Trial Watch

MELANOMA TARGETS

There are few therapeutic options for treating metastatic melanoma, and the prognosis for patients with this disease is poor. However, three recent clinical trials of agents targeting different pathways have reported encouraging results.

In the first trial, ipilimumab, an antibody directed against cytotoxic T lymphocyte-associated antigen 4 (CTLA4) that promotes T cell activation and proliferation, was tested in combination with the chemotherapeutic agent dacarbazine. The Phase III randomized, double-blind study assigned 502 patients with previously untreated metastatic melanoma to receive either ipilimumab plus dacarbazine or dacarbazine plus placebo. Patients receiving ipilimumab had a significantly longer median overall survival (11.2 months; 95% confidence interval (CI) = 9.4–13.6) than those receiving dacarbazine alone (9.1 months; 95% CI = 7.8–10.5). Despite the improvement in survival, more grade 3 or 4 adverse events were experienced by patients receiving ipilimumab (56.3% versus 27.5%, $P<0.001$). The rates of adverse events in this trial differed somewhat from those observed in previous trials of ipilimumab monotherapy, possibly owing to its combination with dacarbazine.

The second Phase III trial examined the efficacy of the BRAF kinase inhibitor vemurafenib (PLX4032) compared with dacarbazine in 675 patients with previously untreated metastatic melanoma whose tumours carried the activating BRAF mutation V600E. Overall survival at 6 months was significantly higher with vemurafenib (84%; 95% CI = 78–89) than dacarbazine (64%; 95% CI = 56–73). Compared with dacarbazine, there was a relative reduction of 63% in the risk of death and 74% in the risk of tumour progression in the vemurafenib group ($P<0.001$ for both). Although there were relatively few grade 3 or 4 adverse events, 38% of patients in the vemurafenib group required dose modification compared with 16% of the dacarbazine group. Furthermore, 18% of patients receiving vemurafenib developed cutaneous squamous-cell carcinoma or keratoacanthoma, and analysis of these is underway.

Results of a Phase II trial studying inhibition of the receptor tyrosine kinase KIT in metastatic melanoma have also been reported. Although not as common as BRAF mutations, mutations or amplification of *KIT* were identified in 51 of 295 patients in this single-group, open-label trial; 28 were treated with the KIT inhibitor imatinib. Complete responses were observed in two patients, two had durable partial responses and two had transient partial responses. Importantly, significantly higher response rates were observed in patients carrying KIT mutations of probable functional relevance.

These three trials have laid the groundwork for improving the treatment of melanoma. Identifying which patients are likely to respond to each therapy and developing effective combination therapies are important next steps.

ORIGINAL RESEARCH PAPERS Carvajal, R. D. *et al.* KIT as a therapeutic target in metastatic melanoma. *JAMA* **305**, 2327–2334 (2011) | Chapman, P. B. *et al.* Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N. Engl. J. Med.* 5 Jun 2011 (doi:10.1056/NEJMoa1103782) | Robert, C. *et al.* Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N. Engl. J. Med.* 5 Jun 2011 (doi:10.1056/NEJMoa1104621)