Novel biomarkers predict benefit with immunotherapy in metastatic breast cancer

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Two novel biomarkers have been found to correlate with improved outcomes with immunotherapy in metastatic breast cancer and may help to identify the patients most likely to benefit from this treatment,

according to exploratory studies reported at the ESMO Breast Cancer Virtual Meeting 2020. The biomarkers are an increase in the number of programmed death ligand-1 (PDL1/CD274) genes measured by copy number alteration (CNA) and the PD-L1 combined positive score (CPS), which assesses PD-L1 expression on both tumour and immune cells.

"Metastatic breast cancer remains incurable, with many unmet needs and challenges. Triple negative breast cancer has the poorest prognosis among breast cancer subtypes and limited treatment options, mainly involving chemotherapy," said Prof. Sherene Loi, Medical Oncologist and Head of Translational Breast Cancer Genomics and Therapeutics at the Peter MacCallum Cancer Centre, Melbourne, Australia, commenting on the relevance of the new studies. "Immunotherapy has resulted in long durations of disease control and even cures with improved quality of life compared with chemotherapy in other cancers. We are hoping this might also be applicable for some breast cancer patients".

"Previous studies show that not all patients with metastatic breast cancer benefit from immunotherapy. Pre-existing immunity, which can be detected by PD-L1 expression, is required for response to PD-1 or PD-L1 targeting immunotherapy agents. The key question is whether we can identify further patients with metastatic breast cancer that respond to immunotherapy using biomarkers other than just PD-L1 expression."

To explore new potential biomarkers for immunotherapy in advanced breast cancer, researchers assessed the predictive value of copy number alteration (CNA) for the PDL1 gene, which measures whether the gene number has decreased, remained the same (2 copies, one on each chromosome) or increased. They measured CNA values in tumour tissue collected from 126 patients with metastatic breast cancer taking part in the SAFIR-IMMUNO study, the first randomised trial comparing immunotherapy with durvalumab to maintenance chemotherapy in this setting.

"The main predictive markers of immunotherapy efficacy in metastatic breast cancer to date are the absence of hormone receptors and PD-L1 positivity on immune cells," said lead author Prof. Thomas Bachelot, Director of the Breast Cancer Unit, Leon Berard Centre, Lyon, France. But he warned, "Immunohistochemistry analysis of PDL1 expression is not standardised and a more robust predictor of response to immunotherapy is needed."

Results showed that nearly one in four (23.8%) of the patients had copy gain (3 or 4 copies) or amplification (> 4 copies) of the PDL1 gene. Improvement of overall survival with durvalumab was limited to this group, with a median overall survival of 9 months (95% confidence interval [CI] 4-18) in the chemotherapy arm and not reached in the durvalumab arm (hazard ratio 0.17, 95% CI 0.05-0.55).

"This exploratory translational analysis suggested a higher efficacy of durvalumab as maintenance treatment for patients with PDL1 copy gain or amplification," said Bachelot. He suggested: "PDL1 copy number alteration could be an important predictive marker for PD-L1 inhibitor efficacy. If confirmed in larger series, this could have important implications for the development of immunotherapy in patients with metastatic breast cancer, enabling us to better identify patients that are sensitive to PD-L1 inhibitors than current testing for PD-L1 positivity on immune cells."

"At the moment patients with ER-positive breast cancer are not treated with immunotherapy because results of trials were poor. But maybe if we can select the subpopulation that will benefit—the 10% of patients with CNA abnormalities—and show immunotherapy is beneficial for them too, then this would be important," he explained.

Commenting on the potential relevance of the data, Loi said, "The study suggests that PD-L1 amplification may be a predictor for benefit to

durvalumab monotherapy, interestingly in all subtypes as well as in triple negative breast cancer." But she cautioned, "It was an unplanned, retrospective analysis so requires further validation in larger studies. There was no analysis presented of whether PD-L1 amplification was associated with overexpression at the protein level, which would be important to understand the underlying biological mechanism of this observation."

Improved health-related quality of life

A second study looked at health-related quality of life (HRQOL) in patients with metastatic triple negative breast cancer randomised to the PD-L1 inhibitor pembrolizumab or chemotherapy in the KEYNOTE-119 trial. Efficacy results for the trial showed no significant difference in overall survival but this analysis described patient reported outcomes for patients by their PD-L1 combined positive score (CPS). CPS is a novel biomarker that assesses PD-L1 expression on both tumour cells and immune cells in contrast to PD-L1 tumour proportion score (TPS), which has been used as a biomarker for immunotherapy in other cancers but fails to take account of immune cell PD-L1 expression.

"The benefit of pembrolizumab versus chemotherapy was observed in nearly all prespecified patient reported outcome endpoints," said lead author Prof. Peter Schmid, Lead of the Centre for Experimental Medicine at Barts Cancer Institute, Queen Mary University of London, UK. "Importantly, time to deterioration score for global health status/QoL scale was longer for patients treated with pembrolizumab compared to those treated with chemotherapy," he reported. The median time to deterioration was 4.3 months for pembrolizumab versus 1.7 months with chemotherapy (hazard ratio 0.70, 95% CI 0.46, 1.05). Scores for symptom scales for fatigue, nausea and vomiting, pain, dyspnoea and loss of appetite all increased with chemotherapy but remained stable or improved slightly with immunotherapy.

"In this CPS-enriched population of patients with metastatic triple negative breast cancer receiving second- and third-line treatments, health-related quality of life was better for patients receiving pembrolizumab than those receiving chemotherapy," said Schmid.

He added: "We are still learning a lot about immunotherapy in metastatic breast cancer. Trials for single agent immunotherapy in the first-line setting have not been positive. But these results clearly show there is a group of patients who do at least as well with single agent immunotherapy as chemotherapy in terms of survival and probably better in terms of quality of life."

Loi commented: "Patients who expressed high levels of PD-L1 protein according to their CPS score had better overall survival with pembrolizumab compared with chemotherapy, and pembrolizumab was far better tolerated than chemotherapy according to HRQOL measures. This underscores the importance of PD-L1 testing in the advanced setting as well as identifying other biomarkers that can help identify those who do best with pembrolizumab monotherapy given its favourable HRQOL impact."

More information: Abstract 128O 'PDL1/CD274 gain/amplification as a predictive marker of checkpoint blockade inhibitor efficacy in metastatic breast cancer: exploratory analysis of the SAFIR02-IMMUNO randomized phase II trial.' will be presented by Thomas Bachelot during the Best Abstracts session on Sunday 24 May 2020 12:45 to 14:15 (CET) on Channel 1. *Annals of Oncology*, Volume 31, Supplement 2, May 2020

The poster of abstract 141P 'Impact of Pembrolizumab Versus Chemotherapy on Health-Related Quality of Life in Patients with Metastatic Triple Negative Breast Cancer' by Peter Schmid will be on display in the e-Poster section of the Virtual Meeting Platform

throughout the Congress days. *Annals of Oncology*, Volume 31, Supplement 2, May 2020

K. Fizazi et al. A phase III trial of empiric chemotherapy with cisplatin and gemcitabine or systemic treatment tailored by molecular gene expression analysis in patients with carcinomas of an unknown primary (CUP) site (GEFCAPI 04), *Annals of Oncology* (2019). DOI: 10.1093/annonc/mdz394

Kulangara K, Zhang N, Corigliano E et al. Clinical utility of the combined positive score for programmed death ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. *Arch Pathol Lab Med* 2019; 143: 330-337

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