Medical Xpress

Combining two targeted therapies results in melanoma patients living significantly longer

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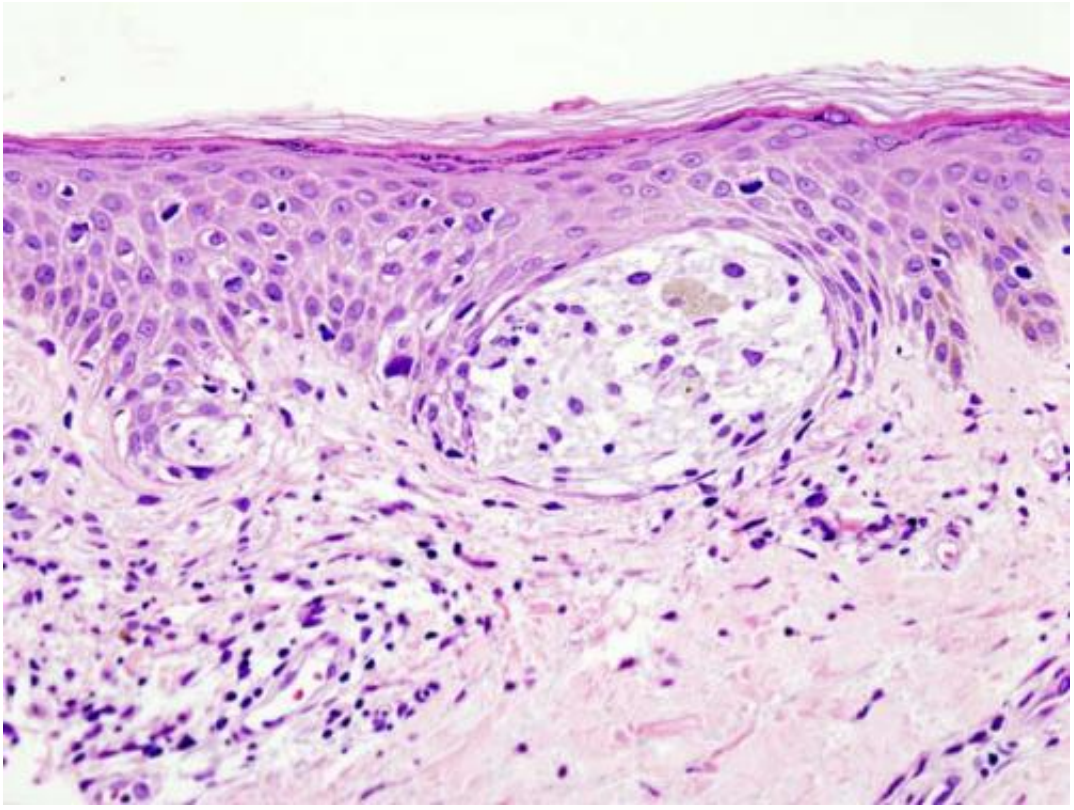

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

Latest results from a trial of a combination of two targeted therapies (dabrafenib and trametinib) to treat advanced melanoma have shown that patients are living significantly longer on the combined therapy than patients treated with another drug, vemurafenib, when used alone.

Professor Caroline Robert, of the Institut Gustave Roussy, Paris, France, will tell the 2015 European Cancer Congress today (Monday) that not only is the median overall survival time longer for patients receiving the combination treatment, but also that 51% of patients receiving the combination treatment are alive after two years, compared to 38% of patients receiving vemurafenib alone.

Analysis of data up to 13 March 2015 showed that the median overall survival time among patients with metastatic melanoma harbouring V600 mutations in the BRAF gene who received the combination treatment was 25.6 months. Among patients receiving vemurafenib alone, it was 18 months. On the basis of this finding, the European Commission approved the combination of dabrafenib and trametinib for use in Europe for these patients on 1 September 2015.

"We observed a statistically significant reduction of 34% in the risk of death among patients receiving the combination therapy," Prof Robert will say. "The increased survival among these patients is remarkable, and this median overall survival of more than two years is the longest in this category of patients in a phase III randomised trial."

These new results come from an analysis of all data from the COMBI-v phase III trial, which randomised previously untreated patients with the V600E or V600K mutations of the BRAF gene to receive either 150 mg dabrafenib twice daily and 2 mg trametinib once a day, or 960 mg vemurafenib alone twice a day.

By March 2015, approximately 50% (349 of the 704) patients had died and the researchers had followed the patients for approximately 18 months.

"Since our last report from this trial we have an additional 11 months of follow-up and 127 more deaths. This provides data that are mature

enough to demonstrate definitively the effect on overall survival and the benefit to patients," said Prof Robert.

The updated analysis also reported that patients receiving the combination treatment survived significantly longer without their disease progressing (disease-free progression) than patients receiving vemurafenib alone: 12.6 and 7.3 months respectively. "The 12.6 months of progression-free survival for patients on the combination treatment is the longest achieved in a randomised study for patients with the BRAF V600 mutation to date," she will say.

Rates of severe side effects remain similar in both groups of patients, with no unexpected effects showing during the longer follow-up. Results from an associated study of the patients' health-related quality of life showed significant and clinically meaningful improvements among those receiving the combination treatment, compared to those receiving vemurafenib alone. Overall health, physical and social functioning, and specific symptoms such as pain, insomnia, loss of appetite, diarrhoea and fatigue were all improved.

The international trial started in 2012 and patients recruited to it have melanoma that either cannot be removed by surgery and/or has spread (metastasised) to other parts of the body. Between 40-60% of melanoma patients have mutations in the BRAF gene that are driving the cancer, and the majority of these patients have the V600E or V600K type of BRAF mutation.

Dabrafenib, vemurafenib and trametinib are targeted therapies that block proteins playing key roles in the cell signalling pathways that are often overactive in cancer; dabrafenib and vemurafenib block the BRAF protein and trametinib blocks the MEK proteins. Because anti-BRAF treatment alone is associated with more than 50% of patients relapsing after six to eight months, researchers wanted to see whether a

combination of the BRAF and MEK inhibitors would produce better outcomes for patients. These latest results from the COMBI-v trial confirm this hypothesis.

Although the study was stopped in July 2014 when it became clear that the combination therapy was superior to vemurafenib alone, patients have the option to continue with their treatment and the researchers are continuing to collect follow-up data.

"This combination therapy is already available in the US and now also in Europe as a result of the European Commission's decision to approve its use. This long-term benefit in terms of overall survival confirms the major potential of this combination in patients with metastatic melanoma. A further question to investigate is the combination treatment versus new immunotherapies or combined with them," concluded Prof Robert.

Professor Peter Naredi, the ECCO scientific co-chair of the Congress, who was not involved in the research, commented: "As Professor Robert says, it is remarkable that patients with advanced melanoma disease now have a median survival time of over two years. With a combination of two targeted drugs inhibiting BRAF and MEK proteins, patients can expect a period of stabilisation of the disease, which from a quality of life perspective is advantageous. Not only did the combination have a better effect than a BRAF inhibitor alone, but quality of life was also improved."

ESMO spokesperson, Professor Reinhard Dummer, head of the skin cancer centre at the UniversitatsSpital Zurich (Switzerland), said: "Pre-clinical and translational research had suggested that dual pathway inhibition might improve the outcome of targeted therapy in BRAF mutated advanced melanoma. This trial now impressively shows the improved response rate, progression-free and overall survival, with an

excellent tolerability. Based on this study, dual pathway inhibition must be integrated into the management algorithms for this patient population."

Provided by ECCO-the European CanCer Organisation