Studies show drug combinations effective for melanoma

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Promising new data on drug combinations to treat metastatic melanoma are presented at the ESMO 2012 Congress of the European Society for Medical Oncology in Vienna.

The phase I and II trials focus on combining drugs to slow the development of resistance to drugs that inhibit BRAF, a gene that is mutated in about half of melanomas. Earlier trials with drugs that target BRAF generated excitement for their ability to quickly shrink melanoma tumors in suitable patients. But for many patients the benefits proved short-lived, as the cancer cells develop resistance to the drugs.

"These studies exemplify an important landmark of some tumors, which has emerged from recent laboratory research: the presence of specific mutations, such as the BRAF mutation in metastatic melanoma which exposes an Achilles' heel—MEK in this case," said Prof Yossef Yarden from the Weizmann Institute of Science, Israel. "In-depth understanding of cancers and their mutations is expected to reveal more of these deadly weaknesses in cancer, which we can exploit using new drugs and drug combinations."

Phase II of the BRAF inhibitor dabrafenib alone vs combination with MEK1/2 inhibitor trametinib

Dr Georgina Long from Westmead Hospital and the Melanoma Institute Australia and colleagues report that combining the new drugs dabrafenib

and trametinib provided a clinically meaningful improvement in progression-free survival, response rate and duration of response in 162 patients with melanoma that had BRAF V600 mutations.

Patients in the study received either dabrafenib 150mg twice daily; twice-daily dabrafenib plus once-daily 1mg trametinib; or twice daily dabrafenib plus once-daily 2mg trametinib. The combination prolonged progresion free survival over single-drug therapy from 5.8 months to 9.4 months, which represents a 60% improvement. Among patients who received both drugs at the higher dose, 41% had not progressed 12 months after treatment began, compared to 9% in the monotherapy arm of the study.

"The combination therapy of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib prolongs the progression-free survival in patients with V600 BRAF mutation-positive metastatic melanoma compared with dabrafenic monotherapy," Dr Long said. "Importantly, the combination also decreases the rate of the cutaneous toxicities compared with dabrafenib monotherapy, particularly the oncogenic cutaneous toxicity of squamous cell carcinoma."

Phase IB study of vemurafenib in combination with the MEK inhibitor, GDC-0973

A Phase I study in 44 patients shows that the combination of the MEK inhibitor GDC-0973 and vemurafenib can be delivered safely, Dr Rene Gonzalez of the University of Colorado Cancer Center, Denver, and colleagues report.

"BRAF inhibition has resulted in high response rates and improved survival in patients with BRAF mutated melanoma," Dr Gonzalez said. "One of several mechanisms of resistance has been reactivation of the

MAPK pathway. Preclinical models show that combined inhibition of BRAF and MEK can delay the acqusition of resistance compared to BRAF inhibitor monotherapy. Inhibition of the pathway downstream from BRAF with the MEK inhibitor GDC-0973 could theoretically overcome or delay this resistance mechanism and improve outcomes."

The study was not designed to evalate efficacy. "While early data in a small number of patients did show tumor reduction, it would be premature to comment on efficacy based on these preliminary results and further research is warranted," Dr Gonzalez said.

Provided by European Society for Medical Oncology