TRIAL SUMMARY: Bevacizumab in unresectable mesothelioma


In this French multicentre randomized phase 3 trial, eligible patients had histologically proven unresectable malignant pleural mesothelioma (MPM). Patients were randomized (1:1) to receive first-line treatment with cisplatinum 75 mg/m2 and pemetrexed 500 mg/m2 with or without bevacizumab (BEV) 15 mg/kg q21d for 6 cycles. If response or stable disease was achieved, patients in the experimental arm then received BEV maintenance therapy until progression or toxicity. Primary endpoint was overall survival (OS).

Results: OS was significantly longer in the experimental arm (median: 18.8 months, 95% CI 15.9–22.6, vs 16.1 months, 95% CI 14.0–17.9; adjusted HR=0.76; 95%CI 0.61–0.94; p=0.012). Progression-free survival (PFS) also favoured the BEV arm (median: 9.6 months, 95% CI 8.5–10.6, vs 7.5 months, 95% CI 6.8–8.1; adjusted HR=0.62; 95% CI 0.50–0.75; p<0.0001). Grade 3–4 hematologic toxicities did not differ significantly between the 2 groups (49.5% vs 47.3%), however there were significantly more grade 3 proteinuria (0.0% vs 3.1%), grade 3 hypertension (0.0% vs 23%), and grade 3–4 thrombotic events (0.0% vs 2.7%) in patients treated with BEV.

COMMENTS: Patients diagnosed with MPM, a cancer linked to asbestos exposure, have limited survival despite optimal treatment with cisplatin-pemetrexed. Furthermore, few advances beyond this standard of care have been made in the past decade. Interestingly, it has been shown that MPM expresses significantly higher levels of both vascular endothelial growth factor (VEGF) and VEGF receptors in cell lines.1

BEV, a recombinant humanized monoclonal antibody that targets VEGF, could therefore benefit patients with MPM. However, a previous randomized phase 2 trial comparing standard first-line chemotherapy with gemcitabine and cisplatin with or without the addition of BEV for the treatment of unresectable MPM failed to improve PFS or OS.2 Authors proposed that the use of a gemcitabine-based chemotherapy might have blunted the effect of BEV, considering preclinical data suggesting a negative interaction between these agents.3 Furthermore, most patients were treated with pemetrexed as second-line chemotherapy after progression, possibly reducing the apparent benefit of first-line agents.

The objective of this randomized multicentre phase 3 trial was therefore to investigate the addition of BEV to a cisplatin-pemetrexed doublet in patients diagnosed with MPM not amenable to curative-intent surgical resection. Patients with histologically proven MPM and good Eastern Cooperative Oncology Group performance status (ECOG 0–2) were randomized to first-line treatment with cisplatin-pemetrexed with or without the addition of BEV after receiving prophylactic radiation therapy to pleural biopsy tracts. Every 3 cycles, enrolled patients were evaluated with a computed tomography (CT) scan, and responses were assessed with modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria. Of note, no crossover between treatment arms was allowed at progression, and patients with central nervous system metastases were excluded from the trial.

The primary endpoint was OS, with PFS, quality of life, biomarker studies and pharmacoeconomics data as secondary outcomes. The trial recruited 448 patients; over 95% of patients were ECOG 0–1, roughly 80% of participants in each arm had epithelioid histology, with the remaining being sarcomatoid/mixed-type, and approximately 55% had a history of tobacco use. Data required to calculate the

IN BRIEF

Already known
- Patients diagnosed with malignant pleural mesothelioma (MPM) have limited survival despite optimal treatment with cisplatin-pemetrexed.
- MPM expresses significantly higher levels of both vascular endothelial growth factor (VEGF) and VEGF receptors in cell lines.

What this study showed
- The addition of BEV to a cisplatin-pemetrexed doublet in patients diagnosed with MPM not amenable to curative-intent surgical resection improved both overall survival and progression-free survival.
- Predictable additional BEV-related toxicities were seen.

Next steps
- Integrate BEV into clinical practice for this group of patients.
European Organisation for Research and Treatment of Cancer (EORTC) prognostic model were also collected. OS and PFS improvement with bevacizumab were consistent across all subgroups, except poor-prognosis patients according to EORTC score. A significant increase in grade 3 and 4 toxicities was noted with the addition of BEV (71.2% vs 62.1%, p=0.04), particularly in regards to hypertension, proteinuria, and arterial and venous thromboembolic events. However, global quality of life was not affected, and patients in both arms reported similar scores on the Lung Cancer Symptom Scale (LCSS) mesothelioma questionnaire.

In conclusion, the addition of BEV to a cisplatin-pemetrexed doublet for the treatment of unresectable MPM improved both PFS and OS in this phase 3 trial. Considering the limited therapeutic options for this disease and acceptable toxicity profile of this regimen, these results are clinically significant.

References