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.

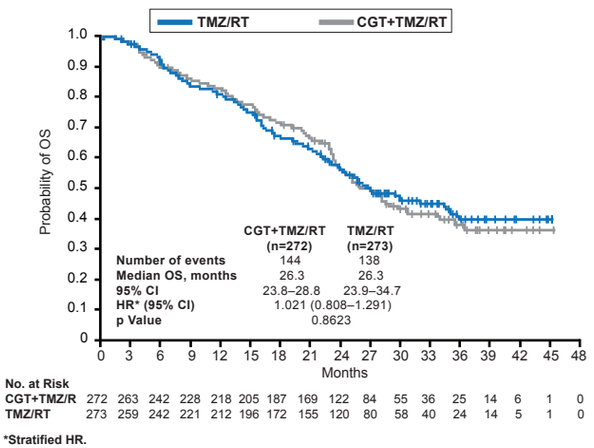
Baseline characteristics in the intention-to-treat population were similar in terms of median age, male sex, ECOG PS, extent of surgery, recursive portioning analysis class, median weeks to randomization, and use of steroid and seizure medications.

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

to 13.4; median control PFS, 7.9 months; 95% CI, 5.9 to 12.5; HR, 0.918; 95% CI, 0.750 to 1.124; p=0.4102).

Toxicity in both arms was mainly related to TMZ and RT. The marginally increased incidence of pulmonary embolism in the CIL-treated patients (12 vs 5 patients) was not considered clinically relevant. Other adverse events in the two study arms were similar in the two treatment arms.

Figure 1. Overall Survival: Intent to Treat



CIL=cilengitide; RT=radiotherapy; TMZ=temozolomide.

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The researchers concluded that CIL applied with the standard therapeutic combination of TMZ and RT did not prolong survival, with no patient subgroup exhibiting a clinical benefit. No new safety concerns were evident.

Bevacizumab Monotherapy Improves DFI in Melanoma Patients at High Risk of Recurrence

Written by Maria Vinall

Results of the preplanned interim analysis of the Adjuvant Avastin Trial in High-Risk Melanoma trial [AVAST-M; ISRCTN81261306; EudraCT 2006-005505-64; Corrie P et al. *J Clin Oncol* 2013 (suppl; abstr LBA9000)] of melanoma patients at high risk of recurrence has shown that adjuvant bevacizumab (BEV) monotherapy is well tolerated and improved disease-free interval (DFI). Longer follow-up is required to determine an impact on the primary endpoint of 5-year overall survival (OS).

BEV is a recombinant humanized monoclonal antibody to vascular endothelial growth factor shown to improve survival in several advanced solid tumors. Modest activity has been reported in advanced melanoma [Kim KB et al. *J Clin Oncol* 2012]. AVAST-M is Phase 3 trial evaluating single-agent BEV as adjuvant therapy following histologically confirmed completely resected stage IIB, IIC, and III cutaneous melanoma (American Joint Committee on Cancer staging). Participants were randomized within 12 weeks of surgery to receive BEV 7.5 mg/kg Q3W for 1 year (maximum of 17 infusions over 1 year or until disease progression; n=671) or to observation only (n=672). Subjects will be followed for 10 years or until death.

The primary study endpoint is OS. Secondary endpoints are DFI, distant metastasis-free interval (DMFI), safety and toxicity, and quality of life (QoL). Pippa Corrie, PhD, University of Cambridge, Cambridge, United Kingdom, presented the results of the first preplanned interim analysis.

Participants (56% men; median age ~56 years) were recruited from 48 sites across the United Kingdom between July 2007 and March 2012. Most (~88%) subjects were ECOG PS 0. Nearly 75% of patients had resected stage III disease (15% stage IIIA, ~36% IIIB, and 21% IIIC). Ulceration status of the primary melanoma was ~38% present, ~47% absent, ~15% unknown. About one third of the patients had undergone sentinel lymph node biopsy; 21% had microscopic lymph node involvement. Median follow-up for survival was 25 months.

The median duration of treatment was 51 weeks (range, 21 to 52 weeks); median dose intensity was 86% (range, 41% to 96%). In all, 54% of BEV-treated patients completed planned treatment. The most common reasons for discontinuation were disease recurrence (38% of cases) and toxicity (33%). Grade 3/4 adverse events (AEs) occurred in 15% of BEV patients and 5% of observation patients. The most common Grade 3/4 AE was hypertension, which occurred in 6% of BEV-treated patients. There was one potential treatment-related death—a hemopericardium associated with an aortic aneurysm dissection in a BEV-treated patient with a history of cardiac events.

On the primary outcome, the 1-year OS was the same in both groups (HR, 0.97; 95% CI, 0.78 to 1.22; p=0.76).

There was a difference on the secondary endpoint of disease recurrence; 39% of patients in the BEV group had a recurrence of disease compared with 44% of patients in the observation group. There were no differences in either locoregional or first distant recurrence. Patients in the treatment arm has significantly improved DFI (HR, 0.83; 95% CI, 0.70 to 0.98; p=0.03) compared with observation patients. DFI at 1 and 2 years were 77% and 59% in the BEV group versus 70% and 57% for observation only.

The treatment effect for DFI was consistent and remained significant after adjustment for disease stage and ulceration. The benefit of BEV appears to be less apparent in patients with stage II disease.