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.

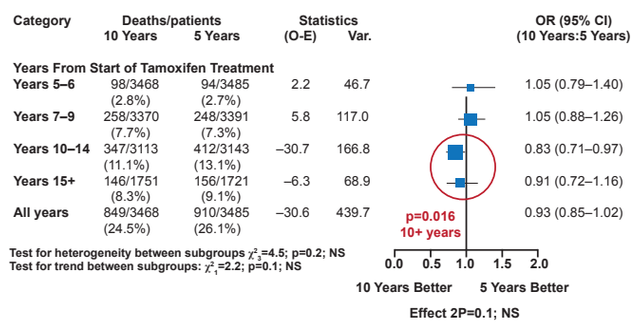
Breast cancer mortality is reduced by about one third over 15 years when women with ER-positive tumors are treated with 5 years of adjuvant tamoxifen. The effect of an additional 5 years of treatment on breast cancer recurrence and death was examined in the randomized Phase 3 Adjuvant Tamoxifen: To Offer 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.

Ten years of tamoxifen reduced breast cancer recurrence by 15% (580 recurrences with allocation to 10 years vs 672 with allocation to 5 years; p=0.003). The number of breast cancer deaths was reduced from 452 with assignment to 5 years to 404 with assignment to 10 years of tamoxifen, a 12% relative reduction in risk (p=0.06). Treatment allocation had little effect on either recurrence rates or death rates from 5 to 9 years after diagnosis but the benefit of longer treatment became evident in the second decade after diagnosis, said Prof. Gray. The relative reduction in the risk of death with assignment to 10 years of tamoxifen increased to 21% in Years 10 to 14 after diagnosis, and to 25% in Year 15 of follow-up and later. These numbers may be underestimates of the true effect of prolonged tamoxifen therapy due to the incluse of the majority of patients with unkown ER status.

Extending the use of tamoxifen increased the risk of endometrial cancer. There were 102 (2.9%) versus 45 (1.3%) endometrial cancers, with a rate ratio (RR) of 2.20 (p<0.0001), with 37 (1.1%) versus 20 (0.6%) endometrial cancer deaths (RR, 1.83; p=0.02). There were no significant differences in the rates of death without recurrence or all-cause mortality between the two groups, although a significant difference in overall survival in favor of 10 years of tamoxifen emerged from Year 10 onward (p=0.016; Figure 1).

Figure 1. Overall Survival by Treatment and Year of Follow-Up



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The findings from aTTom complement and confirm those from the recently published international study, Adjuvant Tamoxifen: Longer Against Shorter [ATLAS; Davies C et al. *Lancet* 2013]. The combined data of aTTom and ATLAS with a total of 17,477 enrolled patients show a significant 15% reduction in breast cancer mortality overall (p=0.001) and an additional 25% reduction in breast cancer mortality 10 years and beyond with 10 years of tamoxifen compared with 5 years of treatment (p=0.00004; Table 1).

Prof. Gray estimates that compared with taking no tamoxifen, 10 years of tamoxifen reduces breast cancer death rate by one third in the first 10 years after diagnosis and by half subsequently.

Table 1. Breast Cancer Mortality: 10 Versus 5 Years

	10 Years Tam vs 5: aTTom Trial (n=6934 ER+UK)	10 Years Tam vs 5: ATLAS Trial* (n=10,543 ER+UK)	10 Years Tam vs 5: aTTom & ATLAS combined (n=17,477 ER+UK)
Years 5–9	1.08 (0.85–1.38)	0.92 (0.77–1.09)	0.97 (0.84–1.15)
Years 10+	0.75[a] (0.63–0.90)	0.75[b] (0.63–0.90)	0.75[c] (0.65–0.86)
All Years	0.88[d] (0.74–1.03)	0.83[e] (0.73–0.94)	0.85[f] (0.77–0.94)

*Inverse variance weighted estimate in the effect of ER+; [a]p=0.007; [b]p=0.002; [c]p=0.00004; [d]p=0.1; [e]p=0.004; [f]p=0.001.

Nintedanib Plus Docetaxel Improves PFS and OS for Patients With Stage IIIB/IV or Recurrent Lung Adenocarcinoma

Written by Maria Vinall

Nintedanib plus docetaxel significantly improved progression-free survival (PFS) independent of histology, and prolonged overall survival (OS) for non-small cell lung cancer (NSCLC) with adenocarcinoma histology. Adverse events (AEs) were generally manageable with dose reductions and symptomatic treatment.

No targeted agent has been shown to prolong OS in combination with second-line chemotherapy in NSCLC. Inhibition of tumor-related angiogenesis has been identified as an attractive target for antitumor therapy. Nintedanib is an oral angiokinase inhibitor targeting vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and fibroblast growth factors. Martin Reck, MD, PhD, Hospital Grosshandorf, Grosshansdorf, Germany, reported results from the BIBF 1120 Plus Docetaxel as Compared to Placebo Plus Docetaxel in Second-Line Non-Small Cell Lung Cancer study [LUME-Lung 1; NCT00805194; Reck M et al. *J Clin Oncol* 2013 (suppl; abstr LBA8011)], a placebo-controlled Phase 3 trial of nintedanib plus docetaxel in patients with locally advanced/metastatic NSCLC progressing after first-line therapy.

Patients with histologically or cytologically confirmed locally advanced (stage IIIB), metastatic stage IV or recurrent NSCLC in whom first-line chemotherapy failed, were randomized to oral nintedanib 200 mg BID on Days 2 to 21 plus intravenous docetaxel 75 mg/m^2 Q21D (n=655) or placebo plus docetaxel (n=659). The number of docetaxel cycles was not restricted. Monotherapy was permitted after ≥4 cycles of combination therapy.

The primary study endpoint was PFS assessed by independent central review using RECIST v1.0. Imaging was performed every 6 weeks. The key secondary endpoint of OS was analyzed hierarchically first in adenocarcinoma