months in the other patient group (p<0.0001). Similarly, OS was enhanced in the predicted target group (20.3 months) versus 10.4 months in the other group (p<0.0001).

The PRoB-GBM unfavorable group (ie, predicted to respond poorly to BEV) correlated with both the unfavorable (ie, more mesenchymal) multigene assay used to stratify patients in the trial as well as to the mesenchymal class identified by transcriptome analysis, suggesting that the predictive responder group was low in mesenchymal gene expression. In multivariate analyses, PRoB-GBM showed a strong interaction with treatment arm (placebo vs BEV) and, within the BEV arm only, was predictive of OS independent of prognostic factors including methylated or unmethylated *MGMT* gene, and RTOG Recursive Partitioning Analysis of Glioma class.

Within the trial, patients who experienced tumor recurrence (including those in the control arm) could be given salvage treatment with BEV. In these patients, PRoB-GBM was not predictive for salvage treatment, indicating that the PRoB-GBM biomarker may be useful only in the newly diagnosed setting.

Thus, the developed biomarkers represent a molecular diagnostic tool that can be used to identify patients for BEV treatment for newly diagnosed glioblastoma using FFPE tissue.

Antiangiogenesis Therapy With Bevacizumab Improves Survival in Metastatic or Relapsed Cervical Cancer

Written by **Wayne Kuznar**

Bevacizumab (BEV) is the first targeted agent that when added to standard chemotherapy improved overall survival (OS) in women with metastatic or relapsed cervical cancer. This finding from a randomized, open-label Phase 3 study represents the first instance in which a targeted therapy has significantly prolonged survival in this setting. Results were presented by Krishnansu S. Tewari, MD, University of California Irvine, Irvine, California, USA.

Acquired drug resistance to platinum-based therapies has rendered these treatments less effective for cervical cancer recurrence, leading to poor outcomes. Tumor neovascularization imparts an aggressive course in cervical cancer, prompting this investigation of an antiangiogenesis therapy targeting the vascular endothelial growth factor A (VEGF-A) in patients with relapsed or advanced disease.

The Paclitaxel and Cisplatin or Topotecan With or Without Bevacizumab in Treating Patients With Stage IVB, Recurrent, or Persistent Cervical Cancer study of the Gynecological Oncology Group [GOG 240; NCT00803062; Tewari KS et al. *J Clin Oncol* 2013 (suppl; abstr 3)] included 452 women with recurrent or metastatic cervical cancer who were randomized to 1 of 4 treatment arms using a 2x2 factorial design: 1) treatment with paclitaxel (PAC) 135 or 175 mg/m^2 intravenously (IV) plus cisplatin (CIS) 50 mg/m^2 IV; 2) PAC/CIS plus BEV 15 mg/kg IV; 3) PAC 175 mg/m^2 IV plus topotecan (TOPO) 0.75 mg/m^2 on Days 1 to 3; or 4) PAC/TOPO plus BEV 15 mg/kg IV. Patients were treated every 21 days until progression, unacceptable toxicity, or complete response. To be eligible, patients had to have measureable disease, a performance status of 0 to 1, and no prior chemotherapy for recurrent disease. The nonplatinum regimen selected was based on laboratory data indicating synergy between TOPO and microtubule-interfering agents and demonstrated activity in recurrent cervical cancer.

A preplanned interim analysis comparing the platinum doublet and the nonplatinum doublet on median OS showed no significant difference between the chemotherapy-alone groups (median OS, 15 months with PAC/CIS versus 12.5 months with PAC/TOPO; one-sided p=0.880).

Median progression-free survival was improved from a mean of 5.9 months with chemotherapy alone to 8.2 months with the addition of BEV. Similarly the response rate was significantly higher with BEV plus chemotherapy compared with chemotherapy alone (48% vs 36%; p=0.0078), with significantly more complete responses in patients treated with anti-VEGF therapy.

Median OS was 17.0 months in BEV-treated patients versus 13.3 months in the arms assigned to chemotherapy alone (HR, 0.71; p=0.0035). Median OS was superior with the addition of BEV to either chemotherapy regimen, although this difference achieved statistical significance when comparing BEV/CIS/PAC to CIS/PAC alone (17.5 vs 14.3 months, respectively; p=0.0348).

There were four fatal adverse events each with BEV and chemotherapy alone. No new side effects were identified with BEV. Gastrointestinal fistula grade ≥3, a recognized complication of BEV, occurred in 7 (3%) of BEV-treated patients and none of those on chemotherapy alone. Grade ≥2 hypertension was a complication in 54 patients (25%) of the BEV group and 4 (2%) of the group that received chemotherapy alone, but no patient withdrew from the study because of hypertension.

Health-related quality of life was measured by the Functional Assessment of Cancer Therapy–Cervical Cancer-Trial Outcome Index. The score on this index ranges from 0 to 116 points, with a clinically meaningful change being 4 to 5 points, said Dr. Tewari. Scores on this index were marginally lower, a maximum of 2.95 points and a mean of 1.2 points lower (p=0.3), in the BEV groups compared with

the groups that received only chemotherapy, indicating no significant deterioration in quality of life.

BEV represents the first targeted agent that improves the outcome of metastatic or relapsed cervical cancer when added to an established chemotherapy regimen.

Sorafenib Delays Progression of Treatment-Resistant Differentiated Thyroid Cancer

Written by Wayne Kuznar

The multitargeted agent sorafenib is the first therapy that has shown promise in a Phase 3 trial to extend progression-free survival (PFS) in patients with metastatic differentiated thyroid cancer that is refractory to standard radioactive iodine (RAI) therapy.

Interim results from a double-blind, placebo-controlled randomized Phase 3 Study of Sorafenib in Locally Advanced or Metastatic Patients With Radioactive Iodine Refractory Thyroid Cancer [DECISION; NCT00984282; Brose MS et al. *J Clin Oncol* 2013 (suppl; abstr 4)], for the treatment of patients with RAI refractory differentiated thyroid cancer were presented by Marcia S. Brose, MD, PhD, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

Differentiated thyroid cancer accounts for the majority of the >60,000 thyroid cancer cases diagnosed each year in the United States [Howlader N et al. *SEER Cancer Statistics Review.* http://seer.cancer.gov/statfacts/html/thyro.html. Accessed June 2013]. Although cure rates of differentiated thyroid cancer are generally high following standard treatment with surgery and RAI, the disease becomes refractory to RAI in ~15% of patients [Pacini F et al. *Expert Rev Endocrinol Metab* 2012; Xing M et al. *Lancet* 2013]. Their median survival after resistance develops is 2.5 to 3.5 years, and bone, pulmonary, and brain complications occur frequently [Durante C et al. *J Clin Endocrinol Metab* 2006; Robbins RJ et al. *J Clin Endocrinol Metab* 2006]. There is no standard therapy for patients with RAI-refractory differentiated thyroid cancer, with palliative care being the main option.

Sorafenib is a multikinase inhibitor with activity against RAF kinase and several receptor tyrosine kinases, including vascular endothelial growth factor receptor 1 to 3, platelet-derived growth factor receptors, BRAF, RET, and c-KIT.

In DECISION, 417 patients with locally advanced or metastatic, RAI-resistant differentiated thyroid cancer whose disease had progressed within the preceding 14 months (as defined by RECIST 1.0 criteria) were randomly assigned in a 1:1 ratio to receive sorafenib 400 mg orally BID or placebo. Allowance was made for crossover from placebo to sorafenib upon disease progression. The study was conducted in 89 centers across North America, Europe, and Asia.

The median PFS by independent central review, the primary endpoint, was 10.8 months in the sorafenib group versus 5.8 months in the placebo arm (HR, 0.587; p<0.0001). The benefit with sorafenib on PFS was consistent across subgroups examined. At disease progression, 150 patients assigned to placebo (71%) and 55 assigned to sorafenib (27%) received open-label sorafenib. The median overall survival has not been reached in either group.

The response rates were 12.2% and 0.5% in the sorafenib and placebo arms, respectively (p<0.0001). All were partial responses; no complete responses were observed.

Dose modification due to adverse events (AEs) was necessary in 77.8% of the sorafenib arm and 30.1% of the placebo arm. Discontinuation due to AEs occurred in 18.8% of sorafenib-treated patients versus 3.8% of the placebo group. Tolerability was consistent with the known sorafenib safety profile. The most common any-grade treatment-emergent AEs in the sorafenib arm were hand-foot skin reaction, diarrhea, alopecia, rash/desquamation, fatigue, weight loss, and hypertension. There was one death in each arm that was attributed to the study drug.

Sorafenib significantly improved PFS and extended median PFS by 5 months compared with placebo in RAI-refractory differentiated thyroid cancer, representing the first effective agent in this a rare cancer with poor prognosis and no established treatment to date.

Tamoxifen in Estrogen Receptor-Positive Breast Cancer: 10 Years Superior to 5 Years

Written by Wayne Kuznar

Ten years of adjuvant tamoxifen is superior to 5 years in reducing the rates of late recurrence and death in women with estrogen receptor (ER)-positive breast cancer.

Breast cancer mortality is reduced by about one third over 15 years when women with ER-positive tumors are treated with 5 years of adjuvant tamoxifen. The effect of an additional 5 years of treatment on breast cancer recurrence and death was examined in the randomized Phase 3 Adjuvant Tamoxifen: To Offer More? study [aTTom; ISRCTN17222211; Gray RG et al. *J Clin Oncol* 2013 (suppl; abstr 5)], which was presented by Richard G. Gray, MSc, University of Oxford, Oxford, United Kingdom.

In aTTom, 6953 women in the United Kingdom who had been taking tamoxifen for 5 years were randomized to continuing treatment for an additional 5 years or stopping treatment. During the 15-year enrollment period, ER status was tested in only ~40% of the women; ER status in the remaining 60% was unknown. About 75% of the women assigned to continue tamoxifen had continued taking it for the 5 extra years.