Sunitinib (Sutent, Pfizer) is an orally administered inhibitor of protein tyrosine kinases associated with the intracellular portions of certain transmembrane receptor molecules. It 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). Sunitinib was approved by the U.S. Food and Drug Administration (FDA) via its accelerated drug approval process for the treatment of advanced renal cell carcinoma and also for treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate (Gleevec®, Novartis).

Use of sunitinib may be considered medically necessary for the treatment of advanced renal cell carcinoma (RCC)* and gastrointestinal stromal tumors (GIST) after disease progression on or intolerance to imatinib.* Use of sunitinib is considered investigational for all other oncologic indications including, but not limited to treatment of breast cancer, colorectal cancer, or non-small-cell lung cancer (NSCLC); or as adjuvant therapy for resected RCC.

*FDA approved indications
Off-label use will be evaluated in consonance with the Blue Cross of Idaho off-label use policy. **Rationale**

The policy is based on a 2007 TEC Assessment of off-label indications of sunitinib and sorafenib, a literature search using MEDLINE®, and Sutent® product labeling information for FDA-approved indications.

**Renal Cell Carcinoma**
For the FDA-approved indication of advanced renal cell carcinoma (also referred to in the product information as metastatic renal cell carcinoma or "MRCC"), a randomized, international, multicenter study was conducted in 750 patients with treatment-naïve MRCC. (1) This study compared progression-free survival (PFS) in those receiving sunitinib (n=375) to those receiving interferon alfa (n=375). Patients were randomized 1:1 to receive either 50mg of sunitinib once daily on a schedule of 4 weeks in therapy, 2 weeks off ("Schedule 4/2") or to receive 9 million IU of interferon alfa administered subcutaneously 3 times weekly. Prior treatment included nephrectomy in approximately 90% of patients and radiotherapy in 14% of patients (in both trial arms). At a planned interim, intention-to-treat analysis, a statistically significant advantage for sunitinib was found over interferon alfa assessed by blinded core radiology laboratory. Median PFS was 47.3 (95% CI: 42.6-50.7) versus 22.0 (95% CI: 3.3-8.1), for the experimental and control groups, respectively (both comparisons statistically significant by O'Brien-Fleming stopping boundary and Pearson Chi-square, respectively). Data on overall survival were not mature at the time of interim analysis. This study was subsequently published in the peer-reviewed literature. (2)

The product information (1) also provides data from two single-arm multicenter studies (n=106, n=63) of single-agent sunitinib in patients with cytokine-refractory MRCC (defined as disease progression on or unacceptable treatment-related toxicity from interferon alfa, interleukin-2, or a combination of the two). ORR as assessed by blinded core radiology laboratory for Study 1 (n=106) was 34% (95% CI: 24.7-49.6%). These trials were also published subsequently in the peer-reviewed literature. (3,4)

Gastrointestinal Stromal Tumors

For the FDA-approved indication of gastrointestinal stromal tumors (GIST) in patients intolerant of or unresponsive to imatinib, a two-arm, international, randomized, double-blind, placebo-controlled study was conducted. (1) Patients with GIST who had disease progression within 6 months (~17% in both trial arms) or longer than 6 months (~79% in both trial arms) after starting imatinib therapy or who were intolerant (~4% in both trial arms) of imatinib were randomized 2:1 to sunitinib or placebo, either with best supportive care. (1) The intention-to-treat population included 312 patients, 207 randomized to sunitinib (50mg daily, Schedule 4/2, as described previously). The primary endpoint was time to tumor progression (TTP). Progression-free survival (PFS) was a secondary endpoint. A planned efficacy and safety analysis was performed after 149 TTP events. Patient taking sunitinib has a statistically longer TTP than those taking placebo (27.3 weeks versus 6.4 weeks; HR 0.33; 95% CI: 0.23-0.47; p less than 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 less than 0.001). This trial was published subsequently in the peer-reviewed literature. (5)

The second study was a single-arm, dose escalation study in patients with GIST who had progression of disease on or intolerance to imatinib. (1) Results were reported on patients who received sunitinib 50mg on the 4/2 treatment schedule. A partial treatment response in 5 out of 55 patients (9.1%; 95% CI: 3-20%).

Off-Label Indications

The 2007 TEC Assessment on off-label uses summarized and evaluated evidence on health outcomes of sunitinib for indications reported in published studies or currently undergoing phase III trials. (6) For sunitinib, indications that met this first-level screen included: breast cancer,
colorectal cancer, non-small-cell lung cancer (NSCLC), and adjuvant therapy for resected RCC. However, the literature search found only one study 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 on line) for sunitinib. Published as the Assessment was in press, Saltz and colleagues (7) reported on a Phase II trial of sunitinib for patients with metastatic colorectal cancer that failed standard therapy. 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 sisease for a time of 22 weeks or more. 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 regimens for metastatic colorectal cancer.

An April 2008 search of ClinicalTrials.gov lists 11 active and recruiting Phase III trials of sunitinib, either as single-agent or combination chemotherapy for indications including adjuvant therapy for resected renal cancer, pancreatic islet cell cancer, metastatic colorectal cancer and breast neoplasms.

Lacking evidence from published studies, no conclusions are possible on outcomes of sunitinib to treat breast cancer, colorectal cancer, or NSCLC, or as adjuvant therapy for resected RCC. In addition, 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.

References:


6. 2007 TEC Assessments. Off-label Uses of Sorafenib and Sunitnib (Volume 22, Number 11)

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