

Off-Label Uses of Sorafenib and Sunitinib



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Executive Summary

Background

Sorafenib (Nexavar[®]) and sunitinib (Sutent[®]) are orally administered inhibitors of protein tyrosine kinases associated with the intracellular portions of certain transmembrane receptor molecules. Each targets the tyrosine kinase activity of more than one receptor, with effects that depend on each cell type's receptor repertoire. Inhibiting these intracellular tyrosine kinases blocks signal transduction after a growth factor, cytokine, or other ligand binds to the receptor's extracellular domain. In different cell types, this can inhibit tumor growth, metastasis, or angiogenesis (growth of new blood vessels). Both sorafenib and sunitinib are approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma. Sunitinib also is indicated to treat gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib.

Objective

The Assessment summarizes and evaluates evidence on health outcomes of sorafenib and sunitinib for off-label indications reported in published studies or currently undergoing phase III trials. Since these medications overlap only partially with respect to the receptor tyrosine kinases each inhibits, sorafenib and sunitinib were assessed separately.

Search Strategy

MEDLINE[®] was searched through October 2007 using the terms "Nexavar" or "sorafenib" and "Sutent" or "sunitinib," limited to English-language articles on human subjects. Online searches of abstracts presented at the 2007 meeting of the American Society of Clinical Oncology (ASCO) supplemented the search.

Selection Criteria

The Assessment includes full-length, peer-reviewed articles reporting on 10 or more patients. Also included are meeting presentations with slides available online, showing results of phase III randomized controlled trials (RCTs) versus placebo or active comparator.

Main Results

For sorafenib, indications that met the first-level screen (i.e., either fully published results are available or a phase III trial is in progress) included: hepatocellular carcinoma (HCC), malignant melanoma, squamous cell cancer of the head and neck (SCCHN), non-small cell lung cancer (NSCLC), GIST, and adjuvant therapy for resected RCC. For sunitinib, indications that met this first-level screen included: breast cancer, colorectal cancer (CRC), NSCLC, and adjuvant therapy for



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resected RCC. However, the literature search found studies meeting selection criteria (i.e., a published full study with 10 or more patients or phase III results presented at a meeting with slide available online) for only 3 sorafenib off-label indications: HCC, melanoma, and SCCHN. No studies met these selection criteria for any sunitinib off-label indication.¹

Two studies evaluated sorafenib as first-line therapy for advanced HCC, a malignancy for which no drug or combination regimen has been shown to increase survival. A placebo-controlled RCT (n=602), presented at ASCO but as-yet unpublished, reported statistically significant improvement in median time to progression (TTP; 5.5 versus 2.8 months; HR: 0.58, 95% CI: 0.44–0.74) and median overall survival (OS; 10.7 versus 7.9 months; HR: 0.69, 95% CI: 0.55–0.88). Adverse effects included absolute increases of 6% in grade 3 or 4 diarrhea and 7–8% in grade 3 or 4 hand/foot skin reactions. A published, single-arm, uncontrolled study (n=137) reported OS was 9.2 months and TTP was 5.5 months.

An as-yet unpublished ASCO presentation was the only study identified on treatment of unresectable or metastatic melanoma. This RCT (n=270) compared carboplatin plus paclitaxel with versus without sorafenib as second-line therapy after progression while on dacarbazine or temozolomide. Results showed no significant difference between arms for objective response rate (ORR), progression-free survival (PFS), or OS, and absolute increases in grades 3 or 4 hand/foot skin reactions, fatigue, and diarrhea of 7%, 6%, and 5%, respectively.

One uncontrolled published study (n=28) reported outcomes of sorafenib as first- or second-line therapy for recurrent or metastatic SCCHN or nasopharyngeal carcinoma. The trial reported OS was 4.2 months.

Author's Conclusions and Comments

Lacking evidence from studies that met selection criteria, no conclusions were possible on outcomes of sorafenib to treat NSCLC or GIST, or as adjuvant therapy for resected RCC. For the same reason, no conclusions were possible on outcomes of sunitinib to treat breast cancer, colorectal cancer, or NSCLC, or as adjuvant therapy for resected RCC. Note also that drug compendia accepted as authoritative sources on off-label uses of oncology drugs by the Centers for Medicare and Medicaid Services (CMS) do not include any of these indications.

While the only available RCT on sorafenib as first-line therapy for advanced HCC has not been published as of this writing, an independent data monitoring committee (DMC) authorized release of the interim analysis showing statistically significant improvement in OS and TTP. No other systemic therapy tested to date has improved survival of patients with advanced HCC. An uncontrolled phase II trial supports conclusions of the RCT. A second RCT recently was also closed early by its DMC (http://www.onyx-pharm.com/wt/page/pr_1188237032), after interim analysis reportedly showed statistically significant improvement in TTP, PFS, and OS. Results of both manufacturer-sponsored RCTs were submitted to FDA to support a supplementary new drug application (sNDA) for adding advanced HCC as approved indication for sorafenib (see TEC criterion 1). Finally, the current guideline on hepatobiliary cancers from the National Comprehensive Cancer Network (available at http://www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf) includes sorafenib among recommended treatment options for HCC patients with Child-Pugh class A or B disease who are not candidates for liver transplant.

¹ As this Assessment went to press, a report was published from a Phase II trial of sunitinib for metastatic colorectal cancer that failed standard therapy (Saltz et al. 2007). The study stratified patients by whether they had (group 1; n=43) or had not (group 2; n=41) previously received bevacizumab. Only one patient (from group 1) achieved a partial response, and 13 patients (2 from group 1, 11 from group 2) achieved stable disease for ≥22 weeks. Median time to progression was 2.2 and 2.5 months, respectively, in groups 1 and 2. The authors concluded that “sunitinib did not demonstrate a meaningful single-agent objective response rate in colorectal cancer refractory to standard chemotherapy.” Data are presently unavailable from studies on sunitinib in combination with standard regimens for metastatic colorectal cancer.

The only available study on sorafenib for second-line therapy of advanced melanoma showed no improvement in response rates, OS, or PFS. An ongoing trial compares paclitaxel plus carboplatin with versus without sorafenib as first-line treatment for patients with advanced melanoma. The only evidence on outcomes of sorafenib for first- or second-line therapy of advanced SCCHN lacks controls and thus does not permit conclusions. Additionally, CMS-accepted drug compendia do not list these indications for sorafenib.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether off-label uses of sorafenib or sunitinib meet the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

The U.S. Food and Drug Administration (FDA) approved sorafenib (Nexavar[®]) in December 2005 to treat advanced renal cell carcinoma (RCC). In January 2006, the FDA approved sunitinib (Sutent[®]) to treat advanced RCC, and to treat gastrointestinal stromal tumors (GIST) when there is disease progression on or intolerance to imatinib (Gleevec[®]). Use of sorafenib to treat patients with hepatocellular carcinoma, melanoma, non-small cell lung cancer, squamous cell head and neck carcinoma or GIST; use of sunitinib to treat patients with colorectal, non-small-cell lung or breast cancers; and use of either drug for adjuvant therapy of resected RCC, all are off-label indications.²

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

This Assessment reviews evidence on health outcomes of sorafenib and sunitinib for off-label indications that either have been reported in published studies or currently are undergoing phase III trials. For off-label indications of sunitinib, no studies were found that met selection criteria for this Assessment (please refer to footnote 1).

Available evidence on outcomes of sorafenib for advanced hepatocellular carcinoma (HCC) included one published, single-arm study (n=137) and one unpublished presentation of a randomized, double-blind, placebo-controlled phase III trial (n=602) from the June 2007 ASCO meeting. The comparative trial reports a statistically significant survival advantage for sorafenib over placebo from an interim analysis reviewed by an independent data monitoring committee (DMC) that authorized early release of results and terminated the study with controls crossed over to active therapy. The single-arm trial supports these results based on similar improvements in TTP and OS. No other systemic therapy for advanced HCC has demonstrated a survival benefit for this rapidly fatal malignancy. In light of this unmet medical need and DMC involvement in analysis of the RCT results, this evidence is judged sufficient to permit conclusions on outcomes of sorafenib for advanced HCC.

One unpublished presentation of a randomized, double-blind, placebo-controlled phase III trial (n=270) from the June 2007 ASCO meeting provides the only available evidence on outcomes of sorafenib for second-line therapy of advanced melanoma. This evidence was judged insufficient to permit conclusions. One published, single-arm trial (n=28) provides the only available evidence on outcomes of sorafenib as first- or second-line therapy for recurrent or metastatic squamous cell head and neck cancer. This evidence was judged insufficient to permit conclusions. No studies that met this Assessment's selection criteria were found for any other off-label indications for sorafenib.

² On November 19, 2007, as this Assessment went to press, FDA approved a supplemental new drug application to add advanced hepatocellular carcinoma as a labeled indication for sorafenib.

- 3. The technology must improve the net health outcome; and**
- 4. The technology must be as beneficial as any established alternatives.**

In the only reported RCT on HCC, sorafenib improved median TTP (5.5 versus 2.8 months; HR=0.58, 95% CI: 0.44–0.74) and median OS (10.7 versus 7.9 months; HR: 0.69, 95% CI: 0.55–0.88) compared with placebo. Adverse effects included absolute increases of 6% in grade 3 or 4 diarrhea and 7–8% in grade 3 or 4 hand/foot skin reactions. Median OS was 9.2 months and median TTP was 5.5 months in the published single-arm uncontrolled study. Advanced hepatocellular carcinoma has been unresponsive to chemotherapy; no agent has shown a survival benefit in treating this tumor. The available evidence suggests that sorafenib is the first agent to improve overall survival in this disease, relative to best supportive care.

Since evidence is lacking, it cannot be determined whether sorafenib improves outcomes, and is at least as good as alternatives, for patients with advanced melanoma, advanced squamous cell head and neck cancer, or any other off-label indication. For the same reason, it cannot be determined whether sunitinib improves outcomes, and is at least as good as alternatives, for patients with any off-label indication.

- 5. The improvement must be attainable outside the investigational setting.**

The outcomes of sorafenib for advanced HCC reported from the multicenter RCT should be achievable outside the clinical trial setting by clinicians experienced with management of HCC patients. Whether sorafenib improves outcomes for patients with any other off-label indication, and whether sunitinib improves outcomes for patients with any off-label indication, has not yet been determined in the investigational setting.

For the reasons outlined above, sorafenib meets the TEC criteria as a treatment for advanced hepatocellular carcinoma. Sorafenib does not meet the TEC criteria for any other off-label uses, including but not limited to advanced melanoma, unresectable or metastatic squamous cell carcinoma of the head and neck, non-small cell lung cancer (NSCLC), gastrointestinal stromal tumor (GIST), or as adjuvant therapy for renal cell carcinoma. Sunitinib does not meet the TEC criteria for any off-label use, including but not limited to treatment for advanced or metastatic breast cancer, metastatic colorectal cancer, advanced or metastatic NSCLC, or as adjuvant therapy for renal cell carcinoma.

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Assessment Objective

Sorafenib (Nexavar[®]) and sunitinib (Sutent[®]) are orally administered inhibitors of protein tyrosine kinase activity associated with certain the intracellular portions of transmembrane receptor molecules. Each anti-cancer drug is a small molecule that acts intracellularly by targeting the tyrosine kinase activity of one or more receptors, depending on the receptor repertoire expressed in each cell type. Inhibiting these intracellular tyrosine kinases blocks signal transduction pathways normally activated after a growth factor, cytokine, or other ligand binds to the receptor's extracellular domain. In different cell types, this can inhibit tumor growth, metastasis, and angiogenesis (growth of new blood vessels).

Both sorafenib and sunitinib are approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma (RCC). Sunitinib has an additional indication for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib.

This Assessment summarizes and evaluates evidence on health outcomes of sorafenib and sunitinib for off-label uses. These medications overlap only partially with respect to the receptor tyrosine kinases each inhibits. These differences help determine the specific malignancies that each may be active against. Therefore, the available evidence for sorafenib and sunitinib is assessed separately.

Introduction

Signal Transduction by Receptor Tyrosine Kinases

Receptor tyrosine kinases (RTKs) are transmembrane glycoproteins that transduce extracellular signals to intracellular biochemical pathways that ultimately control cell proliferation, differentiation, migration, and metabolism (Hubbard 2002). This large family of proteins includes the receptors for many growth factors, including epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF1), the fibroblast growth factors (FGF), and the receptor for insulin. RTK-mediated signals are involved in diverse normal processes such as embryonic development and adult tissue maintenance

and regeneration, and in several pathological conditions, including various cancers, atherosclerotic disease, and diabetic retinopathy (Li and Hristova 2006).

RTKs generally comprise an extracellular binding domain that binds polypeptide ligands; a transmembrane helix; and a cytoplasmic domain, which possesses intrinsic TK activity (Hubbard 2002). The TK domain transfers the gamma phosphate moiety of adenosine triphosphate (ATP) to the side-chain hydroxyl group of tyrosine residues in protein substrates. Each RTK is activated by binding of its cognate ligand to the extracellular binding site, which stabilizes a noncovalent dimeric form of the receptor. Dimerization permits trans-autophosphorylation to occur between tyrosine residues in the two juxtaposed cytoplasmic domains of the dimer. This serves two purposes: it stimulates receptor activity by stabilizing a proper active site configuration and opens up binding sites for downstream signaling proteins that bear phosphotyrosine-recognition modules. Through this mechanism, the RTK essentially sets in motion a signaling cascade that is controlled by combinations of autoinhibitory feedback loops.

Angiogenesis and Cancer Therapy

Folkman first postulated in the early 1970s that tumor growth beyond 2 mm³ in diameter requires development of new blood vessels to supply nutrients and oxygen, which introduced the concept of angiogenesis into cancer research (Folkman 1971). The concept of neovascularization as a necessity to cancer growth and metastasis is now well-founded scientifically, and has opened up new approaches to cancer therapy that involve inhibition of angiogenesis and subsequent signaling pathways (Morabito et al. 2006).

VEGF is a diffusible, homodimeric glycoprotein that regulates vascular permeability, which maintains physiological homeostasis, and stimulates angiogenesis (Herbst 2006). This protein, which also is termed VEGFA, is part of the VEGF-PDGF supergene family that includes VEGFB, -C, -D, -E, and placental growth factor. These glycoproteins share the same basic structure, but exhibit varying degrees of sequence homology. VEGF expression is regulated by hypoxia, TGF, EGF or inflammatory cytokines, mediated through binding of those ligands to two related RTKs, VEGFR-1 (Flt-1) and VEGFR-2 (Flk/KDR). A third receptor,

VEGFR-3, belongs to the same RTK family, but preferentially binds VEGFC and VEGFD.

VEGF expression is upregulated in most cancers, including those of bladder, breast, colorectal, gastrointestinal tract, hematologic, liver, lung, ovary, thyroid, and uterine cervix (Herbst 2006). Overexpression of VEGF also has been correlated with a more advanced stage and poorer prognosis in several cancer types, including bladder, breast, lung, ovary, renal cell, neuroblastoma, and squamous cell carcinoma of the head and neck. Hematologic malignancies, for example, acute myeloid leukemia, also exhibit deregulated expression of VEGF that has been associated with reduced survival (Giles 2001). In addition to VEGF, other signaling pathways are involved in neovascularization, with potential therapeutic targets such as PDGF-B/PDGFR- β , which is associated with recruitment of pericytes and microvasculature development, metastasis and tumor growth in preclinical models.

Therapeutic Antiangiogenic Agents and TKIs

Given the complex interrelatedness of the angiogenesis signaling pathways, it is not surprising that numerous inhibitors are under investigation for their therapeutic efficacy. Several different classes of agents include TKIs, monoclonal antibodies, small molecule inhibitors, and transcription inhibitors. Table 1 summarizes information on two TKIs, sorafenib (Nexavar[®], BAY43-9006) and sunitinib (Sutent[®], SU11248), that have been developed as a means to block tumor angiogenesis and tumor cell growth through inhibition of different signaling kinases that exhibit aberrant expression due to mutation-related overactivation or overexpression secondary to gene amplification. Both drugs commonly inhibit VEGFR-2, PDGFR- β , and c-Kit kinase activity, but diverge in their specificity for other angiogenic targets and kinases. This suggests both drugs may have therapeutic activities in common, and may have activities specific to particular tumor types that vary in their dependence on various aspects of the signaling pathways.

Table 1. Molecular Targets and Actions of Sorafenib and Sunitinib*

Agent	Molecular Target	IC50 (μ M)	Therapeutic Target		FDA Status
			Tumor Cells	Tumor Angiogenesis	
Sorafenib (BAY43-9006)	Raf	0.006	X		FDA-approved for renal cell carcinoma (2005); in phase III for hepatocellular carcinoma, metastatic melanoma, advanced non-small-cell lung cancer
	KIT	0.068	X		
	VEGFR-2 (Flk/KDR)	0.09		X	
	VEGFR-3 (Flt-4)	0.02		X	
Sunitinib (SU11248)	PDGFR- β	0.057		X	FDA-approved for renal cell carcinoma and gastrointestinal stromal tumors (2006)
	KIT	0.022	X		
	Flt-3	0.25	X		
	VEGFR-1 (Flt-1)	0.002		X	
	VEGFR-2 (Flk/KDR)	0.009		X	
	PDGFR- β	(0.002)		X	

Abbreviations/Definitions

VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet-derived growth factor receptor; Flt: fms-like tyrosine kinase; KIT: stem-cell factor receptor; Raf: serine/threonine specific kinase; Flk/KDR: kinase insert domain receptor, alternate name for VEGFR

* adapted from Gridelli et al. (2006); Herbst (2006); Morabito et al. (2006)

Sorafenib. Sorafenib is a novel, multitargeted, orally available, biaryl urea that was initially developed as a specific inhibitor of the Raf kinase, but also has been shown to inhibit TKs VEGFR-2 and -3, as well as c-Kit and PDGFR- β (Flaherty 2007; Schoffski et al. 2006). It received FDA marketing approval in December 2005 to treat patients with advanced renal cell carcinoma (RCC), and is in phase III development for metastatic melanoma and advanced non-small cell lung cancer (NSCLC) (Gridelli et al. 2007). Sorafenib has shown activity against Raf-dependent human tumor xenograft cancer models, including colon, breast, and NSCLC. Phase III trials are evaluating the efficacy of sorafenib in hepatocellular carcinoma, metastatic melanoma, and NSCLC. Several phase I/II studies include sorafenib in combination with chemotherapeutic agents (irinotecan, dacarbazine) or other TKIs (gefitinib) in advanced solid tumors.

Sunitinib. Sunitinib is an orally bioavailable, multitargeted oxindole that inhibits RTKs involved in tumor proliferation and angiogenesis, including VEGFR-1, -2, and -3; PDGFR-A and - β ; Flt-3; and c-Kit (Buckstein et al. 2007; Cabebe and Wakelee 2006). In mouse xenograft studies, sunitinib was shown to inhibit PDGFR- β and VEGFR-2 dependent tumor angiogenesis, inducing regression of small-cell lung cancer, breast cancer, colon cancer, and leukemia. It received FDA marketing approval in January 2006 to treat advanced RCC and gastrointestinal stromal tumors (GIST) that failed imatinib therapy. Phase II and III studies have included single-agent treatment of metastatic breast cancer, NSCLC, carcinoid and islet cell tumors, and advanced gastric cancer.

FDA Status. The U.S. Food and Drug Administration (FDA) approved sorafenib (Nexavar[®]) in December 2005 to treat advanced renal cell carcinoma (RCC). In January 2006, the FDA approved sunitinib (Sutent[®]) to treat advanced RCC, and to treat gastrointestinal stromal tumors (GIST) when there is disease progression on or intolerance to imatinib (Gleevec[®]). Use of sorafenib to treat patients with hepatocellular carcinoma, melanoma, non-small cell lung cancer, squamous cell head and neck carcinoma or GIST; use of sunitinib to treat patients with colorectal, non-small-cell

lung or breast cancers; and use of either drug for adjuvant therapy of resected RCC, all are off-label indications.⁵

Background on Labeled Indications

Advanced Renal Cell Carcinoma. The American Cancer Society estimates 51,190 new cases and 12,890 deaths from kidney cancer (renal cell and renal pelvis cancers) are expected in 2007 (PDQ 2007a; American Cancer Society 2007). It accounts for about 2% of all cancers and has a median age at diagnosis of 65 years (NCCN 2007a). Survival at 5 years after kidney cancer diagnosis is around 40%, as most patients are diagnosed with localized, operable disease. Approximately one-third of patients will experience a relapse after resection. Median survival for patients with metastatic disease is about 13 months.

Kidney cancers occur in several histologies (Linehan et al. 2005; Cohen and McGovern 2005; PDQ 2007a; NCCN 2007a). Approximately 90% of cases are renal cell carcinoma (RCC) and approximately 85% of these have clear-cell histology. Less-common histologies include types 1 and 2 papillary tumors (approximately 15%), chromophobe tumors (approximately 5%), oncocytomas (approximately 5%), and collecting-duct tumors (<1%; includes medullary renal carcinoma).

Staging of renal cancer uses the American Joint Cancer Committee (AJCC) Tumor-Node-Metastasis (TNM) system (for details, see Linehan et al. 2005; Cohen and McGovern 2005; PDQ 2007a; NCCN 2007a). Tumors are grouped as stage I, II, III, or IV, based on the similarity of prognosis and treatment options. Stage I tumors have the best prognosis, and stage IV, the worst. For stage I, II, or III renal cell cancer, surgical resection is the primary treatment and is a cure for most patients. External-beam radiation may be used in patients with resectable tumors and medical contraindications to surgery; however, few of these patients are cured. Advanced stages (metastatic or recurrent) of the disease are, in most cases, not curable as RCC is a chemotherapy-resistant tumor (Cohen and McGovern 2005). Goals of therapy generally include improving survival and quality of life.

⁵ On November 19, 2007, as this Assessment went to press, FDA approved a supplemental new drug application to add advanced hepatocellular carcinoma as a labeled indication for sorafenib.

Therapy for advanced stage clear cell carcinoma may include chemotherapy, cytokine therapy (interleukin-2 or interferon-alfa), or a combination of cytokine therapy plus bevacizumab, a biologic agent. Current chemotherapy recommendations include sunitinib, temsirolimus (for patients with poor prognosis), or sorafenib (NCCN 2007a). Cytokine-based therapies include bevacizumab plus interferon, or, for selected patients, high-dose interleukin-2 (IL-2) as monotherapy. Therapy for advanced stage, non-clear-cell disease is not as well defined because the majority of the data from clinical trials is in patients with clear-cell histology. For patients with non-clear cell RCC, enrollment in a clinical trial is preferred; however, chemotherapy may also be an option for some patients. Current chemotherapy recommendations may include temsirolimus (for patients with poor prognosis), sunitinib, sorafenib, or conventional chemotherapy including gemcitabine, capecitabine, floxuridine, fluorouracil, or doxorubicin (for sarcomatoid histology only).

Although cytokines have been the standard of care for the past 15 years, use is declining as a result of the recent approval of agents such as sorafenib, sunitinib, and temsirolimus. Cytokines are associated with significant adverse effects and are generally poorly tolerated. Administration of high-dose interleukin-2 may require admission of the patient to an intensive care unit. Since approximately 5% of patients achieve durable complete remissions with high-dose interleukin-2, it remains a treatment option for advanced RCC, despite the severe toxicity (PDQ 2007a; Renal cell cancer, available online at: <http://www.cancer.gov/cancertopics/pdq/treatment/renalcell/healthprofessional>; Atkins et al. 1993; Yang et al. 1994).

Sorafenib in Advanced RCC

In December 2005, sorafenib (Nexavar®; Bayer 2007), was approved by the FDA for the treatment of advanced RCC. It is classified as a multitargeted tyrosine kinase inhibitor. Sorafenib inhibits tumor angiogenesis in RCC via its inhibition of VEGF-R1 and VEGF-R2, two intracellular tyrosine kinase components of transmembrane receptors on vascular endothelial cells (Cohen and McGovern 2005; Schrader et al. 2006a, 2006b; PDQ 2007a; NCCN 2007a). Sorafenib also inhibits several other tyrosine kinases, which may contribute to its activity in RCC and which may eventually prove to be

beneficial in the treatment of other types of tumors.

In a single large (n=769) randomized, controlled trial (RCT) in patients with clear-cell metastatic RCC and progression of disease after one systemic treatment within the previous 8 months, sorafenib was shown to improve progression-free survival (PFS) relative to placebo (Escudier et al. 2007). Patients were randomized in a 1:1 ratio to receive either sorafenib 400 mg orally twice daily or placebo. The primary endpoint of the trial was median overall survival; however, after an interim analysis of the data by an independent data monitoring board, crossover was permitted in the trial because of encouraging benefit in PFS. Significant improvement in median overall survival had not been reached at the time of crossover, and future overall survival information is confounded by crossover of patients from placebo to sorafenib. Assessment of PFS was based on RECIST criteria and was made by independent blinded reviewers to minimize the potential for bias.

Sunitinib in Advanced RCC

In January 2006, sunitinib (Sutent®; Pfizer 2007), was approved by the FDA for the treatment of advanced RCC. It is also classified as a multitargeted tyrosine kinase inhibitor. Sunitinib also inhibits tumor angiogenesis in RCC via its inhibition of VEGF-R1 and VEGF-R2 tyrosine kinases (Cohen and McGovern 2005; Schrader et al. 2006a, 2006b; PDQ 2007a; NCCN 2007a). Sunitinib also inhibits several other tyrosine kinases, which may contribute to its activity in RCC and which may eventually prove to be beneficial in the treatment of other types of tumors. Although sorafenib and sunitinib inhibit many of the same receptor tyrosine kinases, there are some differences in selectivity, which may account for efficacy differences against certain malignancies.

Three trials evaluated the efficacy of sunitinib in advanced RCC. Two studied sunitinib in the second-line setting (Motzer et al. 2006a, 2006b) and one compared sunitinib to interferon-alfa as first-line therapy (Motzer et al. 2007). Both trials that studied sunitinib in the second-line setting were single-arm, phase II trials in patients with metastatic RCC whose disease had progressed or who had experienced unacceptable toxicity from one cytokine-based therapy. Patients received sunitinib 50 mg orally daily for 4 weeks followed by 2 weeks

off in 6-week cycles. Dose escalation to 75 mg daily in the absence of toxicity, or dose reduction to 25 mg daily for toxicity, was allowed during the trial. The first study (n=65) evaluated objective response using RECIST criteria as the primary endpoint. Time to progression and median survival were secondary endpoints. Forty percent (95% CI: 28–53%) of patients in this study achieved an objective response. The median time to progression was 8.7 months (95% CI: 5.5–10.7) and median survival was 16.4 months (95% CI: 10.8–[not yet attained]). In the second study (n=109), objective response rate (as measured by an independent evaluator using RECIST criteria) was defined as the primary endpoint, and progression-free survival and overall survival were secondary endpoints. At the time of the independent third-party assessment, 34% (95% CI: 25–44%) of patients achieved a partial response, the median progression-free survival was 8.3 months (95% CI: 7.8–14.5), and the median survival had not yet been reached. The investigator-reported overall response rate was 44% (95% CI: 34–53%). In a pooled analysis of both trials (n=169) the median progression-free survival was 8.2 months (95% CI: 7.8–10.4).

A third trial evaluated sunitinib in patients with metastatic clear-cell RCC as a first-line therapy. The trial was a large (n=750) phase III, international, randomized, controlled, open-label trial that compared sunitinib to interferon alfa. Patients were randomized in a 1:1 ratio to receive either sunitinib 50 mg orally daily for 4 weeks followed by 2 weeks off every 6-week cycle, or interferon-alfa 9 million units given subcutaneously 3 times per week. The primary endpoint was progression-free survival. Response rate (measured by an independent third party using RECIST criteria) and overall survival were reported as secondary outcomes. Median progression-free survival was 11 months (95% CI: 10–12) for sunitinib versus 5 months (95% CI: 4–6) for interferon alfa. The objective response rate was significantly higher in the sunitinib group than in the interferon alfa group (31% versus 6%, $p < 0.001$). Neither treatment arm had reached median overall survival at the time of the analysis.

Sorafenib and Sunitinib as Adjuvant Therapy

There is currently no evidence of improved survival or reduced recurrence of adequately resected RCC with any systemic therapy in the adjuvant setting. A new study is now recruiting patients that will assess whether sorafenib

or sunitinib prevent or delay recurrences. The Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma trial (ASSURE) is a phase III study sponsored by the National Cancer Institute (NCI). This randomized, double-blind trial is comparing the efficacy of sorafenib versus sunitinib versus placebo in patients with locally advanced RCC after radical or partial nephrectomy. The primary endpoint is disease-free survival, and overall survival is a secondary endpoint. There is currently no evidence available from this trial, so there will be no further discussion of this off-label indication in this Assessment.

Gastrointestinal Stromal Tumors.

Gastrointestinal stromal tumors (GIST) are classified as soft tissue sarcomas. GIST is one of the rarest forms of soft-tissue sarcoma. The American Cancer Society estimates 9,220 new cases and 3,560 deaths from soft-tissue sarcomas are expected in the U.S. in 2007 (PDQ 2007b; NCCN 2007b). The size, location and the mitotic rate of the tumor are important prognostic indicators in GIST. Larger tumors with a high mitotic rate have a higher risk of recurrence. Surgery is the primary treatment for localized or potentially resectable GIST lesions; however, surgery does not routinely cure GIST. Approximately 85% of patients are candidates for complete resection at initial diagnosis, but at least 50% of these subsequently develop recurrence or metastasis. The corresponding 5-year survival rate is about 50%. In patients with high-risk GIST, the median time to recurrence after resection is about 2 years. GIST is resistant to conventional cytotoxic chemotherapy. In recurrent, unresectable, or metastatic GIST, continuous therapy with imatinib (Gleevec®), a tyrosine kinase inhibitor, has produced a durable clinical benefit in most patients (PDQ 2007b; NCCN 2007b).

GIST tumors express a transmembrane growth factor receptor with intracellular tyrosine kinase activity. Overexpression of this growth factor is thought to be the principal oncogenic driver in these tumors. This growth factor receptor, called c-KIT (CD117) or stem-cell factor receptor, is mutated in 80 to 85% of cases. The specific set of CD117 mutations play a role in tumor response to tyrosine kinase inhibitors targeting this growth factor. Imatinib (Gleevec®), the first therapy shown to target this receptor, is approved for patients with KIT- (CD117-) positive, unresectable and/or metastatic malignant gastrointestinal stromal

tumors (GIST). In a single open-label trial, patients were randomized in a 1:1 ratio to receive either imatinib 400 mg or 600 mg daily for up to 36 months. Objective tumor response rate (based on SWOG criteria) was the primary outcome of the study. Median duration of response was reported as a secondary outcome. Of the 147 patients enrolled in the study, 99 patients (67.3%; 95% CI: 59–75) were shown to have a tumor response. A complete response was observed in 1 patient (0.7%). There was no difference in response between the two imatinib doses. The median duration of response was 118 weeks (95% CI: 96–not attained)]. No controlled trials have demonstrated a benefit in survival or improvement in disease-related symptoms (Novartis 2007).

Some tumors have primary resistance to imatinib as a result of specific KIT mutations. Resistance to imatinib may also develop during therapy. Progression of disease while on imatinib therapy may indicate resistance. There is some evidence that patients with exon 9 mutations and advanced GIST may benefit from higher doses of imatinib (i.e., 800 mg). In a recent phase III trial, treatment with imatinib 800 mg daily significantly improved progression-free survival (relative risk reduction, 61%; $p=0.0015$) when tumors expressed an exon 9 mutated KIT (NCCN 2007b). When tumors without this mutation become resistant to imatinib, an alternative therapy may be indicated.

Sunitinib in GIST

In January 2006, sunitinib (Sutent®, Pfizer 2007), was approved by the FDA for the treatment of GIST after disease progression on or intolerance to imatinib. As noted, sunitinib is classified as a multitargeted tyrosine kinase inhibitor. Sunitinib has demonstrated activity against stem-cell factor receptor (c-KIT), a growth factor receptor that is overexpressed in GIST. Sunitinib also inhibits several other tyrosine kinases which may contribute to its activity in GIST and which may eventually prove to be beneficial in the treatment of other types of tumors.

Two trials support the effectiveness of sunitinib as second-line therapy for GIST (Sutent®, Pfizer; February 2007). The first is a phase III randomized, double-blind, placebo-controlled trial in 312 patients with unresponsive tumors or who were intolerant to imatinib. Patients were randomized in a 2:1 ratio to sunitinib 50 mg daily for 4 weeks, followed by 2 weeks off therapy

(4/2 schedule), in a series of 6-week cycles, or to placebo (identical dosing schedule). The primary endpoint was time to tumor progression (TTP). Progression-free survival (PFS) was a secondary endpoint. Patients taking sunitinib had a statistically longer TTP than those taking placebo (27.5 weeks versus 6.4 weeks; HR 0.33, 95% CI: 0.23–0.47; $p<0.001$). PFS was also superior to placebo (24.6 weeks versus 6.4 weeks; HR 0.33, 95% CI: 0.24–0.45; $p<0.001$). The second study was a single-arm, dose escalation study in patients with GIST who had progression of disease on or intolerance to imatinib. Results were reported on patients who received sunitinib 50 mg on the 4/2 treatment schedule. A partial treatment response was reported in 5 out of 55 patients (9.1%; 95% CI: 3–20%).

Sorafenib in GIST

There is an ongoing phase II trial that is designed to evaluate the efficacy of sorafenib in patients that progressed during or after treatment with imatinib and sunitinib. The primary outcome of the trial is objective tumor response rate (partial and complete response). PFS and overall survival will be followed as secondary endpoints. There is currently no evidence to support conclusions for this off-label indication so there will be no further discussion regarding the use of sorafenib in GIST in this Assessment.

Methods

Search Methods

MEDLINE® was searched via PubMed using the terms “Nexavar” or “sorafenib” (as a text word or MeSH® substance name), and “Sutent” or “sunitinib” (as a text word or MeSH® substance name), and indexed as a clinical trial. Search was performed through October 2007, limited to English-language articles on human subjects. Electronic search was supplemented with online searches of abstracts presented at the 2007 meeting of the American Society of Clinical Oncology (ASCO).

Study Selection

Studies were selected for inclusion in the Assessment if they were:

- full-length, peer-reviewed articles published in an English-language journal; and
- studied cancers other than advanced renal cell carcinoma (RCC) or gastrointestinal stromal tumors (GIST); and

- reported on at least one relevant efficacy outcome (response rate; overall, progression-free, or disease-free survival) and treatment-related mortality.

To provide more complete information, data from interim analyses of phase III trials presented at ASCO were also abstracted and included in evidence tables, if slides were available online.

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association's Medical Advisory Panel (MAP) on October 17, 2007. To maintain the timeliness of the scientific information in this Assessment, literature search updates were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the text and tables where appropriate. There were no studies that would change the conclusions of the Assessment.

Overview of the Review

We selected potential off-label indications based on currently open, phase III trials for the given study drug as indexed on the National Cancer Institute's website (available online at: <http://www.cancer.gov/clinicaltrials/search>). For sorafenib, these indications included: hepatocellular carcinoma (HCC), malignant melanoma, squamous cell cancer of the head and neck (SCCHN), non-small cell lung cancer (NSCLC), and adjuvant therapy in renal cell carcinoma (RCC). For sunitinib, these include breast cancer, colorectal cancer (CRC), NSCLC, and adjuvant therapy in RCC. We added GIST as an indication of interest for sorafenib since it is a labeled indication for sunitinib and since sorafenib is known to inhibit the c-KIT tyrosine kinase overexpressed in GIST and targeted by imatinib and sunitinib. Table 2 summarizes the findings of the literature search.

We identified a total of 201 records on sorafenib and 176 on sunitinib. Upon review of these records (titles and abstracts), we found a total

Table 2. Literature Search Results

Indication	Single-arm Trials	Comparative Trials	Found Evidence to Include in Review?
sorafenib			
Hepatocellular carcinoma (HCC)	1 (published)	1 (unpublished)	Yes
Malignant melanoma	0	1 (unpublished)	Yes
Squamous cell cancer of the head and neck (SCCHN)	1 (published)		Yes
Non-small cell lung cancer (NSCLC)	0	0	No
Gastrointestinal stromal tumor (GIST)	0	0	No
Adjuvant therapy/renal cell carcinoma (RCC)	0	0	No
sunitinib			
Breast cancer	0	0	No
Colorectal cancer (CRC)*	0	0	No
Non-small cell lung cancer (NSCLC)	0	0	No
Adjuvant therapy/renal cell carcinoma (RCC)	0	0	No

*See footnote 4, next page

of 4 studies that met selection criteria for sorafenib and none for sunitinib. Both published sorafenib trials were single-arm, uncontrolled studies. The two comparative trials were unpublished studies presented at ASCO in June 2007. Evidence that met study selection criteria was available on 3 indications for sorafenib, including hepatocellular carcinoma, malignant melanoma, and squamous cell cancer of the head and neck.

No studies on sorafenib met selection criteria in the treatment of:

- non-small cell lung cancer (NSCLC),
- gastrointestinal stromal tumor (GIST), or
- adjuvant therapy in renal cell carcinoma.

There also were no studies with sunitinib that met selection criteria in the treatment of:

- breast cancer,
- colorectal cancer⁴,
- non-small cell lung cancer, or
- adjuvant therapy in renal cell carcinoma.

Since there is insufficient evidence to draw conclusions on health outcomes in these conditions, they are not discussed further in this Assessment.

Background on Included Indications

Advanced Hepatocellular Carcinoma

The American Cancer Society estimates 19,160 new cases and 16,780 deaths from liver and intrahepatic bile duct cancer are expected in the U.S. in 2007 (PDQ 2007c; NCCN 2007c). Although hepatocellular carcinoma (HCC) is relatively uncommon in the U.S., the incidence is increasing. Hepatitis B and hepatitis C infection appear to be the primary cause of hepatocellular carcinoma worldwide. Studies indicate that the Raf-regulated kinase pathway has a role in HCC. Hepatitis C core virus proteins trigger an increase in basal Raf-1 activity in hepatocytes, which increases the risk of neoplastic transformation. Vascular endothelial growth factor (VEGF) also plays a role in augmenting the development and metastasis of HCC (Abou-Alfa et al. 2006).

Tumor staging is based on American Joint Committee of Cancer (AJCC) criteria. Tumors are classified as stage I, II, IIIa, IIIb, IIIc, and IV. For purposes of treatment, tumors are grouped as localized and resectable, localized and unresectable, or advanced (metastatic).

For resectable tumors, partial hepatectomy is the primary treatment option. Liver transplantation may also be an option, depending on the size and location of the tumor. For localized and locally advanced unresectable tumors, systemic chemotherapy, regional chemotherapy (chemoembolization), and/or labeled or radio-labeled antibodies have been used (PDQ 2007c; NCCN 2007c). There is currently no standardized therapy for patients with advanced metastatic liver cancer. Systemic therapy with conventional cytotoxic chemotherapy drugs has resulted in few responses and has shown no clear survival benefit (Bartlett et al. 2005).

Advanced Melanoma

The American Cancer Society estimates 59,940 new cases and 8,110 deaths from melanoma are expected in 2007. It is the fifth most common malignancy in men and the sixth most common malignancy in women. The median age at diagnosis is 45 to 55 years (PDQ 2007d; American Cancer Society 2007). Staging of melanoma uses the American Joint Cancer Committee (AJCC) Tumor-Node-Metastasis (TNM) system (for details, see PDQ 2007d; NCCN 2007d). Approximately 82% to 85% of patients present with localized disease (stage I or II), 10% to 13% with regional disease (stage III), and 2% to 5% with distant metastatic disease (stage IV). Metastatic melanoma has a poor prognosis. The 5-year survival rate for patients with distant metastatic melanoma is less than 10%.

The primary treatment for melanoma is surgical excision and, when necessary, resection of affected lymph nodes. For patients with unresectable stage III and stage IV melanoma (metastatic) consensus is lacking on choice of chemotherapy regimen, which is likely due to poor responses to these agents. Dacarbazine or temozolomide have both shown some activity in treating melanoma and may be used alone

⁴ As this Assessment went to press, a report was published from a Phase II trial of sunitinib for metastatic colorectal cancer that failed standard therapy (Saltz et al. 2007). The study stratified patients by whether they had (group 1; n=43) or had not (group 2; n=41) previously received bevacizumab. Only one patient (from group 1) achieved a partial response, and 15 patients (2 from group 1, 11 from group 2) achieved stable disease for ≥ 22 weeks. Median time to progression was 2.2 and 2.5 months, respectively, in groups 1 and 2. The authors concluded that "sunitinib did not demonstrate a meaningful single-agent objective response rate in colorectal cancer refractory to standard chemotherapy." Data are presently unavailable from studies on sunitinib in combination with standard regimens for metastatic colorectal cancer.

or in combination (PDQ 2007; NCCN 2007). These agents have demonstrated response rates of 10 to 20% with median durations of response of 3 to 4 months. Alternately, high-dose interleukin-2 (IL-2) is FDA-approved for use in treating metastatic melanoma (Proleukin®; Chiron 2000). Overall response rates with IL-2 are in the range of 12 to 21%; however, the incidence of toxicity is high with this regimen. Combination chemotherapy regimens such as CVD (dacarbazine plus cisplatin and vinblastine) have also been studied, but have not been found superior to dacarbazine alone. Combination of CVD with IL-2 (biochemotherapy) appears to improve response rates, but with much greater frequency and severity of toxicity. Attempts to limit the toxicity of this regimen by using lower doses of IL-2 have resulted in no additional benefit over CVD alone (PDQ 2007d; NCCN 2007d). Drugs that inhibit tyrosine kinases (those with activity against Raf-1) are currently being investigated in the treatment of malignant melanoma because increased signaling via the RAF/MEK/ERK pathway is thought to contribute to melanoma growth, invasion, and metastasis.

Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

An estimated 39,250 new cases of oral cavity, pharyngeal, and laryngeal cancers were expected in 2005. The estimated number of deaths from head and neck cancers in the U.S. in 2005 was expected to be 11,090 (NCCN 2007e). These cancers typically begin in the squamous cells that line the mucosal surfaces of the head and neck. Prognosis depends on the tumor site, tumor bulk, and the degree of infiltration.

The best predictive factor for survival in head and neck cancer is stage at diagnosis. The American Joint Committee on Cancer (AJCC) classifies head and neck tumors as either stage I, II, III, IVA, IVB, or IVC. Stage I and II tumors are usually small without any nodal involvement. They have a good prognosis and are treated with either surgery or radiotherapy (cure rates of 75% to 95%). Approximately 60% of patients present with locally advanced (stage III and IV) disease at diagnosis. Advanced stage disease includes large primary tumors which may invade local tissues and/or spread to lymph nodes. Patients with advanced disease have a poorer prognosis than those diagnosed with early stage tumors. Survival rates are typically 50% of those for stage I or II disease.

The cure rate for advanced head and neck cancers is low.

Treatment of advanced disease typically involves combinations of surgery, radiation, and/or chemotherapy. Cisplatin-based chemotherapy in combination with radiation is the current standard of care for the treatment of unresectable head and neck cancers (NCCN 2007). Cisplatin-based regimens improve relapse-free survival; however, they have not demonstrated any effect on overall survival. The majority of squamous cell carcinomas of the head and neck overexpress the kinases Raf and EGFR. Drugs that target these pathways are being investigated as possible therapies for these cancers. Cetuximab (Erbix®), a monoclonal antibody that binds to EGFR receptors and thereby inhibits its activity, was recently approved by the FDA for treatment of head and neck carcinomas. It is indicated for patients with locally or regionally advanced disease in the first-line setting when used in combination with radiation therapy, or in the second-line setting (after failure of platinum-based therapy) as a single agent (Erbix®; ImClone/Bristol-Myers Squibb 2007).

Formulation of the Assessment

Patient Indications

Patient indications included in this review of evidence are:

- sorafenib for patients with advanced hepatocellular carcinoma;
- sorafenib for patients with unresectable Stage III or Stage IV melanoma; and
- sorafenib for patients with recurrent or metastatic squamous cell carcinoma of the head and neck.

Technologies to be Compared

For each indication, outcomes of sorafenib will be compared with outcomes of one or more treatment regimens presently recommended for the same disease stage in the National Comprehensive Cancer Network (NCCN) guidelines or the National Cancer Institute's PDQ summary of treatment options. Sorafenib may be used alone or in combination with other antineoplastic drugs.

Health Outcomes

Primary health outcomes of interest include overall, progression-free, or disease-free survival; adverse effects attributable to sorafenib;

and treatment related mortality. Response rates (overall responses, as the sum of complete and partial responses) are a secondary outcome.

Specific Assessment Question

For each of the above malignancies, does treatment with sorafenib improve health outcomes compared with presently recommended treatment regimen(s)?

Review of Evidence

Advanced Hepatocellular Carcinoma

The literature search identified one published single-arm phase II trial that studied sorafenib in patients with unresectable hepatocellular carcinoma (HCC). In addition, a search of the American Society of Clinical Oncology (ASCO) website identified one unpublished randomized placebo-controlled phase III trial in patients with advanced HCC. A full slide set of these data, which was presented at the June 2007 ASCO meeting, is available online at: http://www.asco.org/portal/site/ASCO/menuitem.64cfbd0f85cb37b2eda2be0aee37a01d/?vgnnextoid=09f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=vm_session_presentations_view&index=y&confID=47&trackID=201&sessionID=407 (Llovet et al. 2007; Table 3).

Abou-Alfa et al. (2006) reported a single-arm trial on use of sorafenib as monotherapy in patients with unresectable HCC. It is unknown whether patients with central nervous system (CNS) metastasis were included in the study. Patients in the trial received sorafenib 400 mg orally twice daily (n=137). Tumor response, assessed using bidimensional tumor measurements according to modified WHO criteria, was the primary endpoint. Independent radiologic assessment of tumor response was performed for the majority (77%) of patients. Time-to-progression (TTP) and median overall survival were reported as secondary endpoints. The arm had macroscopic vascular invasion and/or extrahepatic spread of their tumor. It is not reported whether patients with metastasis to the central nervous system (CNS) were included in the study. Patients were randomized in a 1:1 ratio to receive sorafenib 400 mg twice a day or placebo. Primary endpoints included median overall survival and time to symptomatic progression (TTSP).

A data monitoring committee recommended stopping the trial to allow crossover to active

treatment after an interim analysis showed a statistically significant improvement in overall survival (HR: 0.69; 95% CI: 0.55–0.88; p=0.00058). Median overall survival was 10.7 months (46.3 weeks; 95% CI: 40.9–57.9) for sorafenib and 7.9 months (34.4 weeks; 95% CI: 29.4–39.4) for placebo. TTP (done by independent central review) was 5.5 months (24.0 weeks; 95% CI: 18.0–30.0) and 2.8 months (12.3 weeks; 95% CI: 11.7–17.1) for sorafenib and placebo, respectively (Table 3, Llovet et al. 2007). Overall tumor response was 2.3% in the sorafenib treatment arm and 0.7% in the placebo arm. There were no complete responses. Severe hand-foot skin reactions (grade III or IV) were observed in 8% and <1% of patients, respectively. Other severe adverse events (grade III or IV) that occurred with a greater incidence in the sorafenib versus placebo group included diarrhea (8% versus 2%).

Advanced Melanoma

The literature search identified no published trials that studied sorafenib in patients with advanced melanoma. A search of the American Society of Clinical Oncology (ASCO) website identified one unpublished randomized placebo-controlled phase III trial in patients with advanced melanoma in the second-line setting. A full slide set of these data, which was presented at the June 2007 ASCO meeting, is available online at: http://www.asco.org/portal/site/ASCO/menuitem.64cfbd0f85cb37b2eda2be0aee37a01d/?vgnnextoid=09f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=vm_session_presentations_view&index=y&confID=47&trackID=9&sessionID=385.

The unpublished trial (Agarwala et al. 2007) presented at the June 2007 ASCO meeting reports on a multicenter randomized, double-blind, placebo-controlled, phase III trial (n=270) in patients with unresectable stage III or stage IV (metastatic) melanoma who progressed on dacarbazine or temozolomide. Patients with active metastasis to the brain were excluded from the study. Patients received carboplatin plus paclitaxel on day 1 with (n=135) or without (n=135) sorafenib 400 mg twice daily on days 2 through 19 of each 21-day cycle. The primary endpoint was PFS (reported by independent assessors using RECIST criteria). There was no difference in PFS, tumor response, or median overall survival observed between the two treatment groups (Table 3, Agarwala et al. 2007). Severe adverse effects (grade 3

Table 3. Outcomes of Sorafenib for Hepatocellular carcinoma, Melanoma, and Squamous Cell Carcinoma of the Head and Neck

Study/ Design	Disease Stage	Regimens Compared	n	ORR (CR/PR)	TTP	PFS at 6 mos	Median PFS	OS at 1 year	Median OS	Diarrhea 3/4	Hand/foot			Tx-related Deaths	
											Skin Rxn Grd 3/4	Fatigue Grd 3/4	Bleeding Grd 3/4		
Llovet et al. 2007; ASCO slides	Advanced hepatocellular carcinoma; no prior systemic treatment	sorafenib	299	2.3% (0/2.3%)	5.5 mos	~ 45%*	not reported	~ 45%	10.7 mos	8%	8%	10%	6%	not reported	
		placebo	303	0.7% (0/0.7%)	2.8 mos	~ 22%*	not reported	~ 33%	7.9 mos	2%	< 1%	15%	9%	not reported	
						HR=0.58 (0.44- 0.74) log rank p=0.000007	* progression-free probability	HR=0.69 (0.55- 0.88) log rank p=0.00058	all grade 3	all grade 3					
Abou-Alfa et al. 2006; published phase II (no controls)	Advanced hepatocellular carcinoma; no prior systemic treatment	sorafenib	137	2.2% (0/2.2%)	5.5 mos	not reported	not reported	not reported	9.2 mos	8%	5.1%	9.5%	none reported	0.7% (intracranial hemorrhage)	
											grade 3	grade 3	grade 3		
Agarwala et al. 2007; ASCO slides	Advanced stage III & IV melanoma; no brain mets; 2nd line Tx	carboplatin + paclitaxel + sorafenib	135	12% (0/12%)	not reported	32%	4.1 mos	not reported	9.8 mos	8%	7%	16%	none reported	1.5% (28% thrombo- cytopenia)	
		carboplatin + paclitaxel	135	11% (0/11%)	not reported	29%	4.2 mos	not reported	9.8 mos	3%	0%	10%	none reported	none reported (12% thrombo- cytopenia)	
					NS	NS	NS								
Elser et al. 2007; published phase II (no controls)	Squamous cell carcinoma of the head and neck (recurrent or metastatic) or nasopharyngeal carcinoma; 1st or 2nd line	sorafenib	28	3.7% (0/3.7%; of n=27 evaluabile); 95% CI: 0.1–19%	1.8 mos 95% CI: 1.6–3.4	not reported	not reported	11.6% 95% CI: 4.0–33.5	4.2 mos 95%CI: 3.6–8.7	none reported	4%	15%	none reported	none reported	
											grade 3	grade 3			

or 4) occurring with greater frequency in the sorafenib treatment arm include thrombocytopenia (28% versus 12%), fatigue (16% versus 10%), hand-foot skin reaction (7% versus 0%), and diarrhea (8% versus 3%). There were 2 deaths in the sorafenib plus carboplatin plus paclitaxel treatment arm that were possibly related to treatment.

Advanced Squamous Cell Head and Neck Carcinoma

The literature search identified one published single-arm phase II trial that studied sorafenib in patients with recurrent or metastatic squamous cell cancer of the head and neck or nasopharyngeal carcinoma (Table 3, Elser et al. 2007). Sorafenib 400 mg twice a day was administered to all patients (n=28) on a continuous basis. Fourteen patients (52%) received sorafenib as first-line therapy for their recurrent or metastatic disease, and 13 patients (48%) received sorafenib as a second-line treatment. One patient withdrew treatment prior to receiving treatment and was not assessable. The primary endpoint of the study was objective response rate based on RECIST criteria. The objective response rate was 3.7% (95% CI: 0.1–19.0). There were no complete responses. The median TTP was 1.8 months (95% CI: 1.6–3.4) and median overall survival was 4.2 months (95% CI: 3.6–8.7). Severe adverse events (grade 3) reported during the trial include fatigue (15%) and hand-foot skin reaction (4%).

Discussion

Advanced Hepatocellular Carcinoma

It is widely acknowledged that there are no effective therapies for advanced HCC. Recently sorafenib, a multi-targeted kinase inhibitor, was shown to improve survival in this disease in a large, randomized, placebo-controlled trial (SHARP trial; Llovet et al. 2007). This is the first time that any medication has shown benefit in the treatment of advanced HCC. Results from an additional trial that studied sorafenib in advanced HCC were recently released (press release available at: http://www.onyx-pharm.com/wt/page/pr_1188237032). This large phase III trial, conducted in Asia, reports improvement in TTP, PFS, and median OS with sorafenib versus placebo. Although results have not yet been published, preliminary reports appear to support the benefit of sorafenib in advanced HCC.

Sorafenib appears to be well-tolerated relative to cytotoxic chemotherapy. The primary severe adverse effects (grade 3 and 4) observed in clinical trials include fatigue, hand-foot skin reactions and diarrhea. Other adverse events include hypertension, mucositis, sensory neuropathy, and hemorrhage (Nexavar®, Bayer/Onyx; February 2007). Grade 3 and 4 reactions were managed by interrupting therapy until toxicity improved to grade 2 or better, at which point sorafenib was reintroduced at a lower dose. Therapy was permanently discontinued if recovery time was more than three weeks, or if adverse effects worsened after reintroduction of sorafenib. Clinical trials were not large enough to detect less common adverse events; additional risks may be found through large, well-done studies and through post-marketing studies.

At this time, sorafenib has only been studied in advanced HCC as monotherapy. It is possible that inhibition of tumor angiogenesis may make these tumors more sensitive to treatment with conventional chemotherapy. In the future, there may be trials that use this approach. At this point in time, however, sorafenib in combination with conventional chemotherapy has not been studied.

Advanced Melanoma

As a second-line treatment for advanced melanoma, available evidence shows that sorafenib does not provide any benefit. There is an ongoing trial studying sorafenib in the first-line setting for the treatment of advanced or metastatic melanoma (ECOG-E2603; protocol available online at: <http://clinicaltrials.gov/ct/show/NCT00110019>). This phase III trial is studying carboplatin plus paclitaxel with or without sorafenib. The primary endpoint is overall survival. This is very different from the trial described in this Assessment, which was conducted in patients who had progressive disease after at least one cycle of dacarbazine or temozolomide.

Recurrent or Metastatic Squamous Cell Head and Neck Carcinoma

The one published trial studying sorafenib in recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) does not allow conclusions because of its single-arm design. There are no phase III trials in progress that are studying sorafenib in SCCHN.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether off-label uses of sorafenib or sunitinib meet the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

The U.S. Food and Drug Administration (FDA) approved sorafenib (Nexavar[®]) in December 2005 to treat advanced renal cell carcinoma (RCC). In January 2006, the FDA approved sunitinib (Sutent[®]) to treat advanced RCC, and to treat gastrointestinal stromal tumors (GIST) when there is disease progression on or intolerance to imatinib (Gleevec[®]). Use of sorafenib to treat patients with hepatocellular carcinoma, melanoma, non-small cell lung cancer, squamous cell head and neck carcinoma or GIST; use of sunitinib to treat patients with colorectal, non-small-cell lung or breast cancers; and use of either drug for adjuvant therapy of resected RCC, all are off-label indications.⁵

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

This Assessment reviews evidence on health outcomes of sorafenib and sunitinib for off-label indications that either have been reported in published studies or currently are undergoing phase III trials. For off-label indications of sunitinib, no studies were found that met selection criteria for this Assessment.⁶

Available evidence on outcomes of sorafenib for advanced hepatocellular carcinoma (HCC) included one published single-arm study (n=137) and one unpublished, presentation of a randomized, double-blind, placebo-controlled phase III trial (n=602) from the June 2007 ASCO meeting. The comparative trial reports

a statistically significant survival advantage for sorafenib over placebo from an interim analysis reviewed by an independent data monitoring committee (DMC) that authorized early release of results and terminated the study with controls crossed over to active therapy. The single-arm trial supports these results based on similar improvements in TTP and OS. No other systemic therapy for advanced HCC has demonstrated a survival benefit for this rapidly fatal malignancy. In light of this unmet medical need and DMC involvement in analysis of the RCT results, this evidence is judged sufficient to permit conclusions on outcomes of sorafenib for advanced HCC.

One unpublished presentation of a randomized, double-blind, placebo-controlled phase III trial (n=270) from the June 2007 ASCO meeting provides the only available evidence on outcomes of sorafenib for second-line therapy of advanced melanoma. This evidence was judged insufficient to permit conclusions. One published, single-arm trial (n=28) provides the only available evidence on outcomes of sorafenib as first- or second-line therapy for recurrent or metastatic squamous cell head and neck cancer. This evidence was judged insufficient to permit conclusions. No studies that met this Assessment's selection criteria were found for any other off-label indications for sorafenib.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

In the only reported RCT on HCC, sorafenib improved median TTP (5.5 versus 2.8 months; HR=0.58, 95% CI: 0.44–0.74) and median OS (10.7 versus 7.9 months; HR: 0.69, 95% CI: 0.55–0.88) compared with placebo. Adverse effects included absolute increases of 6% in grade 3 or 4 diarrhea and 7–8% in grade 3 or 4 hand/foot skin reactions. Median OS was 9.2 months and median TTP was 5.5 months in the published single-arm uncontrolled study. Advanced hepatocellular carcinoma has been unresponsive to chemotherapy; no agent has shown a survival benefit in treating this tumor.

⁵ On November 19, 2007, as this Assessment went to press, FDA approved a supplemental new drug application to add advanced hepatocellular carcinoma as a labeled indication for sorafenib.

⁶ As this Assessment went to press, a report was published from a Phase II trial of sunitinib for metastatic colorectal cancer that failed standard therapy (Saltz et al. 2007). Results of this trial do not change the Assessment's conclusions. Please refer to the footnote 4 for further details.

The available evidence suggests that sorafenib is the first agent to improve overall survival in this disease, relative to best supportive care.

Since evidence is lacking, it cannot be determined whether sorafenib improves outcomes, and is at least as good as alternatives, for patients with advanced melanoma, advanced squamous cell head and neck cancer, or any other off-label indication. For the same reason, it cannot be determined whether sunitinib improves outcomes, and is at least as good as alternatives, for patients with any off-label indication.

5. The improvement must be attainable outside the investigational setting.

The outcomes of sorafenib for advanced HCC reported from the multicenter RCT should be achievable outside the clinical trial setting by clinicians experienced with management of HCC patients. Whether sorafenib improves outcomes for patients with any other off-label indication, and whether sunitinib improves outcomes for patients with any off-label indication, has not yet been determined in the investigational setting.

For the reasons outlined above, sorafenib meets the TEC criteria as a treatment for advanced hepatocellular carcinoma. Sorafenib does not meet the TEC criteria for any other off-label uses, including but not limited to advanced melanoma, unresectable or metastatic squamous cell carcinoma of the head and neck, non-small cell lung cancer (NSCLC), gastrointestinal stromal tumor (GIST), or as adjuvant therapy for renal cell carcinoma. Sunitinib does not meet the TEC criteria for any off-label use, including but not limited to treatment for advanced or metastatic breast cancer, metastatic colorectal cancer, advanced or metastatic NSCLC, or as adjuvant therapy for renal cell carcinoma.

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