

The U.S. Food and Drug Administration (FDA) Approves Bevacizumab for Metastatic Renal Cell Carcinoma

On August 3, the FDA approved bevacizumab (Avastin, Genentech), a humanized monoclonal antibody that blocks vascular endothelial growth factor, in combination with interferon alpha-2a for treatment of renal cell carcinoma that has metastasized. The approval was based on the results of the AVOREN study—a randomized, double-blind, placebo-controlled, phase III study. Study findings demonstrated that progression-free survival (PFS) nearly doubled in patients receiving bevacizumab plus interferon compared to patients who received interferon alone (median PFS, 10.2 and 5.4 months, respectively). No significant differences in overall survival were observed in the 2 groups (23 and 21 months, respectively). Reduction in tumor size was larger in the patients receiving bevacizumab plus interferon (30% vs 12%).

Regulatory authorities in the United States and Europe accepted PFS as the endpoint for approval of bevacizumab for treatment of renal cell carcinoma, the fifth FDA-approved indication for the drug. Bevacizumab alone and in combination is currently being studied in various cancers.

Bendamustine More Effective than Chlorambucil for Advanced Chronic Lymphocytic Leukemia

In a randomized phase III clinical trial reported in the August 3 issue of *Journal of Clinical Oncology*, bendamustine (Treanda, Cephalon) demonstrated significantly higher response rates and longer PFS than chlorambucil. The study randomized 319 previously untreated patients (mean age, 63 years) with advanced stage disease to receive bendamustine (n=162) or chlorambucil (n=157). The safety population comprised 312 patients, as 7 patients did not receive treatment. Patients received bendamustine 100 mg/mg²/day intravenously on days 1 and 2 or chlorambucil 0.8 mg/kg orally on days 1 and 15 (or in smaller doses on days 1, 2, 15, and 16). This treatment cycle was repeated

every 4 weeks for a maximum of 6 cycles. Complete or partial response was observed in 68% of patients receiving bendamustine and 31% of patients receiving chlorambucil. PFS was more than double in patients receiving bevacizumab (21.6 vs 8.3 months).

The analysis of the safety population found a higher incidence of grade 3/4 hematologic adverse events (40% vs 19%) and infections (8% vs 3%) in the bendamustine group compared to the chlorambucil group. The patients were observed for a median of 35 months; however, a longer observation is needed to ascertain differences in overall survival between the groups.

STAT3 Gene is Found to Regulate Cancer Stem Cells in Brain Cancer

Researchers from Tufts University reported in the August 5 issue of *Stem Cells* that the STAT3 gene could be a target for cancer therapy in brain cancer, particularly in glioblastoma multiforme, an aggressive brain tumor with a survival expectancy of 12–14 months (with treatment). The researchers found that inhibiting STAT3 caused the cancer stem cells in glioblastomas to permanently lose their stem cell characteristics, which suggests that STAT3 in fact controls growth and self-renewal of stem cells within glioblastomas. Although STAT3 has been shown to be activated in various human tumors, this is one of the first studies to show that STAT3 regulates cancer stem cells and controls processes that are involved in the 6 stages of cancer (growth, metastasis, angiogenesis, evasion of apoptosis, tissue invasion, and cell immortalization). The researchers isolated cancer cells from surgically removed samples of glioblastoma tumors and treated them with small-molecule inhibitors of STAT3, STA-21, and S3I-201. After a few days of treatment with these inhibitors, cell growth was found to be minimal compared to the growth in the control cultures, and in the STAT-inhibited cultures, proteins that help maintain stem-cell characteristics were turned off. This finding provides evidence that STAT3 will be a good target for cancer therapy.

7th Edition of the TNM Classification of Malignant Tumors is Released

Dr. Peter Goldstraw of the International Association for the Study of Lung Cancer reported at the World Conference on Lung Cancer that the 7th edition of the TNM staging system has been released. The revisions to the previous TNM system are based on contributions from the worldwide lung cancer community, which differs from past staging classifications dictated by a small group of experts, and based on restricted numbers of mostly surgical patients. With the new system, which will now be a singular method of nodal staging, 1 in 6 cancer patients will receive a different staging category.

Some of the key changes to the staging system are detailed below:

- New subcategories of stage T1 (early-stage) disease are based on size: Tumors ≤ 2 cm will be classified as T1a, tumors > 2 cm and up to 3 cm will be classified as T1b. T2 disease will also be subdivided into T2a (tumors > 3 cm and up to 5 cm) and T2b (tumors > 5 cm and up to 7 cm).
- A new category (T3) will be used to describe tumors > 7 cm.
- Patients previously considered T4 because of additional tumor nodules in the same lung as the primary tumor will now be classified as T3. If these patients are node negative, they will be considered to have stage IIB disease.
- Patients with additional tumor nodules in the bilateral lung (previously M1) will now receive a designation of T4, and they will be down-staged from stage IV to stage IIIA.
- The presence of malignant pleural effusions, referred to as “wet IIIBs” and treated as if the patient had disseminated disease, will now be officially staged that way, as stage IV disease.
- Specifically, pleural dissemination will no longer be classified T4, but will fall into a new category (M1a), the same designation given when additional nodules are found in the contralateral lung.
- Distant metastases will be subclassified within M1 as M1b disease.
- Staging changes will include the reclassification of patients with T2b tumors (5–7 cm) who have node-negative disease to stage IIA.
- Patients with T3 tumors (> 7 cm) will be considered to have stage IIB disease if they are node negative, but stage IIIA if they have associated features of M1, listed above.
- The “N” classification within TNM that describes the number of involved lymph nodes will remain unchanged in the 7th edition.

Long-term Use of Tamoxifen Increases Risk of Aggressive Second Breast Cancer

The findings published in the August 25 issue of *Cancer Research* showed that although long-term use of tamoxifen in breast cancer survivors reduces the risk of developing estrogen receptor (ER) positive second breast cancer, it is also associated with a more than 4-fold increase in the risk of developing ER-negative contralateral breast cancer. The study evaluated tamoxifen use in 1,103 breast cancer survivors aged 40–79 years from the Seattle-Puget Sound region who were initially diagnosed with ER-positive breast cancer. The researchers found that while tamoxifen does reduce the occurrence of ER-positive second breast cancer (60%), it also seems to increase the risk of ER-negative second cancer by 440%. Of all patients, 369 developed second breast cancer. These recent findings corroborate the preliminary research performed by Li and colleagues in 2001 that hinted at a link between long-term tamoxifen use and increased risk of ER-negative second cancers. Although this new study demonstrates a strong association between long-term tamoxifen use and increased risk of ER-negative second cancers, the researchers are not suggesting that breast cancer survivors discontinue tamoxifen use.

Escalated-Dose BEACOPP in Patients with Advanced-Stage Hodgkin Lymphoma: Ten-year Follow-up of the GHSG HD9 Study

The HD9 trial of the German Hodgkin Study Group compared 2 doses (baseline and escalated) of the BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) in 1,196 patients with advanced-stage Hodgkin lymphoma. The 10-year follow-up data are reported in the August 24 issue of the *Journal of Clinical Oncology*. Patients enrolled in the study received either 8 cycles of COPP alternating with doxorubicin, bleomycin, vincristine, and dacarbazine (ABVD; arm A); 8 cycles of baseline dose BEACOPP (arm B); or 8 cycles of escalated dose BEACOPP (arm C). The median follow-up was 111 months. At 10 years, freedom from treatment failure (FFTF) was 64%, 70%, and 83%, and overall survival (OS) was 75%, 80%, and 84% for patients in arms A, B, and C, respectively ($P < .001$). FFTF and OS were significantly improved in the escalated dose of BEACOPP compared to the baseline dose. The safety analysis found 74 second malignancies, including acute myeloid leukemia, non-Hodgkin lymphoma, and solid tumors. The results of this 10-year follow-up dispute ABVD as the standard of care for advanced-stage Hodgkin lymphoma.