HEM/ONC News

By Stacey Small

Regorafenib Approved in GIST

In February 2013, the US Food and Drug Administration (FDA) approved regorafenib (Stivarga, Bayer) for the treatment of patients with unresectable metastatic gastrointestinal stromal tumors (GIST) that no longer respond to imatinib (Gleevec, Novartis) and sunitinib (Sutent, Pfizer). Approval was based on results from GRID (GIST-Regorafenib in Progressive Disease), a randomized, phase III trial that involved 199 patients with metastatic and/or unresectable GIST that had become resistant to imatinib and sunitinib. Demetri and associates published results of the trial in the February issue of *The Lancet*. Patients were randomized to receive best supportive care plus regorafenib (160 mg orally once daily on a 3-weeks-on, 1-week-off cycle; 133 patients) or placebo (66 patients). For patients randomized to placebo, crossover to open-label regorafenib was allowed upon disease progression. Eighty-five percent of patients in the placebo arm went on to cross over to regorafenib. Regorafenib treatment resulted in a 3.9-month improvement in progression-free survival, as compared with placebo (4.8 months vs 0.9 months; hazard ratio [HR], 0.27; 95% confidence interval [CI], 0.19–0.39; $P<.0001$). Less than 1% of patients treated with regorafenib experienced adverse events, which included severe bleeding, intestinal perforations, peeling and blistering of the skin, liver damage, extreme hypertension requiring emergency treatment, and heart attacks. The most common adverse events associated with treatment, reported by at least 30% of those treated, included hand-foot syndrome, diarrhea, mucositis, dysphonia, asthenia/fatigue, hypertension, reduced appetite and food intake, and rash.

Sipuleucel-T Delays the Time to First Use of Opioid Analgesics in mCRPC: Retrospective Analysis of the IMPACT Trial

Sipuleucel-T immunotherapy demonstrated significant improvement in overall survival in patients with metastatic castration-resistant prostate cancer (mCRPC) who were enrolled in the phase III IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) trial. Small and associates presented an additional analysis of the IMPACT trial at the 2013 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium (abstract 74). This retrospective analysis evaluated the relationship of sipuleucel-T with time to first use of opioid analgesics (TFOA) in men with mCRPC. Using a Cox regression model and adjusting for baseline prostate-specific antigen (PSA) and lactate dehydrogenase (LDH), the researchers concluded that relative to placebo, sipuleucel-T delayed the TFOA in patients with asymptomatic or minimally symptomatic mCRPC. There were a number of baseline predictors that were significantly associated with a shorter TFOA: higher PSA and alkaline phosphatase levels; younger age; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 versus 0; Gleason score of 8 or higher versus 7 or lower; increased weight; previous primary radiotherapy treatment; and a higher number of bone metastases.

In the February 14, 2013 edition of the *ASCO GU Daily News*, Drs. Ravi Madan and William Dahut of the National Cancer Institute discussed "The Growing Understanding of the Potential Influence of Immunotherapy in Prostate Cancer." In addition to the analysis of the IMPACT trial, several other studies from this year's symposium also suggested that, with the use of immune-based treatments like sipuleucel-T, the tumor growth rate may be slowed over time without leading to marked short-term tumor shrinkage (Figure 1). This effect could yield improved overall survival without improved time to progression (TTP, trajectory A in Figure 1). As such, administering immunotherapies early in the disease process may be the most effective strategy, as it would offer adequate time for any potential effect on tumor growth.

Robust Effects Observed With Bevacizumab Plus Capecitabine in Elderly CRC Patients: Results of the Phase III AVEX Trial

A trend toward a survival benefit was observed for bevacizumab (Avastin, Genentech) plus capecitabine (Xeloda, Roche) in elderly patients with treatment-naïve metastatic colorectal cancer (CRC), according to results from the prospective, international, phase III AVEX (Avastin With Xeloda in the Elderly) trial. Presented at the 2013 ASCO Gastrointestinal Cancers Symposium by Cunningham and colleagues (abstract 337), AVEX was the first phase III trial to prospectively investigate a biologic in elderly patients with metastatic CRC. Although the median age for patients with metastatic CRC is 69 years, older patients remain undertreated. A total of 280 patients aged 70 years or older (mean age, 76 years) with treatment-naïve metastatic CRC and an ECOG PS of 0–2 were enrolled across 10 countries. As

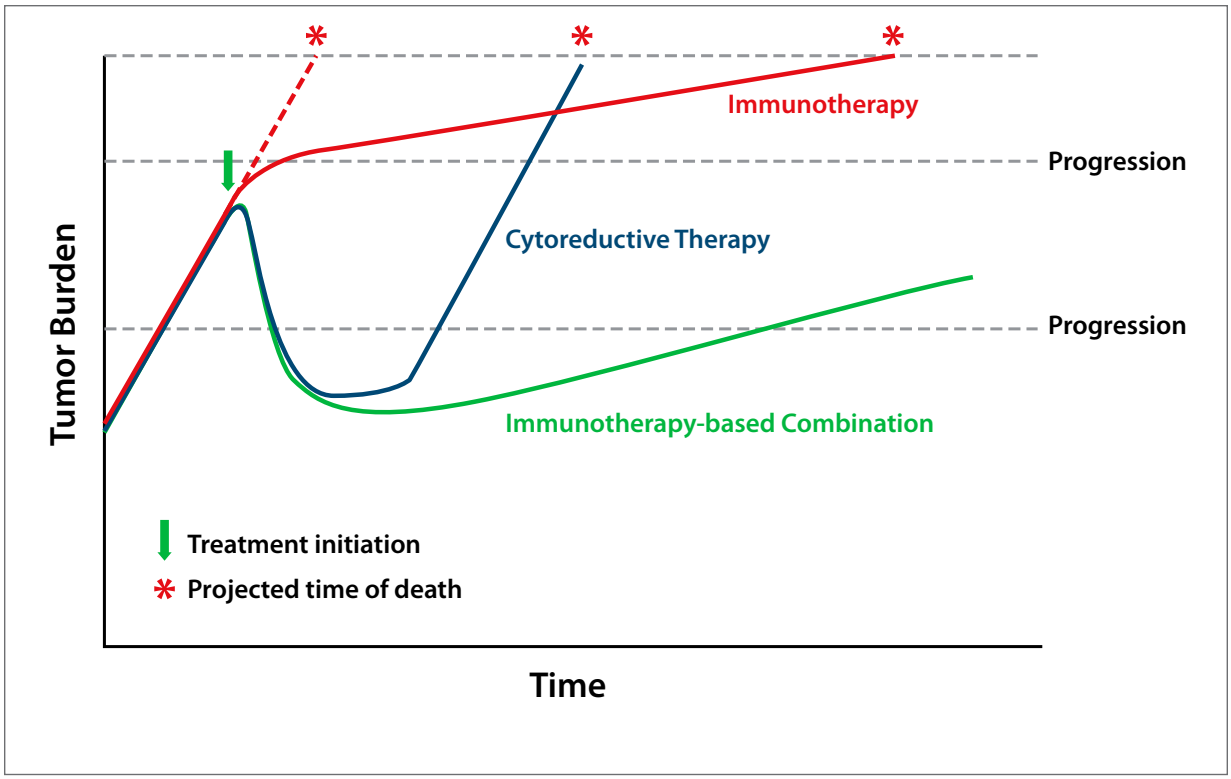

Figure 1. Potential growth-moderating effects of immune-based therapies.

Adapted from Madan RA, Bilusic M, Heery C, et al. Clinical evaluation of TRICOM vector therapeutic cancer vaccines. *Semin Oncol.* 2012;39:296-304, as cited by Madan RA and Dahut WL in the February 14 edition of the *ASCO GI Daily News*.

first-line treatment for metastatic disease, patients were randomly assigned to receive 7.5 mg/kg bevacizumab every 3 weeks plus 1,000 mg/m^2 capecitabine twice daily on days 1–14, or 1,000 mg/m^2 capecitabine alone twice daily on days 1–14. The primary endpoint was progression-free survival; secondary endpoints included overall response rate, time to response, duration of response, overall survival, and safety. The addition of bevacizumab to capecitabine significantly improved progression-free and overall survival. Progression-free survival was 9.1 months for the capecitabine plus bevacizumab arm versus 5.1 months for the capecitabine-only arm (HR, 0.53; *P*<.001). This was consistent with virtually all subgroups examined in subset analyses, including those based on sex, age, ECOG PS, metastatic site, and location of primary disease. The overall response rate was nearly doubled with the addition of bevacizumab, from 10.0% to 19.3% (*P*=.042). The addition of bevacizumab also resulted in improvement in the disease control rate, which included patients with stable disease (74.3% vs 57.9%; *P*=.005). A numerically longer overall survival was observed with bevacizumab—20.7 months versus 16.8 months—but this did not reach statistical significance (HR, 0.79; *P*=.182). Despite the fact that the combination treatment group had greater study drug exposure (median of 5.8 cycles vs 4.2 cycles in the capecitabine-only arm), rates of any adverse events were similar between the 2 groups. Grade 3 or 4 adverse events were more common with the combination than with capecitabine alone (59% vs 44.1%), but grade 5 adverse events were more common in patients who received capecitabine alone (11.8% vs 8.2%). Adverse events of special interest with bevacizumab included bleeding and/or hemorrhage (25.4% vs 6.6%), hypertension (19.4% vs 5.1%), venous thrombolic events (11.9% vs 5.1%), and proteinuria (7.5% vs 0.7%). Hypertension was more common in the combination group, but hypertension of grade 3 and higher was observed in only 2.2% of patients in the combination group versus 1.5% of patients in the capecitabine group. Venous and atrial thromboembolisms were also more common, but grade 3 and higher events were rare. The safety profile for patients treated with bevacizumab was consistent with previously reported data for bevacizumab in CRC. The investigators concluded that the combination of bevacizumab plus capecitabine is an effective and well-tolerated treatment in metastatic CRC patients aged 70 years or older.