# MEK1/2 inhibition delays progression of uveal melanoma

A multicentre, phase 2 trial has shown that selumetinib (an inhibitor of MEK1 and MEK2) provided significantly better progression-free survival and tumour response than did chemotherapy in patients with advanced uveal melanoma.

"Mutations in G-proteins GNAQ and GNA11 are present in 90–95% of patients with metastatic uveal melanoma", explained senior author Gary Schwartz (Columbia University School of Medicine, Herbert Irving Comprehensive Cancer Center, New York, NY, USA). "These mutations activate a majority of signalling pathways, including MAPK, AKT, and PKC. In laboratory studies, selumetinib completely blocked the MEK pathway, and inhibited growth of uveal melanoma cells in culture."

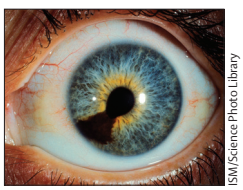
To study the efficacy of inhibiting MEK1/2 in uveal melanoma, 101 patients were randomly assigned to receive oral selumetinib or standard chemotherapy. Progression-free survival was significantly longer with selumetinib (15·9 weeks [95% CI 8·4–21·1]) than with chemotherapy (7 weeks [4·3–8·4]; hazard ratio [HR] 0·46 [0·30–0·71], p<0·001); no significant difference in overall survival was seen (11·8 months [95% CI 9·8–15·7] *vs* 9·1 months [6·1–11·1], respectively; HR 0·66 [0·41–1·06], p=0·09). 49% of patients assigned to selumetinib had tumour regression, whereas no objective responses were reported in the chemotherapy group. 65 (97%) of 67 patients receiving selumetinib had treatment-related adverse events, and 25 (37%) needed dose reductions.

"Targeted therapy is a promising way forward in uveal melanoma", commented Patrick Ott (Dana-Farber Cancer Institute, Boston, MA, USA). "No systemic treatment was previously shown to work in this disease."

Lead author Richard Carvajal (Memorial Sloan Kettering Cancer Center, New York, NY, USA) said that future studies include SUMIT (NCT01974752), a phase 3 trial of selumetinib in combination with dacarbazine versus chemotherapy alone, and (based on preclinical data showing that efficacy of MEK inhibition can be enhanced with the addition of AKT or PKC inhibition) a study of trametinib alone or in combination with GSK2141795 and a study of MEK162 and AEB071.

Sapna Patel (MD Anderson Cancer Center, Houston, TX, USA) said, "For the first time in uveal melanoma, we can use targeted therapy to effect tumour response…Targeted therapy with a MEK inhibitor really can potentially be the backbone of new therapy for this tumour."

*Judith A Gilbert*



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For **Cavajal and collegues' study** see *JAMA* 2014; **311:** 2397–405