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New data on combination treatments for melanoma

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Combination therapy with both BRAF inhibitor vemurafenib and MEK inhibitor cobimetinib achieves greater progression-free survival and response rates than vemurafenib plus placebo in BRAF-mutation positive melanoma, according to phase III data presented at the ESMO 2014 Congress in Madrid, Spain.

"Before the results of this study, we knew that cobimetinib plus vemurafenib could be safely delivered together with highly promising rates of tumour shrinkage; however until the performance of a scientifically rigorous randomised trial the potential magnitude of this benefit could not be measured," says lead author Dr Grant McArthur, head of the Cancer Therapeutics Program at the Peter MacCallum Cancer Centre, Melbourne, Australia.

The ongoing CoBRIM study enrolled 495 treatment-naive patients with BRAFV600-mutation-positive unresectable locally advanced or metastatic melanoma. Patients were randomised to received a 28-day treatment cycle of vemurafenib (960 mg, twice daily), and either cobimetinib or placebo (60 mg daily from days 1-21), with a primary end-point of progression-free survival.

Patients in the combination arm of the study showed a significantly improved median progression-free survival of 9.9 months, compared to 6.2 months in the placebo arm, and a 49% reduction in the risk of progression. Researchers observed a response rate of 68% in the combination arm and 45% in the control arm, including a complete

response in 10% of patients treated with combination therapy compared to 4% of patients treated with vemurafenib alone.

"This study is very important as it shows that using drugs together to turn off two individual proteins (BRAF and MEK), that interact and bind to each other in the cell, gives much improved results for patients. This is fundamental concept that could have far reaching consequences for how we treat many cancers," says McArthur.

Combination therapy did lead to a greater number of grade 3 and above adverse events compared to vemurafenib alone, but treatment with cobimetinib plus vemurafenib also seemed to reduce the incidence of skin-related side-effects known to occur with vemurafenib.

In summary, McArthur says, "We anticipate that the combination of a BRAF and MEK inhibitor will become a new standard treatment for advanced BRAF-mutant melanoma. The data lay the foundation for the addition of treatments either in sequence or in further combination to obtain even better results."

Improved response rate and survival with dabrafenib plus trametinib versus vemurafenib alone

Targeting BRAF V600E/K mutation-positive melanoma with a combination of dabrafenib plus trametinib achieves longer overall survival and progression-free survival as well as better response rates, compared to treatment with vemurafenib alone, according to data from an open-label phase III trial, also presented at ESMO 2014 in Madrid.

"We knew from previous studies of dabrafenib plus trametinib that the response rates were higher than those observed with dabrafenib monotherapy and that the progression-free survival was also significantly

longer," says lead author Dr Caroline Robert, head of Dermatology at the Institute Gustave Roussy, Paris, France.

The ongoing two-arm study has randomised 704 patients with advanced BRAF V600E/K mutation-positive melanoma either to a combination of dabrafenib (150 mg twice daily) plus trametinib (2 mg once daily), or to vemurafenib (960 mg, twice daily) alone. The primary endpoint is overall survival, with secondary endpoints of progression-free survival, objective response rate, duration of response, and safety.

A pre-planned interim analysis shows a 31% improvement in overall survival among patients on combination therapy, and a 44% reduction in the risk of disease progression compared to vemurafenib monotherapy. Researchers found a median progression-free survival of 11.4 months for dabrafenib plus trametinib, and 7.3 months for vemurafenib.

Patients in both arms of the study had similar rates of severe adverse events, although treatment with combination therapy was associated with a much lower rate of cutaneous squamous cell carcinoma.

In July this year, the study was stopped, and patients originally randomised to the vemurafenib arm of the trial were allowed to cross over to the combination arm.

In summary, Robert says, "These results further corroborate the early preclinical data that more complete blockade of the MAP kinase pathway delays the emergence of resistance, translating into longer survival for the patients."

Commenting on the results from these two studies, Dr Reinhard Dummer, from the University of Zurich Hospital, ESMO Faculty Coordinator for melanoma, says: "While monotherapy with a BRAF inhibitor is currently considered as a standard of care for patients with

BRAF mutated advanced melanoma, the data from these two trials, along with trial data presented earlier this year, provide convincing evidence that combination therapy with either dabrafenib and trametinib, or vemurafenib and cobimetinib will be the standard systemic therapy for this patient population."

"The combination provides more efficacy concerning response rate and progression-free survival and overall survival documented for the trametinib and dabrafenib combination with a similar to lower load of adverse reactions," Dummer says.

"Of special relevance is the lower risk for new cutaneous malignancies which might be a surrogate for other secondary malignancies associated with the use of monotherapy BRAF inhibitors."

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