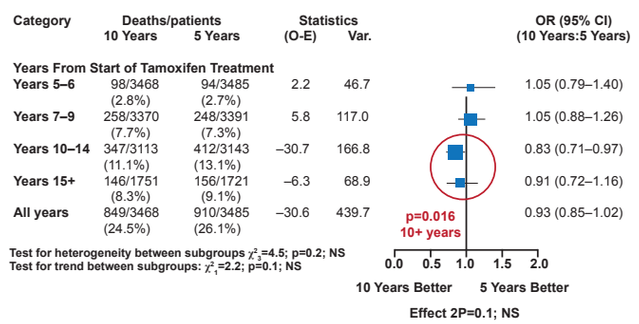
Ten years of tamoxifen reduced breast cancer recurrence by 15% (580 recurrences with allocation to 10 years vs 672 with allocation to 5 years; p=0.003). The number of breast cancer deaths was reduced from 452 with assignment to 5 years to 404 with assignment to 10 years of tamoxifen, a 12% relative reduction 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

patients <9 months since start of first-line therapy (T <9 months; identified as a prognostic/predictive biomarker), followed by all adenocarcinoma patients, and then all patients. Additional secondary analyses included response rate, safety, and patient reported outcomes.

The study participants were mostly men (73%), with a mean age of ~68 years; ~75% of participants were current or past smokers. Approximately 50% of patients had adenocarcinoma histology and 42% had squamous cell carcinoma. At randomization ~90% of patients had metastatic disease and >90% had received platinum-based chemotherapy as first-line treatment.

Nintedanib plus docetaxel significantly prolonged PFS versus placebo plus docetaxel (HR, 0.79; 95% CI, 0.68 to 0.92; p=0.0019; median 3.4 vs 2.7 months) regardless of histology (squamous HR, 0.77; p=0.0200; adenocarcinoma HR, 0.77; p=0.0193). The results were also consistent among all previously specified subgroups.

There was no difference in OS in the intention-to-treat population of all patients. OS was significantly prolonged in patients with adenocarcinoma histology (HR, 0.83; p=0.0359; median 12.6 vs 10.3 months) but not those with squamous cell carcinoma. Tumor response was comparable between both arms and between the major histologies; however, there was a significant increase in disease control rates (complete response+partial response+stable disease) with nintedanib plus docetaxel in patients with adenocarcinoma (OR, 1.93; p<0.0001) and squamous cell carcinoma (OR, 1.78; p<0.0009).

There was a higher incidence of drug-related adverse events (AEs) and severe drug-related AEs in the combination-therapy group. However, there was no difference in the number of AEs leading to drug discontinuation or the incidence of serious AEs. The most common AEs associated with combination therapy were gastrointestinal (diarrhea 42.3% vs 21.8%, and nausea) and transient elevation of transaminases (28.5% vs 8.4%). The side effects were mostly low to moderate in intensity, and nearly all were reversible. Further investigations are warranted to identify molecular and clinical determinants of benefit for nintedanib in NSCLC.

CENTRIC Trial Results

Written by **Brian Hoyle**

Roger Stupp, MD, University of Zurich, Zurich, Switzerland, discussed the results of the multicenter, randomized, open-label, controlled, Phase 3 Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Methylated Gene Promoter Status study [CENTRIC; NCT00689221; *J Clin Oncol* 2013 (suppl; abstr LBA2009)].

Cilengitide (CIL) is a cyclic arginine, glycine, and aspartic acid-containing pentapeptide that inhibits αvβ3 and αvβ5 integrins, which are expressed on glioblastoma cells. The CENTRIC study explored the use of CIL combined with standard treatment comprising temozolomide (TMZ) and radiation therapy (RT) for patients with newly diagnosed glioblastoma and methylated *O-6 Methylguanine-DNA Methyltransferase (MGMT)* gene promoter. Prior Phase 2 trials had suggested a benefits of CIL doses of 500 and 2000 mg on overall survival (OS) and progression-free survival (PFS), with superior outcome of higher versus lower dosage of CIL (2000 vs 500 mg) and little added toxicity [Reardon DA et al. *J Clin Oncol* 2008; Nabors LB et al. *Cancer* 2012]. In comparison with historical controls the enhanced benefits of the combination of CIL added to standard TMZ/RT→TMZ concomitant and adjuvant TMZ and RT treatment sequence was particularly pronounced in tumors containing a *MGMT* gene promoter methylation [Stupp R et al. *J Clin Oncol* 2010].

This pivotal Phase 3 trial was conducted at over 200 sites worldwide. Eligibility criteria for the 545 patients were aged ≥18 years, newly diagnosed and histologically proven glioblastoma, methylated *MGMT* promoter, ECOG PS 0 to 1, and stable or decreasing use of steroids. A total of 545 patients were randomized to standard treatment [Stupp R et al. *N Engl J Med* 2005] with TMZ/RT→TMZ and CIL (2000 mg IV BIW) or standard therapy alone. Maintenance TMZ was given for up to 6 cycles, CIL was to be given until disease progression up to 2 years.

The primary endpoint was OS, secondary endpoints were PFS, safety and tolerability, QT/QTc elevation, population pharmacokinetics, general health and work status, and quality of life. The median follow-up was 29 months.

Baseline characteristics in the intention-to-treat population were similar in terms of median age, male sex, ECOG PS, extent of surgery, recursive portioning analysis class, median weeks to randomization, and use of steroid and seizure medications.

This study failed to meet the primary endpoint as no differences in OS were evident (median treatment OS, 26.3 months; 95% CI, 23.8 to 28.8; median control OS, 26.3 months; 95% CI, 23.9 to 34.7; HR, 1.021; 95% CI, 0.808 to 1.291; p=0.8623; Figure 1). Further analyses of the patients according to parameters including age, ethnicity, region of origin, and extent of surgery did not reveal any significance in terms of OS. Similarly, no differences between the patient groups were apparent for PFS as determined by the individual investigators (median treatment PFS, 13.5 months; 95% CI, 10.8 to 15.9; median control PFS, 10.7 months; 95% CI, 8.1 to 13.3; HR, 0.926; 95% CI, 0.757 to 1.133; p=0.4570) and an overall determination by independent assessors (median treatment OS, 10.6 months; 95% CI, 8.2