Researchers discover genetic link to predict positive response to immunotherapy in patient

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A Singapore team led by clinician-scientists and researchers from the National Cancer Centre Singapore (NCCS) discovered a genetic link to better predict treatment response for relapsed/refractory patients with

natural-killer T-cell lymphoma (NKTCL), a highly aggressive form of blood cancer. The team performed whole-genome sequencing, to identify mutation in PD-L1 gene as a reliable biomarker to identify lymphoma patients with a high likelihood of positive response to anti-PD-1 therapy, a type of immunotherapy, which has shown promising therapeutic results. The landmark findings were recently published in high-impact factor journal, *Leukemia*.

Natural-killer T-cell lymphoma (NKTCL) is a type of non-Hodgkin lymphoma which is prevalent in Asia. It is a rare and aggressive cancer that currently has no targeted therapy options. Standard treatment for NKTCL is a combination of chemotherapy and radiotherapy. However, patients with NKTCL have poor prognosis and often face relapses. The three-year overall survival rate is under 30 percent for high-risk patients.

The NCCS team embarked on this study in 2016, when a group of clinicians from Singapore and Hong Kong observed that some relapsed/refractory NKTCL patients responded very well to Pembrolizumab when standard treatment was no longer effective. Pembrolizumab, an anti-PD-1 monoclonal antibody, is a form of immunotherapy commonly used to treat lung cancer. Encouraging responses were observed with some patients eventually achieving complete remission with no trace of detectable cancer.

This positive observation led the team to delve into a deeper study of the use of anti-PD-1 therapy in NKTCL patients. The team sequenced the whole genome of the patients' pre-pembrolizumab treated tumors and studied their molecular profile. Upon discovering a structural alteration in the patient's PD-L1 gene, the team worked with collaborators in Singapore and countries including China, Hong Kong and South Korea to study more patients treated with pembrolizumab. A total of 19 relapsed/refractory patients were studied. An overall response of 47% (9/19) was observed of which 7 achieved complete response with no

trace of cancer detected in their blood and/or bone marrow. The gene alteration was found amongst 4 out of the 7 patients who responded favorably to pembrolizumab.

In 2017, SingHealth, the public healthcare cluster which NCCS is a part of, filed a patent for the technology, which was a result of the team's research on this genome response. A licensing agreement with Lucence Diagnostics has enabled the biotech company to develop this technology into a diagnostic test, to determine which patients will benefit from the targeted treatment. Development of this clinical assay has been completed and is ready for deployment.

Professor Lim Soon Thye, Deputy Group Chairman Medical Board, SingHealth; Deputy Medical Director, NCCS (Clinical); Senior Associate Dean, MD Programmes, Duke-NUS Medical School and Principal Investigator of the study said, "Guiding the choice of therapy is critical for cancer patients, where treatment must be timely and drugs can be costly. It is not easy to bridge the gap from bench to bedside, so it is particularly gratifying to be able to translate our findings into clinical applications that will directly benefit patients and healthcare systems."

Dr. Ong Choon Kiat, Principal Investigator, Division of Cellular and Molecular Research (CMR)—Lymphoma Genomic Translational Laboratory, NCCS, added, "The study of how NKTCL patients respond to immunotherapy has been limited to date. We are pleased that our study has identified robust biomarkers that reliably improve treatment selection for patients who will have a high likelihood of responding positively. This discovery of PD-L1 gene as a reliable response indicator was made possible with the participation of our patients and collaboration with multi-site partners."

Professor William Hwang, Medical Director, National Cancer Centre Singapore said, "This significant bench-to-bedside translation, will

provide patients with this aggressive form of blood cancer, with significant benefits in terms of health outcomes and cost savings. We are gratified to work with partners like Lucence Diagnostics who are developing test kits that will improve clinical outcomes and reduce healthcare costs for patients globally."

Dr. Tan Min-Han, Founding CEO and Medical Director of Lucence Diagnostics said, "Our vision is a world without cancer, and this partnership with National Cancer Centre Singapore will enable Lucence to deliver this innovative technology worldwide to achieve better treatment selection for NKTCL patients. We have already completed the assay development, and the test will be progressively made available in Asia and the United States."

More information: Jing Quan Lim et al, Whole-genome sequencing identifies responders to Pembrolizumab in relapse/refractory natural-killer/T cell lymphoma, *Leukemia* (2020). DOI: 10.1038/s41375-020-1000-0

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