8.6 Females of Reproductive Potential

Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. Long term effects of Avastin exposure on fertility are unknown.

In a prospectively designed substudy of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin arm (34%) compared to the control arm (2%). After discontinuation of Avastin and chemotherapy, recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients. [See *Warnings and Precautions (5.10), Adverse Reactions (6.1).*]

10 OVERDOSAGE

The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of 16 patients and with severe headache in three of 16 patients.

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ABSTRACT SUMMARY Incidence and Severity of Cardiotoxicity in Metastatic Renal Cell Carcinoma (RCC) Patients Treated With Targeted Therapies

Data were gathered regarding all RCC patients treated with therapies targeting the VEGF or mTOR axes at Stanford Medical Center (Abstract 4610). The incidence of hypertension, left ventricular dysfunction, changes in serum markers of cardiovascular toxicity, and heart failure were assessed and graded according to Common Terminology Criteria for Adverse Events 4.0. Out of 159 patients identified, cardiovascular toxicity developed in 116 (73%). Excluding hypertension, 52 (33%) patients developed cardiovascular toxicity, including asymptomatic reductions in LVEF, increased NT-proBNP, and heart failure. Asymptomatic cardiotoxicity, defined as a decrease in LVEF or increase in NT-proBNP, occurred in 43 (27%) patients. Symptomatic, grade 2/3 heart failure and grade 3/4 decrease in LVEF each occurred in 4% of patients. Of the 101 patients who had received sunitinib treatment, 66 (65%) developed some form of cardiovascular toxicity, including 32 (32%) with cardiotoxicity other than hypertension. In patients treated with bevacizumab, sorafenib, or pazopanib, cardiovascular toxicity was observed in 68%, 66%, and 51% of patients, respectively. The mTOR inhibitors showed significantly less cardiovascular toxicity, but sample sizes were small. The authors recommend close monitoring of cardiovascular toxicity in RCC patients receiving targeted therapies.

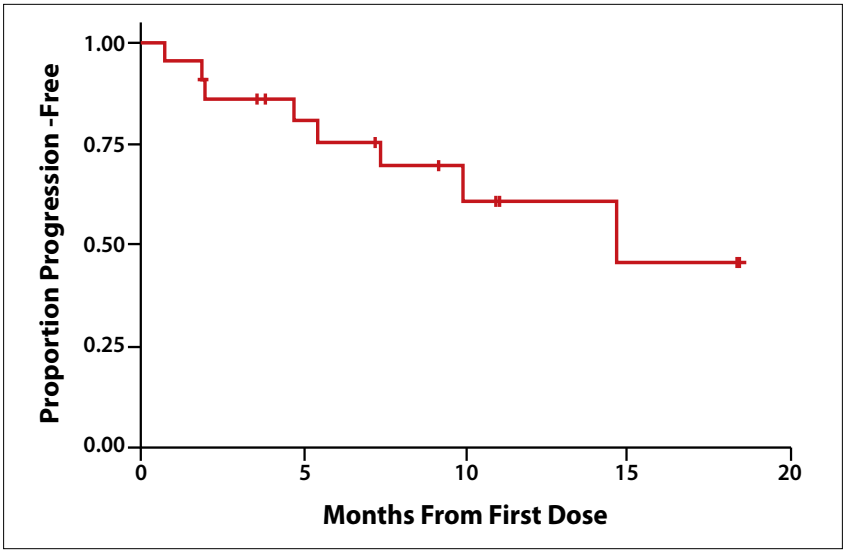

Figure 4. Progression-free survival with cabozantinib. Data from Choueiri TK et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 4504.

enrolled 25 patients with metastatic RCC who had failed prior therapy. Patients received cabozantinib at a dose of 140 mg/day, based on the maximum tolerated dose from a phase I trial, plus a single dose of rosiglitazone. Dose reductions were allowed to optimize tolerability. The study endpoints included safety and tolerability of cabozantinib and the drug's antitumor activity.

Key eligibility criteria included Karnofsky performance status of at least 70 or ECOG performance status of 0 or 1; metastatic RCC with clear cell components; refractory disease or progression following standard therapies, with no limit on prior therapies; and measurable disease per RECIST 1.0. Patients were assessed for safety and activity per RECIST 1.0. Pharmacokinetic and pharmacogenetic sampling were performed but were not discussed in the current presentation.

The patients had a median age of 61 years, and 21 patients were male. Based on Heng prognostic criteria, 8% of patients were poor risk and 80% were intermediate risk. Patients had a median 2 prior systemic agents, and 32% of patients had received at least 4 prior systemic agents. Prior anticancer therapies included anti-VEGF therapy in 88% of patients, anti-mTOR therapy in 60% of patients, and both of these therapies in 52% of patients. Bone metastases were present in 16% of patients at baseline. At the time of the presentation, 7 patients remained on-study and 18 patients had discontinued, mainly as a result of progressive disease.

Median PFS was 14.7 months (Figure 4). After a median follow-up of 14.7 months, overall survival (OS) was not yet reached. Confirmed partial responses were observed in 28% of patients, stable disease in 52% of patients, and progressive disease in 4% of patients. The disease control rate at 16 weeks was 72%. The median duration of response could not yet be determined but ranged from approximately 1.9 months to 10.6 months.

Significant tumor reduction was observed in the majority of the 21 patients who underwent a post-baseline scan. In addition, some patients experienced a reduction in pain, as evidenced by reduced narcotic use in 1 patient and complete resolution of pain in another patient that occurred after 4 weeks and continued beyond 90 weeks.

The most common adverse events of any grade occurring in at least 50% of patients included fatigue (80%),

Table 6. Most Frequent Adverse Events Associated With Cabozantinib

Adverse Events	All Grades, n (%)	Grade 3/4, n (%)
Fatigue	20 (80)	4 (16)
Diarrhea	16 (64)	3 (12)
Hypophosphatemia	14 (56)	9 (36)
Hypothyroidism	11 (44)	–
Nausea	11 (44)	–
Hypomagnesemia	10 (40)	–
Proteinuria	9 (36)	2 (8)
Decreased appetite	9 (36)	1 (4)
Vomiting	9 (36)	1 (4)
Hyponatremia	8 (32)	5 (20)
Hand-foot syndrome	8 (32)	1 (4)
Dyspnea	8 (32)	–

Data from Choueiri TK et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 4504.

diarrhea (64%), and hypophosphatemia (56%; Table 6). The most common grade 3/4 events occurring in at least 15% of patients were hypophosphatemia (36%), hyponatremia (20%), and fatigue (16%). Hypertension of any grade was reported in 16% of patients and grade 3/4 hypertension occurred in 8% of patients. No grade 5 events were reported.

The authors concluded that cabozantinib demonstrated encouraging activity in the heavily pretreated population of patients with metastatic RCC. The safety profile was similar to that of other tyrosine kinase inhibitors, and adverse events were manageable with an extended treatment period of more than 600 days.

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Clinical Activity and Safety of Anti-PD-1 (BMS-936558, MDX-1106) in Patients With Previously Treated Metastatic Renal Cell Carcinoma (mRCC)

An initial report on the clinical activity and safety of an antibody against the programmed death (PD) 1 receptor in patients with previously treated metastatic RCC was presented by David F. McDermott, MD.[1] The last 6 years have seen impressive advances in medical therapy for advanced kidney cancer. Many new therapies have proven superior to cytokine therapy, raising the question of whether immunotherapy may still have a role in the treatment of advanced kidney cancer. In the 20 years since interleukin-2 was introduced, groundbreaking research has provided a wealth of knowledge regarding how the immune response to cancer is regulated, thus leading to new opportunities to leverage the immune system.

T cells are regulated by both positive and negative signaling pathways, and one of the most important negative pathways involves the interaction between the PD1 receptor on T cells and its ligand, PD-L1, on antigen-presenting cells. PD-L1 is expressed on many tumors, either endogenously or induced by association with T cells, a process known as adaptive immune resistance. The interaction between T cells and tumor-expressed PD-L1 can act as an immune checkpoint that suppresses activated T cells. In RCC, investigators at the Mayo Clinic have shown that PD-L1 expression can be associated with more aggressive disease and shorter survival.[2] In preclinical models, monoclonal antibodies that bind the PD1 receptor have been shown to improve T-cell priming and prevent tumor-induced T-cell suppression.[3]

The clinical impact of an anti-PD1 antibody was therefore explored in a phase I clinical trial. BMS-936558 is a fully human IgG4 antibody that binds with high affinity to human PD1. It has no known Fc function, but it blocks binding of PD-L1 and PD-L2, the 2 known ligands for PD1. In a first-in-human, single-dose, dose escalation study, the antibody exhib-

ABSTRACT SUMMARY PFS to Predict Long-Term OS After First-Line Treatment for Advanced Renal Cell Carcinoma (aRCC): Correlation and Power Analysis of Randomized Trials (RCT)

The correlation between PFS and OS is unknown. This study aimed to determine the relationship between PFS and OS in studies of patients receiving first-line therapy for advanced renal cell carcinoma (Abstract 4541). Six randomized controlled trials, which included a total of 4,096 patients, were analyzed to identify correlations between 6-, 9-, and 12-month PFS and OS rates according to parametric (Pearson's r) and nonparametric (Spearman's Rho and Kendall's Tau) coefficients (with 95% CI). PFS at 3 and 6 months was significantly correlated with overall survival at 9 months. Pearson's coefficients for the correlation between PFS at 3 months and overall survival at 6 and 12 months were 0.70 (*P*=.01) and 0.67 (*P*=.01). The correlation between PFS at 6 months and overall survival at 12 months was significant (Pearson 0.74, *P*=.005; Spearman 0.83, *P*=.005; Tau 0.71, *P*=.001). A significant correlation was also found between disease-control rates and OS.

Table 7. Adverse Events Associated With BMS-936558*

Drug-Related Adverse Event	All Grades		Grades 3/4	
	Total Population	RCC	Total Population	RCC†
	Number of Patients (%), All Doses			
Any Adverse Event	207 (70)	28 (82)	41 (14)	6 (18)
Fatigue	72 (24)	13 (38)	5 (2)	–
Rash	36 (12)	8 (24)	–	
Diarrhea	33 (11)	5 (15)	3 (1)	–
Pruritus	28 (9)	6 (18)	1 (0.3)	1 (3)
Nausea	24 (8)	2 (6)	1 (0.3)	–
Decreased Appetite	24 (8)	3 (9)	–	–
Decreased Hemoglobin	19 (6)	2 (6)	1 (0.3)	–
Pyrexia	16 (5)	3 (9)	–	–

*This list includes adverse events that occurred in ≥5% of the total population.

†The most common grade 3/4 adverse events in RCC patients were respiratory disorders, which occurred in 2 patients, and hypophosphatemia, which occurred in 2 patients.

Data from Topalian SF et al. *N Engl J Med*. 2012;366:2443-2454.

ited a manageable safety profile and yielded preliminary evidence of clinical activity in patients with solid tumors that were refractory to treatment.[4]

The phase I study presented by McDermott and colleagues enrolled patients with advanced melanoma, RCC, non–small cell lung cancer, colorectal cancer, or castration-resistant prostate cancer who had progressive disease after 1–5 systemic therapies.[1] Patients were given escalating doses of BMS-936558 every 2 weeks for up to 96 weeks or until they developed a confirmed CR, their progressive disease worsened, or toxicity was unacceptable.

The study's primary objective was to assess the safety and tolerability of the antibody. Secondary objectives included assessment of antitumor activity and pharmacodynamic evaluation. Accrual was completed in December 2011, with 296 patients enrolled in the study; patient assessments are ongoing.

Analysis of the entire patient population revealed that, with doses of up to 10 mg/kg, the maximum tolerated dose had not been reached. No relationship between drug dose and adverse events emerged. Tumor activity was observed only in patients with non–small cell lung cancer, melanoma, and RCC. Upon completion of the dose escalation phase of the trial, more patients with specific tumor types were enrolled for dose expansion, including 17 RCC patients at 1 mg/kg and 16 RCC patients at 10 mg/kg. In the analysis presented by McDermott and colleagues of patients treated through February 2012, 34 patients were evaluable for safety and 33 were evaluable for clinical activity.[1]

Median age for the RCC cohort was 58 years, and all had an ECOG performance status of 0 or 1. Forty-four percent of patients had received 3 or more prior therapies. For the entire cohort, prior therapies included immunotherapy (59%) and anti-angiogenic therapy (74%).

Toxicity findings from the current study have been reported (Table 7).[5] Adverse events of any grade occurring with a frequency of at least 15% in the RCC cohort included fatigue (38%), rash (24%), pruritus (18%), and diarrhea (15%), all of which were consistent with the proposed mechanism of action of the anti-PD1 antibody. The most common grade 3/4 toxicities in the RCC patients included pulmonary disorders and hypophosphatemia, each of which occurred in 2 patients. In total, 18% of the RCC patients experienced a grade 3/4 toxicity.

In the total study population of 296 patients, grade 3/4 drug-related adverse events occurred in 14% of patients. Treatment was discontinued in 5 patients due to toxicity. Three drug-related deaths occurred in patients with pneumonitis, including 2 patients

Table 8. Clinical Activity of BMS-936558

Population	Dose (mg/kg)	Patients (n)	Overall Response Rate (n [%])	Duration of Response (Months)	Stable Disease ≥24 Weeks (n [%])	Progression-Free Survival Rate at 24 Weeks (%)
All RCC Patients	1, 10	33	9 (27)	5.6+ to 22.3+	9 (27)	56
RCC Patients Divided by Dose	1	17	4 (24)	5.6+ to 17.5+	4 (24)	47
	10	16	5 (31)*	8.4 to 22.3+	5 (31)	67

*There was 1 complete response.

Data from McDermott DF et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 4505.

ABSTRACT SUMMARY Association of Inherited Genetic Variation With Clinical Outcome in Patients With Advanced Renal Cell Carcinoma Treated With mTOR Inhibition

Predictive biomarkers for response are lacking in RCC. This study examined whether the presence of 2 critical genes in the mammalian target of rapamycin (mTOR) pathway—phosphoinositide-3-kinase catalytic alpha (PIK3CA) and mTOR—affect outcome in patients with advanced RCC treated with mTOR inhibition (Abstract 4543). Among the 76 patients in this study, 66% were at poor or intermediate risk and 89% had received prior systemic therapies. After a median follow-up of 23.7 months, median PFS was 4.3 months and median OS was 12.7 months. Two intronic PI3KCA single-nucleotide polymorphisms (SNPs) were significantly associated with PFS and OS. A SNP in the 5′ UTR of mTOR was associated with OS. These associations were maintained after adjustment for age, sex, and MSKCC RCC risk categories according to a Cox proportional hazard model.

with non–small cell lung cancer and 1 patient with colorectal cancer.

Responses in the population of 33 patients evaluable for clinical efficacy included 1 CR and 8 PRs. Nine patients had stable disease lasting for at least 6 months (Table 8). Response duration has not yet reached a maximum and ranges from 5 months to longer than 22 months. The PFS rate at 24 weeks was 56%. Two patients showed a persistent reduction in baseline target lesions in the presence of new lesions. These patients were classified as having progressive disease based on RECIST criteria, and the ORR was 27%. No obvious difference in activity was apparent between the dose levels of 1 mg/kg versus 10 mg/kg.

Approximately 50% of the patients receiving the antibody at the 1 mg/kg dose had not progressed by 24 weeks on therapy. One patient developed numerous new liver lesions early during the treatment; however, because the patient felt better and his liver function tests improved, the patient qualified to continue treatment. Subsequently, this patient developed a PR in his target lesions, and his liver lesions resolved. Two patients in this group are now off study treatment and have yet to progress.

In the group of patients receiving treatment at 10 mg/kg, approximately 70% of patients were progression-free at 24 weeks. Four of these patients have ceased treatment after 96 weeks, according to the trial design, and these patients still show no signs of disease progression.

A 48-year-old patient in the trial had a low volume of disease, but his RCC was very poorly differentiated. He experienced disease progression after sunitinib, sorafenib, and thoracic surgery. He received the anti-PD1 antibody at 1 mg/kg during the study; however, his therapy was halted by the investigators after 3 cycles after a confirmed nearly complete response. His response has continued for 3 years after cessation of therapy.

The potential correlation between PD-L1 expression on tumor biopsies prior to treatment and clinical outcomes is also under investigation. Data from 5 patients with RCC for whom pretreatment biopsies were available suggested that only patients whose tumors expressed PD-L1 on the surface experienced a response to the study treatment, and patients whose tumors did not express PD-L1 did not respond. Despite the small sample size, the data support hypotheses regarding specific mechanisms that may be invoked by the anti-PD1 antibody and the potential for patient selection.

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Commentary

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Several interesting studies in renal cell carcinoma (RCC) were presented at the 2012 American Society of Clinical Oncology (ASCO) meeting. New data were presented regarding agents such as sorafenib, sunitinib, tivozanib, axitinib, and pazopanib.

In 2005, sorafenib became the first targeted therapy approved by the US Food and Drug Administration (FDA) for RCC. A randomized phase II trial compared sorafenib and tivozanib, a potent vascular endothelial growth factor (VEGF) receptor inhibitor.[1] Tivozanib showed an advantage in progression-free survival (PFS), demonstrating that biochemical potency may translate into clinical efficacy in this setting. In addition, this drug appeared very well tolerated, consistent with prior experience in RCC. Tivozanib will likely be approved by the FDA based on these data.

A cardiac safety analysis[2] of the ongoing ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma) trial[3] was presented. The analysis showed a very low incidence of cardiac side effects in this population. There are 2 important caveats to consider when interpreting these data: patients received only a limited amount of treatment throughout 6–8 months, and many of the sunitinib and sorafenib patients dropped out before all cardiac safety analyses were performed. Despite these limitations, this analysis confirms the experience in the metastatic setting, which is that these drugs do have cardiac side effects, although their incidence in clinical practice is relatively low.

I presented preliminary results from a study of axitinib as initial systemic therapy for patients with metastatic RCC.[4] This trial was primarily designed to examine dose escalation of this drug, which is required based on pharmacokinetic parameters. The final unblinded results are not yet available. Data were presented for overall efficacy, which showed a long median PFS of 14.5 months. This analysis has also confirmed that higher drug levels and axitinib-induced blood pressure elevations are associated with superior clinical outcomes. We await the full data from this trial as well as a separate randomized trial examining axitinib in the frontline setting[5] for further understanding of the utility of this agent in previously untreated RCC.

In a retrospective analysis of renal cell carcinoma patients treated with sunitinib, patients who achieved an objective response had a long median survival of more than 40 months.[6] Patients who did not achieve an objective response to sunitinib had a much shorter overall survival of approximately 1 year. This observation is useful in clinical practice, because patients who show a response at their first scan can be told with confidence that their

ABSTRACT SUMMARY Phase II Trial of RAD001 in Renal Cell Carcinoma Patients With Non-Clear Cell Histology

A phase II trial evaluated the use of everolimus in patients with non–clear cell RCC (Abstract 4544). Patients (N=45) from 5 centers were enrolled. Exclusion criteria included previous therapy with a mammalian target of rapamycin (mTOR) inhibitor. Previous therapy with a VEGF tyrosine kinase inhibitor (TKI) was permitted, and 23 patients had received it. The patients ranged in age from 24–75 years (median, 57 years). There were more men than women in the study. RCC histology included papillary (n=29), chromophobe (n=8), collecting duct (n=2), sarcomatoid (n=4), and unclassifiable (n=6). All patients received everolimus at 10 mg/day until disease progression or unacceptable toxicity. The primary endpoint of the study was PFS. Forty-six patients underwent radiologic response assessment after they received everolimus. Five patients (10.2%) achieved a partial response, and 25 patients (51.0%) achieved stable disease. Disease progressed in 16 patients (32.7%). An objective response was observed in 5 patients; their RCC histology was chromophobe carcinoma (n=2), papillary carcinoma (n=2) and unclassifiable carcinoma (n=1). The median PFS was 5.2 months. The longest PFS was observed in patients with chromophobe histology (median PFS 18.8 months vs 3.5 months for other histologies; *P*=.027). There was no significant difference in estimated median PFS between patients who had or had not received previous VEGF-TKI treatment (median PFS of 7.1 months vs 3.7 months; *P*=.110). Toxicity profiles were similar to those reported in previous studies.

prognosis is measured in years. In contrast, patients who do not have a response have a much shorter prognosis and require alternative treatments.

In the PISCES (Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer) trial, untreated RCC patients were randomized to receive either 1 cycle of pazopanib or 1 cycle of sunitinib.[7] After a wash-out period of 2 weeks, the patients received the other agent for 1 cycle. The patients were then asked which agent they preferred. Approximately 70% preferred pazopanib. This finding is not surprising, based on tolerability outcomes in previous trials. One limitation of this study was that patient response—that is, tumor shrinkage in response to the drug—was not incorporated into patient preference. In my experience, patients are more willing to tolerate a drug if they know that they are responding to it. Further results from this trial are needed. In addition, a large, randomized trial comparing the efficacy of these drugs is ongoing.[8]

Data were reported on the clinical activity and safety of the novel agent BMS-936558, an antibody against the programmed death 1 receptor.[9] This exciting, sophisticated immunotherapeutic agent belongs in a class called checkpoint inhibitors, which aim to release the natural break on an immune response. This subset analysis of a much larger phase I study[10] showed that the drug is well tolerated and was associated with impressive tumor shrinkage in kidney cancer patients, many of whom maintained that disease control for long periods. BMS-936558 is being studied further in many different settings in RCC, and we look forward to more data.

ABSTRACT SUMMARY Phase III AXIS Trial of Axitinib Versus Sorafenib in Metastatic Renal Cell Carcinoma: Updated Results Among Cytokine-Treated Patients

The phase III AXIS (Axitinib [AG 013736] as Second Line Therapy for Metastatic Renal Cell Cancer) trial (Rini BI, et al. *Lancet*. 2011;378:1931-1939) compared axitinib (5 mg twice daily [BID] starting dose) and sorafenib (400 mg BID) in patients with metastatic RCC. Axitinib was associated with a significantly increased PFS as compared with sorafenib (6.7 months vs 4.7 months; HR, 0.665; 95% CI, 0.544–0.812; 1-sided *P*<.0001). A study presented at the 2012 ASCO meeting reported updated PFS and OS data for the AXIS trial according to patients' previous treatments (Abstract 4546). Among patients who had received previous treatment with cytokines, median PFS was 12.0 months with axitinib and 6.6 months with sorafenib (HR, 0.519; 95% CI, 0.375–0.720; *P*<.0001). Among patients who had previously received a regimen containing interleukin-2, median PFS was 15.7 months in the axitinib group and 8.3 months in the sorafenib group. Among patients who had received previous treatment with an interferon-alpha, median PFS was 12.0 months with axitinib and 6.5 months with sorafenib. In patients who had received previous cytokine therapy, median OS was 29.4 months with axitinib and 27.8 months with sorafenib (*P*=.144). Adverse events were similar in both arms.

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AVASTIN® (bevacizumab)

Solution for intravenous infusion
Initial U.S. Approval: 2004

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE

Gastrointestinal Perforations

The incidence of gastrointestinal perforation, some fatal, in Avastin-treated patients ranges from 0.3 to 2.4%. Discontinue Avastin in patients with gastrointestinal perforation. [See ***Dosage and Administration (2.4), Warnings and Precautions (5.1).***]

Surgery and Wound Healing Complications

The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Discontinue Avastin in patients with wound dehiscence. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue at least 28 days prior to elective surgery. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. [See ***Dosage and Administration (2.4), Warnings and Precautions (5.2), Adverse Reactions (6.1).***]

Hemorrhage

Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous systems (CNS) hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis. [See ***Dosage and Administration (2.4), Warnings and Precautions (5.3), Adverse Reactions (6.1).***]

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer (mCRC)

Avastin is indicated for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil–based chemotherapy.

1.2 Non-Squamous Non–Small Cell Lung Cancer (NSCLC)

Avastin is indicated for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer in combination with carboplatin and paclitaxel.

1.3 Glioblastoma

Avastin is indicated for the treatment of glioblastoma with progressive disease in adult patients following prior therapy as a single agent.

The effectiveness of Avastin in glioblastoma is based on an improvement in objective response rate. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin. [See *Clinical Studies (14.3).*]

1.4 Metastatic Renal Cell Carcinoma (mRCC)

Avastin is indicated for the treatment of metastatic renal cell carcinoma in combination with interferon alfa.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations

Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in Avastin treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3 to 2.4% across clinical studies. [See *Adverse Reactions (6.1).*]

The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess and fistula formation. The majority of cases occurred within the first 50 days of initiation of Avastin.

Discontinue Avastin in patients with gastrointestinal perforation. [See *Boxed Warning, Dosage and Administration (2.4).*]

5.2 Surgery and Wound Healing Complications

Avastin impairs wound healing in animal models. [See *Nonclinical Toxicology (13.2).*] In clinical trials, administration of Avastin was not allowed until at least 28 days after surgery. In a controlled clinical trial, the incidence of wound healing complications, including serious and fatal complications, in patients with mCRC who underwent surgery during the course of Avastin treatment was 15% and in patients who did not receive Avastin, was 4%. [See *Adverse Reactions (6.1).*]

Avastin should not be initiated for at least 28 days following surgery and until the surgical wound is fully healed. Discontinue Avastin in patients with wound healing complications requiring medical intervention.

The appropriate interval between the last dose of Avastin and elective surgery is unknown; however, the half-life of Avastin is estimated to be 20 days. Suspend Avastin for at least 28 days prior to elective surgery. Do not administer Avastin until the wound is fully healed. [See *Boxed Warning, Dosage and Administration (2.4).*]

5.3 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3 hemorrhagic events among patients receiving Avastin ranged from 1.2 to 4.6%. [See *Adverse Reactions (6.1).*]

Serious or fatal pulmonary hemorrhage occurred in four of 13 (31%) patients with squamous cell histology and two of 53 (4%) patients with non-squamous non-small cell lung cancer receiving Avastin and chemotherapy compared to none of the 32 (0%) patients receiving chemotherapy alone.

In clinical studies in non–small cell lung cancer where patients with CNS metastases who completed radiation and surgery more than 4 weeks prior to the start of Avastin

were evaluated with serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of 83 Avastin-treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

Intracranial hemorrhage occurred in 8 of 163 patients with previously treated glioblastoma; two patients had Grade 3–4 hemorrhage.

Do not administer Avastin to patients with recent history of hemoptysis of ≥ 1/2 teaspoon of red blood. Discontinue Avastin in patients with hemorrhage. [See *Boxed Warning, Dosage and Administration (2.4).*]

5.4 Non-Gastrointestinal Fistula Formation

Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheo-esophageal, bronchopleural, biliary, vaginal, renal and bladder sites occurs at a higher incidence in Avastin-treated patients compared to controls. The incidence of non-gastrointestinal perforation was ≤ 0.3% in clinical studies. Most events occurred within the first 6 months of Avastin therapy.

Discontinue Avastin in patients with fistula formation involving an internal organ. [See *Dosage and Administration (2.4).*]

5.5 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a higher incidence in patients receiving Avastin compared to those in the control arm. Across indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.6% compared to 0.8% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the risk of developing ATE during therapy was increased in patients with a history of arterial thromboembolism, or age greater than 65 years. [See *Use in Specific Populations (8.5).*]

The safety of resumption of Avastin therapy after resolution of an ATE has not been studied. Discontinue Avastin in patients who experience a severe ATE. [See *Dosage and Administration (2.4).*]

5.6 Hypertension

The incidence of severe hypertension is increased in patients receiving Avastin as compared to controls. Across clinical studies the incidence of Grade 3 or 4 hypertension ranged from 5-18%.

Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension after discontinuation of Avastin.

Temporarily suspend Avastin in patients with severe hypertension that is not controlled with medical management. Discontinue Avastin in patients with hypertensive crisis or hypertensive encephalopathy. [See *Dosage and Administration (2.4).*]

5.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS has been reported with an incidence of < 0.1% in clinical studies. The onset of symptoms occurred from 16 hours to 1 year after initiation of Avastin. RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of RPLS.

Discontinue Avastin in patients developing RPLS. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating Avastin therapy in patients previously experiencing RPLS is not known. [See *Dosage and Administration (2.4).*]

5.8 Proteinuria

The incidence and severity of proteinuria is increased in patients receiving Avastin as compared to controls. Nephrotic syndrome occurred in < 1% of patients receiving Avastin in clinical trials, in some instances with fatal outcome. [See *Adverse Reactions (6.1).*] In a published case series, kidney biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during Avastin therapy. Patients with a 2 + or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection.

Suspend Avastin administration for ≥ 2 grams of proteinuria/24 hours and resume when proteinuria is < 2 gm/24 hours. Discontinue Avastin in patients with nephrotic syndrome. Data from a postmarketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24 hour urine protein (Pearson Correlation 0.39 (95% CI 0.17, 0.57). [See *Use in Specific Populations (8.5).*] The safety of continued Avastin treatment in patients with moderate to severe proteinuria has not been evaluated. [See *Dosage and Administration (2.4).*]

5.9 Infusion Reactions

Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion reactions with the first dose of Avastin were uncommon (< 3%) and severe reactions occurred in 0.2% of patients.

Stop infusion if a severe infusion reaction occurs and administer appropriate medical therapy. [See *Dosage and Administration (2.4).*]

5.10 Ovarian Failure

The incidence of ovarian failure was higher (34% vs. 2%) in premenopausal women receiving Avastin in combination with mFOLFOX chemotherapy as compared to those receiving mFOLFOX chemotherapy alone for adjuvant treatment for colorectal cancer, a use for which Avastin is not approved. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. [See *Adverse Reactions (6.1), Use in Specific Populations (8.6).*]

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Gastrointestinal Perforations [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.1).*]
- Surgery and Wound Healing Complications [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2).*]
- Hemorrhage [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).*]
- Non-Gastrointestinal Fistula Formation [See *Dosage and Administration (2.4), Warnings and Precautions (5.4).*]
- Arterial Thromboembolic Events [See *Dosage and Administration (2.4), Warnings and Precautions (5.5).*]
- Hypertensive Crisis [*See Dosage and Administration (2.4), Warnings and Precautions (5.6).*]
- Reversible Posterior Leukoencephalopathy Syndrome [See *Dosage and Administration (2.4), Warnings and Precautions (5.7).*]
- Proteinuria [See *Dosage and Administration (2.4), Warnings and Precautions (5.8).*]
- Ovarian Failure [See *Warnings and Precautions (5.10), Use in Specific Populations (8.6).*]

The most common adverse reactions observed in Avastin patients at a rate > 10% and at least twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.

Across all studies, Avastin was discontinued in 8.4 to 21% of patients because of adverse reactions.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to Avastin in 4198 patients with CRC, non-squamous NSCLC, glioblastoma, or mRCC trials including controlled (Studies 1, 2, 4, and 7) or uncontrolled, single arm (Study 5) treated at the recommended dose and schedule for a median of 8 to 23 doses of Avastin. [See *Clinical Studies (14).*] The population was aged 18-88 years (median 60 years), 43.6% male and 83.8% white. The population included 1783 first- and second-line mCRC patients who received a median of 10 doses of Avastin, 480 first-line metastatic NSCLC patients who received a median of 8 doses of Avastin, 163 glioblastoma patients who received a median of 9 doses of Avastin, and 337 mRCC patients who received a median of 16 doses of Avastin. These data also reflect exposure to Avastin in 363 patients with metastatic breast cancer (MBC) who received a median of 9.5 doses of Avastin, 669 female adjuvant CRC patients who received a median of 23 doses of Avastin and exposure to Avastin in 403 previously untreated patients with diffuse large B-cell lymphoma (DLBCL) who received a median of 8 doses of Avastin. Avastin is not approved for use in MBC, adjuvant CRC, or DLBCL.

Surgery and Wound Healing Complications

The incidence of post-operative wound healing and/or bleeding complications was increased in patients with mCRC receiving Avastin as compared to patients receiving only chemotherapy. Among patients requiring surgery on or within 60 days of receiving study treatment, wound healing and/or bleeding complications occurred in 15% (6/39) of patients receiving bolus-IFL plus Avastin as compared to 4% (1/25) of patients who received bolus-IFL alone.

In Study 5, events of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma: 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm. [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2).*]

Hemorrhage

The incidence of epistaxis was higher (35% vs. 10%) in patients with mCRC receiving bolus-IFL plus Avastin compared with patients receiving bolus-IFL plus placebo. All but one of these events were Grade 1 in severity and resolved without medical intervention. Grade 1 or 2 hemorrhagic events were more frequent in patients receiving bolus-IFL plus Avastin when compared to those receiving bolus-IFL plus placebo and included gastrointestinal hemorrhage (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs. 2%). [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).*]

Venous Thromboembolic Events

The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo. In Study 1, more patients in the Avastin containing arm experienced deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

The risk of developing a second thromboembolic event while on Avastin and oral anticoagulants was evaluated in two randomized studies. In Study 1, 53 patients (14%) on the bolus-IFL plus Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin following a venous thromboembolic event (VTE). Among these patients, an additional thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3% (1/30) of patients receiving bolus-IFL alone.

In a second, randomized, 4-arm study in 1401 patients with mCRC, prospectively evaluating the incidence of VTE (all grades), the overall incidence of first VTE was higher in the Avastin containing arms (13.5%) than the chemotherapy alone arms (9.6%). Among the 116 patients treated with anticoagulants following an initial VTE event (73 in the Avastin plus chemotherapy arms and 43 in the chemotherapy alone arms), the overall incidence of subsequent VTEs was also higher among the Avastin treated patients (31.5% vs. 25.6%). In this subgroup of patients treated with anticoagulants, the overall incidence of bleeding, the majority of which were Grade 1, was higher in the Avastin treated arms than the chemotherapy arms (27.4% vs. 20.9%). [See *Dosage and Administration (2.4).*]

Neutropenia and Infection

The incidences of neutropenia and febrile neutropenia are increased in patients receiving Avastin plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients receiving IFL alone (14%). In Study 4, the incidence of Grade 4 neutropenia was increased in NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26.2%) compared with patients receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs. 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious infections including pneumonia, febrile neutropenia, catheter infections and wound infections was increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm [29 patients (6.6%)].

In Study 5, one fatal event of neutropenic infection occurred in a patient with previously treated glioblastoma receiving Avastin alone. The incidence of any grade of infection in patients receiving Avastin alone was 55% and the incidence of Grade 3-5 infection was 10%.

Proteinuria

Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4 and 7. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 7, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 7). [See *Warnings and Precautions (5.8).*]

Congestive Heart Failure (CHF)

The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in patients receiving Avastin compared to 0.6% in the control arm across indications. In patients with metastatic breast cancer (MBC), an indication for which Avastin is not approved, the incidence of Grade 3–4 CHF was increased in patients in the Avastin plus paclitaxel arm (2.2%) as compared to the control arm (0.3%). Among patients receiving prior anthracyclines for MBC, the rate of CHF was 3.8% for patients receiving Avastin as compared to 0.6% for patients receiving paclitaxel alone. The safety of continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

In previously untreated patients with diffuse large B-cell lymphoma (DLBCL), an indication for which Avastin is not approved, the incidence of CHF and decline in left-ventricular ejection fraction (LVEF) were signficantly increased in the Avastin plus R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) arm (n=403) compared to the placebo plus R-CHOP arm (n=379); both regimens were given for 6 to 8 cycles. At the completion of R-CHOP therapy, the incidence of CHF was 10.9% in the Avastin plus R-CHOP arm compared to 5.0% in the R-CHOP alone arm [relative risk (95% CI) of 2.2 (1.3, 3.7)]. The incidence of a LVEF event, defined as a decline from baseline of 20% or more in LVEF or a decline from baseline of 10% or more to a LVEF value of less than 50%, was also increased in the Avastin plus R-CHOP arm (10.4%) compared to the R-CHOP alone arm (5.0%). Time to onset of left-ventricular dysfunction or CHF was 1-6 months after initiation of therapy in at least 85% of the patients and was resolved in 62% of the patients experiencing CHF in the Avastin arm compared to 82% in the control arm.

Ovarian Failure

The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months, FSH level ≥ 30 mIU/mL and a negative serum β-HCG pregnancy test) was prospectively evaluated in a subset of 179 women receiving mFOLFOX chemotherapy alone (n = 84) or with Avastin (n = 95). New cases of ovarian failure were identified in 34% (32/95) of women receiving Avastin in combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone [relative risk of 14 (95% CI 4, 53)]. After discontinuation of Avastin treatment, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the Avastin-treated women. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Long term effects of Avastin exposure on fertility are unknown. [See *Warnings and Precautions (5.10), Use in Specific Populations (8.6).*]

Metastatic Colorectal Cancer (mCRC)

The data in Table 1 and Table 2 were obtained in Study 1, a randomized, double-blind, controlled trial comparing chemotherapy plus Avastin with chemotherapy plus placebo. Avastin was administered at 5 mg/kg every 2 weeks.

All Grade 3–4 adverse events and selected Grade 1–2 adverse events (hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Severe and life-threatening (Grade 3–4) adverse events, which occurred at a higher incidence (≥ 2%) in patients receiving bolus-IFL plus Avastin as compared to bolus-IFL plus placebo, are presented in Table 1.

Table 1
NCI-CTC Grade 3–4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥ 2 %] Avastin vs. Control))

	Arm 1 IFL+ + Placebo (n = 396)	Arm 2 IFL+ + Avastin (n = 392)
NCI-CTC Grade 3-4 Events	74%	87%
Body as a Whole		
Asthenia	7%	10%
Abdominal Pain	5%	8%
Pain	5%	8%
Cardiovascular		
Hypertension	2%	12%
Deep Vein Thrombosis	5%	9%
Intra-Abdominal Thrombosis	1%	3%
Syncope	1%	3%
Digestive		
Diarrhea	25%	34%
Constipation	2%	4%
Hemic/Lymphatic		
Leukopenia	31%	37%
Neutropenia[a]	14%	21%

[a] Central laboratories were collected on Days 1 and 21 of each cycle. Neutrophil counts are available in 303 patients in Arm 1 and 276 in Arm 2.

Grade 1–4 adverse events which occurred at a higher incidence (≥ 5%) in patients receiving bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm are presented in Table 2. Grade 1–4 adverse events were collected

for the first approximately 100 patients in each of the three treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + Avastin) was discontinued.

Table 2
NCI-CTC Grade 1-4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥ 5%] in IFL + Avastin vs. IFL)

	Arm 1 IFL + Placebo (n = 98)	Arm 2 IFL + Avastin (n = 102)	Arm 3 5-FU/LV + Avastin (n = 109)
Body as a Whole			
Pain	55%	61%	62%
Abdominal Pain	55%	61%	50%
Headache	19%	26%	26%
Cardiovascular			
Hypertension	14%	23%	34%
Hypotension	7%	15%	7%
Deep Vein Thrombosis	3%	9%	6%
Digestive			
Vomiting	47%	52%	47%
Anorexia	30%	43%	35%
Constipation	29%	40%	29%
Stomatitis	18%	32%	30%
Dyspepsia	15%	24%	17%
GI Hemorrhage	6%	24%	19%
Weight Loss	10%	15%	16%
Dry Mouth	2%	7%	4%
Colitis	1%	6%	1%
Hemic/Lymphatic			
Thrombocytopenia	0%	5%	5%
Nervous			
Dizziness	20%	26%	19%
Respiratory			
Upper Respiratory Infection	39%	47%	40%
Epistaxis	10%	35%	32%
Dyspnea	15%	26%	25%
Voice Alteration	2%	9%	6%
Skin/Appendages			
Alopecia	26%	32%	6%
Skin Ulcer	1%	6%	6%
Special Senses			
Taste Disorder	9%	14%	21%
Urogenital			
Proteinuria	24%	36%	36%

Avastin in Combination with FOLFOX4 in Second-line mCRC

Only Grade 3-5 non-hematologic and Grade 4–5 hematologic adverse events related to treatment were collected in Study 2. The most frequent adverse events (selected Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events) occurring at a higher incidence (≥2%) in 287 patients receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting mechanisms used in Study 2.

Unresectable Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in Study 4. Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events (occurring at a higher incidence (≥2%) in 427 patients receiving PC plus Avastin compared with 441 patients receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs. 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile neutropenia (5% vs. 2%), pneumonitis/ pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3% vs. 0%).

Glioblastoma

All adverse events were collected in 163 patients enrolled in Study 5 who either received Avastin alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide. Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan. Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

In patients receiving Avastin alone (N = 84), the most frequently reported adverse events of any grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%) and diarrhea (21%). Of these, the incidence of Grade ≥ 3 adverse events was infection (10%), fatigue (4%), headache (4%), hypertension (8%) and diarrhea (1%). Two deaths on study were possibly related to Avastin: one retroperitoneal hemorrhage and one neutropenic infection.

In patients receiving Avastin alone or Avastin plus irinotecan (N = 163), the incidence of Avastin-related adverse events (Grade 1–4) were bleeding/ hemorrhage (40%), epistaxis (26%), CNS hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%), and RPLS (1%). The incidence of Grade 3–5 events in these 163 patients were bleeding/hemorrhage (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and gastrointestinal perforation (2%).

Metastatic Renal Cell Carcinoma (mRCC)

All grade adverse events were collected in Study 7. Grade 3–5 adverse events occurring at a higher incidence (≥ 2%) in 337 patients receiving interferon alfa (IFN-α) plus Avastin compared to 304 patients receiving IFN-α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

Grade 1–5 adverse events occurring at a higher incidence (≥ 5%) in patients receiving IFN-α plus Avastin compared to the IFN-α plus placebo arm are presented in Table 3.

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Table 3
NCI-CTC Grades 1–5 Adverse Events in Study 7
(Occurring at Higher Incidence [≥ 5%] in IFN-α + Avastin vs. IFN-α + Placebo)

System Organ Class/ Preferred term[a]	IFN-α + Placebo (n = 304)	IFN-α + Avastin (n = 337)
Gastrointestinal disorders		
Diarrhea	16%	21%
General disorders and administration site conditions		
Fatigue	27%	33%
Investigations		
Weight decreased	15%	20%
Metabolism and nutrition disorders		
Anorexia	31%	36%
Musculoskeletal and connective tissue disorders		
Myalgia	14%	19%
Back pain	6%	12%
Nervous system disorders		
Headache	16%	24%
Renal and urinary disorders		
Proteinuria	3%	20%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	4%	27%
Dysphonia	0%	5%
Vascular disorders		
Hypertension	9%	28%

[a]Adverse events were encoded using MedDRA, Version 10.1.

The following adverse events were reported at a 5-fold greater incidence in the IFN-α plus Avastin arm compared to IFN-α alone and not represented in Table 3: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs.0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs.1); tinnitus (7 vs. 1); tooth abscess (7 vs.0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Avastin has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with Avastin, primarily in combination with chemotherapy. High titer human anti-Avastin antibodies were not detected.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Avastin with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Avastin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Polyserositis

Cardiovascular: Pulmonary hypertension, RPLS, Mesenteric venous occlusion

Eye disorders (from unapproved intravitreal use for treatment of various ocular disorders): Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort

Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration

Hemic and lymphatic: Pancytopenia

Hepatobiliary disorders: Gallbladder perforation

Musculoskeletal: Osteonecrosis of the jaw

Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)

Respiratory: Nasal septum perforation, dysphonia

Systemic Events (from unapproved intravitreal use for treatment of various ocular disorders): Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

7 DRUG INTERACTIONS

A drug interaction study was performed in which irinotecan was administered as part of the FOLFIRI regimen with or without Avastin. The results demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan or its active metabolite SN38.

In a randomized study in 99 patients with NSCLC, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with Avastin. However, 3 of the 8 patients receiving Avastin plus paclitaxel/carboplatin had substantially lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel/carboplatin without Avastin had a greater paclitaxel exposure at Day 63 than at Day 0.

In Study 7, there was no difference in the mean exposure of interferon alfa administered in combination with Avastin when compared to interferon alfa alone.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate or well controlled studies of bevacizumab in pregnant women. While it is not known if bevacizumab crosses the placenta, human IgG is known to cross the placenta Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab demonstrated teratogenicity, including an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Other observed effects included decreases in maternal and fetal body weights and an increased number of fetal resorptions. [See *Nonclinical Toxicology (13.3).*]

AVASTIN® (bevacizumab)

Because of the observed teratogenic effects of bevacizumab in animals and of other inhibitors of angiogenesis in humans, bevacizumab should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether Avastin is secreted in human milk. Human IgG is excreted in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from bevacizumab, a decision should be made whether to discontinue nursing or discontinue drug, taking into account the half-life of the bevacizumab (approximately 20 days [range 11–50 days]) and the importance of the drug to the mother. [See *Clinical Pharmacology (12.3).*]

8.4 Pediatric Use

The safety, effectiveness and pharmacokinetic profile of Avastin in pediatric patients have not been established.

Antitumor activity was not observed among eight children with relapsed glioblastoma treated with bevacizumab and irinotecan. There is insufficient information to determine the safety and efficacy of Avastin in children with glioblastoma.

Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

8.5 Geriatric Use

In Study 1, severe adverse events that occurred at a higher incidence (≥ 2%) in patients aged ≥65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of Avastin on overall survival was similar in elderly patients as compared to younger patients.

In Study 2, patients aged ≥65 years receiving Avastin plus FOLFOX4 had a greater relative risk as compared to younger patients for the following adverse events: nausea, emesis, ileus, and fatigue.

In Study 4, patients aged ≥65 years receiving carboplatin, paclitaxel, and Avastin had a greater relative risk for proteinuria as compared to younger patients. [See *Warnings and Precautions (5.8).*]

Of the 742 patients enrolled in Genentech-sponsored clinical studies in which all adverse events were captured, 212 (29%) were age 65 or older and 43 (6%) were age 75 or older. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients, in addition to those described above, were dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients aged ≥65 years and 1127 patients <65 years of age. The overall incidence of arterial thromboembolic events was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the increase in arterial thromboembolic events incidence was greater in patients aged ≥65 years (8.5% vs. 2.9%) as compared to those <65 years (2.1% vs. 1.4%). [See *Warnings and Precautions (5.5).*]

8.6 Females of Reproductive Potential

Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. Long term effects of Avastin exposure on fertility are unknown.

In a prospectively designed substudy of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin arm (34%) compared to the control arm (2%). After discontinuation of Avastin and chemotherapy, recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients. [See *Warnings and Precautions (5.10), Adverse Reactions (6.1).*]

10 OVERDOSAGE

The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of 16 patients and with severe headache in three of 16 patients.

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Avastin® (bevacizumab)

Manufactured by:
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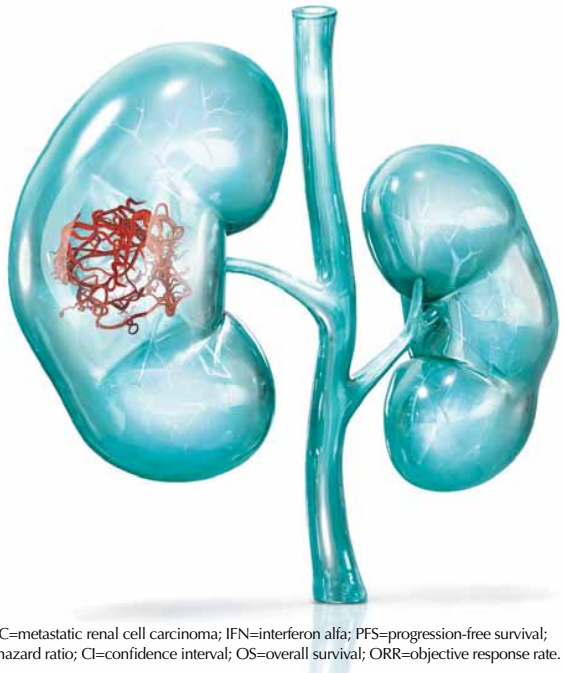
06/12 AVA0000759203
10127309
Initial U.S.Approval: February 2004
Code Revision Date: May 2012

To confront the threat of angiogenesis in mRCC…

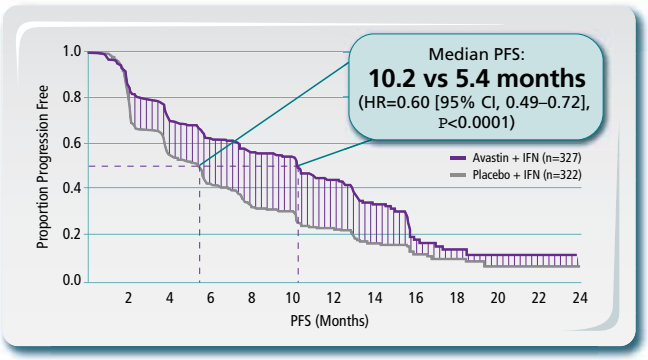
Think Avastin

Because anti-angiogenesis matters



mRCC=metastatic renal cell carcinoma; IFN=interferon alfa; PFS=progression-free survival; HR=hazard ratio; CI=confidence interval; OS=overall survival; ORR=objective response rate.

Avastin plus IFN improved median PFS by 89% over placebo plus IFN (10.2 vs 5.4 months) in AVOREN[1]



- PFS benefit of Avastin plus IFN was observed as early as 2 months and was sustained through the duration of the study[1,2]
- Median OS with Avastin plus IFN was 23 months, a nonsignificant increase vs placebo plus IFN (21 months, HR=0.86 [95% CI, 0.72–1.04], *P*=0.1291)[1,3]
- Avastin plus IFN more than doubled ORR vs placebo plus IFN (30% vs 12%, *P*<0.0001), as confirmed by an independent review facility[1,3]

Indication

Avastin is indicated for the treatment of metastatic renal cell carcinoma in combination with interferon alfa.

Boxed WARNINGS

- **Gastrointestinal (GI) perforation**
  - — Serious and sometimes fatal GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls
  - — The incidences of GI perforation ranged from 0.3% to 2.4% across clinical studies
  - — Discontinue Avastin in patients with GI perforation
- **Surgery and wound healing complications**
  - — The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients
  - — Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined
  - — Discontinue Avastin at least 28 days prior to elective surgery and in patients with wound healing complications requiring medical intervention
- **Hemorrhage**
  - — Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 1.2% to 4.6%
  - — Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (≥1/2 tsp of red blood)
  - — Discontinue Avastin in patients with serious hemorrhage (ie, requiring medical intervention)

Additional serious adverse events

- Additional serious and sometimes fatal adverse events with increased incidence in the Avastin-treated arm vs control included
  - — Non-GI fistula formation (≤0.3%)
  - — Arterial thromboembolic events (grade ≥3, 2.4%)
  - — Proteinuria including nephrotic syndrome (<1%)
- Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included
  - — Hypertension (grade 3–4, 5%–18%)
  - — Reversible posterior leukoencephalopathy syndrome (RPLS) (<0.1%)
- Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients
- Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin

Most common adverse events

- Most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were
  - — Epistaxis
  - — Headache
  - — Hypertension
  - — Rhinitis
  - — Proteinuria
  - — Taste alteration
  - — Dry skin
  - — Rectal hemorrhage
  - — Lacrimation disorder
  - — Back pain
  - — Exfoliative dermatitis
- Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions

Pregnancy warning

- Avastin may impair fertility
- Based on animal data, Avastin may cause fetal harm
- Advise patients of the potential risk to the fetus during and following Avastin and the need to continue adequate contraception for at least 6 months following the last dose of Avastin
- For nursing mothers, discontinue nursing or Avastin, taking into account the importance of Avastin to the mother
- The most common grade 3–5 adverse events in AVOREN, occurring at a ≥2% higher incidence in Avastin-treated patients vs controls, were fatigue (13% vs 8%), asthenia (10% vs 7%), proteinuria (7% vs 0%), hypertension (6% vs 1%), and hemorrhage (3% vs 0.3%)

Please see accompanying brief summary of Prescribing Information, including **Boxed WARNINGS,** for additional important safety information.

References: 1. Avastin Prescribing Information. Genentech, Inc. September 2011.
2. Escudier B, Pluzanska A, Koralewski P, et al. *Lancet.* 2007;370:2103-2111.
3. Escudier B, Bellmunt J, Negrier S, et al. Slides presented at: Annual Meeting of the American Society of Clinical Oncology; May 29–June 2, 2009; Orlando, FL.

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