Time will show whether the results reported by Zhu and colleagues’ can be achieved in other centres and whether this technique will become an accepted palliative treatment option. Regional differences in infrastructure, expertise, and health-care economics will continue to be essential factors as clinicians tailor appropriate therapy for patients with advanced oesophageal cancer.

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I declare that I have no competing interests.

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**Setting the bar for adjuvant treatment of melanoma**

There is universal agreement about the need to improve adjuvant treatment for patients who have melanoma and are at high risk of disease recurrence after surgery.1,2 Medical management of metastatic melanoma has improved greatly, with the approval of four new drugs that have shown clear survival benefits in phase 3 randomised trials, beginning with the approvals of ipilimumab and vemurafenib in 2011. Effective adjuvant treatment—whether with approved drugs or those in development—is important to minimise melanoma recurrence and death. The American Society of Clinical Oncology has published guidance that aims to improve the standard of clinical trials in metastatic breast, colon, lung, and pancreatic cancers by setting a higher bar for treatment expectations.3 Where should the bar then be set for clinical trials of adjuvant treatment in patients with melanoma? How do the results of the AVAST-M trial,4 which assessed the role of bevacizumab as adjuvant treatment for patients with stage III melanoma at high risk of recurrence, help inform our deliberations?

The availability of new drugs with clear effects on metastatic melanoma provides a strong rationale for their investigation in adjuvant trials. AVAST-M began before the approval of ipilimumab and vemurafenib, but even today there is little evidence from trials in metastatic disease to suggest that adjuvant bevacizumab would be beneficial in patients with melanoma. Findings from a randomised phase 2 study5 of carboplatin and paclitaxel plus bevacizumab or placebo in patients with metastatic melanoma showed no improvement in progression-free survival. Moreover, adjuvant use of bevacizumab has not improved survival in patients with any other tumour type to date.4 Dosage is also an important consideration: the AVAST-M investigators studied bevacizumab given at a dose of 7.5 mg/kg whereas other studies have assessed bevacizumab given at a dose of 10–15 mg/kg, which could have affected the results. Future adjuvant trials in patients with melanoma need a strong rationale and design, but whether known efficacy of the agent in metastatic melanoma is an absolute requirement for successful adjuvant therapy remains to be defined.

The choice of overall survival as the primary endpoint of the AVAST-M study was clearly an appropriate one, with no significant difference noted between patients in the bevacizumab group and those in the observation group (hazard ratio [HR] 0·97, 95% CI 0·78–1·22; p=0·76). The suitability of relapse-free survival as the primary endpoint in melanoma adjuvant trials bears further scrutiny: does having drugs that improve overall survival in patients with stage IV melanoma negate the value of relapse-free survival in the adjuvant setting, or might rapidly evolving and improving treatment...
strategies actually accentuate the importance of delaying recurrence? When relapse-free survival is used as a primary or key secondary endpoint, the investigational agent should be compared with the standard already set by interferon. Previous studies of adjuvant interferon have shown improvements in relapse-free survival in the range of 13–38%, and results for relapse-free survival from the imatinib adjuvant trials (ClinicalTrials.gov, numbers NCT00636168 and NCT01274338) are eagerly awaited.

In the AVAST-M trial, disease-free interval was improved in patients in the bevacizumab group compared with those in the observation group (HR 0.83, 95% CI 0.70–0.98; p=0.03). Disease-free interval is subtly different from relapse-free survival because deaths due to non-melanoma causes are not included in its calculation; as such, relapse-free survival should remain the standard relapse endpoint for trials of adjuvant melanoma. Even if we assume that relapse-free survival was improved by the same amount as disease-free interval in the AVAST-M trial, and that this improvement was statistically significant, bevacizumab does not surpass the effectiveness of interferon sufficiently enough to justify its use in clinical practice.

In the preplanned interim analysis of AVAST-M, patients in the bevacizumab group with BRAF mutant melanoma had a longer disease-free interval than did those in the observation group, whereas no difference was noted between groups for patients with BRAF wild-type melanoma. Enthusiasm for this observation should be tempered by the finding that the test for interaction between treatment and BRAF status was not significant (p=0.10). Furthermore, a phase 2 study of bevacizumab plus temozolomide chemotherapy in patients with metastatic melanoma showed the opposite result—better survival for BRAF wild-type melanoma. Either way, the rationale for improved outcomes for patients given bevacizumab in mutation-defined subsets is not well elucidated, and would need further study in prospective trials prior to acceptance as established fact.

Although major gains have been shown in systemic treatments for metastatic melanoma, prevention of recurrence in high-risk resected patients remains a priority. Interferon is the only approved adjuvant treatment for resected melanoma, with several studies showing improvement in relapse-free survival and meta-analyses showing small improvements in overall survival, thus setting the bar for future adjuvant trials. Adjuvant bevacizumab has not yet improved overall survival, and although disease-free interval is statistically improved in the AVAST-M trial, its benefits seem to be, at best, similar to the relapse-free-survival benefit of interferon. Other variables should also be considered, such as patient selection and toxic effects (of note, only 361 [54%] of 652 patients completed the planned treatment, with unacceptable toxic effects nearly as common as disease recurrence as a reason for discontinuation), and balanced with the observed efficacy. Longer follow-up of patients in the AVAST-M trial will help to better define the risk versus the benefits of adjuvant bevacizumab, but in the meantime, we all need to think about where to set the bar for future progress.

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