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MEDIA RELEASE

DUAL-PATHWAY BLOCKADE THERAPY OFFERS HOPE FOR RARE, HARD-TO-TREAT GYNAECOLOGICAL CLEAR CELL CANCERS

International study demonstrates promising clinical activity of pembrolizumab plus lenvatinib in recurrent disease, addressing a longstanding treatment gap

SINGAPORE – Before her cancer diagnosis in early 2017, 48-year-old Caitlin Delaney, who is based in Australia, had been struggling with a troubling mix of symptoms comprising extreme fatigue, chronic sinusitis, and appetite changes including a sudden aversion to foods such as chocolate and alcohol. Detailed tests and scans eventually revealed the cause - an advanced stage of clear cell ovarian cancer. For another patient, Michelle (not her real name), aged 49, the road to diagnosis came in late 2022 after months of persistent acid reflux, bloating, and ongoing indigestion, which similarly pointed to the same cancer – clear cell carcinoma of the ovary.

Both women underwent the conventional course of treatment involving surgery and chemotherapy, but their cancers later returned and spread to areas including the lymph nodes. Their conditions began to stabilise only after turning to a newer treatment approach that combines two medicines, pembrolizumab and lenvatinib. Caitlin accessed the treatment in Australia on the recommendation of Associate Professor David Tan, Senior Consultant, Department of Haematology-Oncology, National University Cancer Institute, Singapore (NCIS). Michelle received it as part of a new international clinical trial led by clinicians and scientists from Singapore and South Korea[1], for which Assoc Prof Tan was the corresponding author.

The trial, known as the LARA trial, was initiated through the Asia Pacific Gynecologic Oncology Trials Group (APGOT) that was founded by Assoc Prof Tan, and Professor Byoung Gie Kim of Chung-Ang University Gwang-myeong Hospital, one of the study's lead investigators from South Korea. Assoc Prof Tan is also Associate Professor in the Department of Medicine at the Yong Loo Lin School of Medicine (NUS Medicine) and Principal Investigator at the Cancer Science Institute of Singapore (CSI Singapore) at NUS.

The other lead investigators included Professor Jung Yun Lee of Yonsei Cancer Centre and Severance Hospital, Professor Jae-Weon Kim of Seoul National University College of Medicine, and Professor Chel Hun Choi of Samsung Medical Centre.

Besides NCIS, the Singapore institutions involved in this study included the National University Hospital, the National Cancer Centre Singapore, and the National University of Singapore (NUS) through CSI Singapore at NUS, NUS Saw Swee Hock School of Public Health and NUS Medicine.

[1] Participating institutions include Yonsei Cancer Center and Severance Hospital, Yonsei University College of Medicine, Soonchunhyang University College of Medicine, Seoul National University College of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine and Chung-Ang University Gwang-myeong Hospital.

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Advancing new options for clear cell gynaecological cancer treatment

Published in *The Lancet Oncology*[2], the multicentre, single-arm Phase 2 trial (LARA) found that combining pembrolizumab with lenvatinib shows promise for patients with recurrent clear cell endometrial (womb) and ovarian cancers who had previously developed resistance to standard ovarian cancer treatments. While similar drug combinations have been studied in other parts of the world, LARA provides the first Asia-led, multicentre data set showing that pembrolizumab plus lenvatinib can achieve encouraging responses in this rare and difficult-to-treat cancer subtype.

Clear cell cancers of the ovary and endometrium are widely recognised as clinically challenging, with many patients showing poor responses to standard chemotherapy. In a previous APGOT study in recurrent ovarian clear cell carcinoma, the MOCCA trial[3], response rates to immunotherapy alone were only 9.7 per cent, and responses to chemotherapy were only 18.8 per cent with 50 per cent of patients progressing by 1.7 months and 3.5 months respectively. Although clear cell cancer makes up an estimated one to 12 per cent of epithelial ovarian cancers in North America and Europe[4], the proportion is noticeably higher in Singapore and South Korea[5], reaching up to nearly 30 per cent in Japan[6]. This underscores the need for more effective treatment strategies for ovarian clear cell cancer patients in this region.

One reason these cancers are difficult to treat is their unique biology. Clear cell tumours often have unusual cell features, abnormal blood vessel growth and a tumour environment that helps them evade the immune system. To tackle this, the LARA trial explored a dual-pathway approach. Lenvatinib was used to block signals that support tumour growth and blood-vessel formation, while also helping to make the tumour environment more accessible to immune cells. Pembrolizumab then boosted the body's immune response to recognise and attack cancer cells. This combination is already approved for use in patients with recurrent clear cell endometrial cancer, but not for patients with clear cell ovarian cancers, which represent 30 per cent of all new patients diagnosed with ovarian cancer in Singapore.

Conducted between March 2021 and October 2023 in Singapore and South Korea, the study enrolled patients with either ovarian or endometrial clear cell cancers. Each patient received pembrolizumab as an intravenous infusion every three weeks, together with a daily oral dose of lenvatinib. Among the 25 patients, only three were diagnosed with endometrial cancers and the majority of patients had recurrent clear cell ovarian cancer.

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[2] Ngoi NYL, Lee JY, Lim D, Thian YL, Lim YW, Chan JJ, Chay WY, Zhang Z, Gopinathan A, Lim SE, Low J, Ng J, Tong P, Lee YJ, Park J, Kim JW, Tan TZ, Zhu J, Tai BC, Choi CH, Kim BG, Tan DSP. Pembrolizumab plus lenvatinib in recurrent gynaecological clear cell carcinoma (LARA): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2026 Jan 15:S1470-2045(25)00662-X. doi: 10.1016/S1470-2045(25)00662-X.

[3] Ngoi NYL, Choi CH, Zhu J, Lim D, Tan TZ, Sun H, Heong V, Ow SGW, Chay WY, Kim HS, Lim YW, Lim SE, Goss G, Goh JC, Kim JW, Friedlander M, Tai BC, Kim K, Tan DSP. Durvalumab versus Physician's Choice Chemotherapy in Recurrent Ovarian Clear Cell Adenocarcinoma (MOCCA/APGOT-OV2/GCGS-OV3): A Multicenter, Randomized, Phase 2 Trial. Clin Cancer Res. 2025 Sep 15;31(18):3907-3915. doi: 10.1158/1078-0432.CCR-25-0201. PMID: 40705396; PMCID: PMC12440240.

[4] del Carmen MG, Birrer M, Schorge JO. Clear cell carcinoma of the ovary: a review of the literature. Gynecol Oncol. 2012 Sep;126(3):481-90. doi: 10.1016/j.ygyno.2012.04.021. Epub 2012 Apr 21. PMID: 22525820.

[5] Wijaya ST, Ngoi NY, Loh JW, Tan TZ, Lim D, Khan IS, Thian YL, Lai A, Ang BW, Tong P, Ng J, Low JJ, Ilancheran A, Lim SE, Lim YW, Tan DS. Comprehensive characterization of genomic features and clinical outcomes following targeted therapy and secondary cytoreductive surgery in OCCC: a single center experience. J Gynecol Oncol. 2024 Sep;35(5):e69. doi: 10.3802/jgo.2024.35.e69. Epub 2024 Mar 29. PMID: 38606821; PMCID: PMC11390249.

[6] Machida H, Matsuo K, Yamagami W, Ebina Y, Kobayashi Y, Tabata T, Kanauchi M, Nagase S, Enomoto T, Mikami M. Trends and characteristics of epithelial ovarian cancer in Japan between 2002 and 2015: A JSGO-JSOG joint study. Gynecol Oncol. 2019 Jun;153(3):589-596. doi: 10.1016/j.ygyno.2019.03.243. Epub 2019 Mar 21. PMID: 30905436; PMCID: PMC7526703.

When assessed for the primary outcome, 40 per cent experienced confirmed tumour response (shrinkage of 30 per cent or more) within the first 24 weeks of treatment, with median progression free survival of 6.4 months (meaning an estimated 50 per cent of patients survived beyond 6.4 months without disease progression). Side effects were manageable, and importantly, no treatment-related deaths were reported. Supporting these clinical findings, the bioinformatic analyses for the LARA trial were conducted at CSI Singapore. These included RNA sequencing, molecular subtyping, pathway interrogation and statistical modelling to correlate tumour biology with patient outcomes.

Assoc Prof David Tan said, “Our study points to the potential for immunotherapy plus targeted therapy to provide benefit in this hard-to-treat disease, and reinforces the need to explore this regimen further for patients with clear cell cancers of the ovary whose disease has progressed after previous treatment. Ovarian clear cell cancers are a clinically aggressive subtype that is rare in western countries but relatively common in Singapore where currently approved treatments often fall short. That is why exploring this combination matters as it could offer a much-needed option to better outcomes.”

Assoc Prof Tan added, “The response rates from the LARA trial far exceeded historical data in this disease. Furthermore, a US study[7] also recently presented similar results with this combination in recurrent clear cell ovarian cancers, hence providing further validation of our results. Currently approved therapeutic options have only shown limited activity in this tumour type, and we, as a scientific community, have a duty to advocate for our patients and adopt the treatments that provide the best available evidence for efficacy. We are currently working to try to get this combination into the US National Comprehensive Cancer Network (NCCN) guidelines, which would then guide our subsequent efforts to make this treatment available for patients in Singapore.”

Both Caitlin and Michelle experienced meaningful gains from this new therapy, even though it did not remove cancer from their lives. For Caitlin, the nearly two and a half years on the therapy brought some of the most stable and fulfilling moments of her journey, allowing her to continue social activities, exercise, and patient advocacy before she had to stop the treatment as her cancer progressed. For Michelle, despite discontinuing the trial after just a month due to rising liver enzymes, the tumours in her neck and pelvic lymph nodes continued to shrink even after stopping treatment. In different ways, the therapy helped each woman achieve better disease control, improved energy, and the ability to continue doing the things that mattered most to them.

Dr Natalie Ngoi, Consultant, Department of Haematology-Oncology, NCIS, who was the first author of the study, said, “We must not forget to credit our patients who believed in this idea. At the end of the day, it is all about the patients. Trials like ours are small but mean a lot for patients with rare cancer subtypes who are often excluded from larger randomised trials that focus on the common cancer subtypes. Rare cancers like clear cell gynaecological cancers are an area of urgent unmet clinical need where more trials should be dedicated to their study, in order to improve clinical outcomes for our patients.”

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[7] Lee, Elizabeth & Zhou, Yinglu & Hendrickson, Andrea & Fleming, Gini & Krasner, Carolyn & Konstantinopoulos, Panagiotis & Stover, Elizabeth & Horowitz, Neil & Porter, Rebecca & Wright, Alexi & Matulonis, Ursula & Xiong, Niya & Sawyer, Hannah & Tayob, Nabihah & Liu, Joyce. (2025). A phase II trial of pembrolizumab and lenvatinib in recurrent or persistent clear cell ovarian carcinoma (NCT05296512).. Journal of Clinical Oncology. 43. 5515-5515. 10.1200/JCO.2025.43.16_suppl.5515.

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Chinese Glossary

National University Cancer Institute, Singapore (NCIS)	新加坡国立大学癌症中心 (国大癌症中心)
National University Hospital (NUH)	国立大学医院(国大医院)
National Cancer Centre Singapore	新加坡国立癌症中心
National University of Singapore (NUS)	新加坡国立大学
Cancer Science Institute of Singapore at NUS (CSI Singapore)	国大新加坡癌症科学研究所
NUS Saw Swee Hock School of Public Health	国大苏瑞福公共卫生学院
NUS Yong Loo Lin School of Medicine	国大杨潞龄医学院
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About the National University Cancer Institute, Singapore

The National University Cancer Institute, Singapore (NCIS) is an academic, national specialist centre for cancer under the National University Health System (NUHS), and is the only public cancer centre in Singapore that treats both paediatric and adult cancers in one facility.

As one of two national cancer centres in Singapore, NCIS (pronounced as “n-sis”) offers a broad spectrum of cancer care and management from screening, diagnosis and treatment to rehabilitation and survivorship, as well as palliative and long-term care. NCIS’ strength lies in the multi-disciplinary approach taken by our clinician scientists and clinician-investigators to develop a comprehensive and personalised plan for each cancer patient.

NCIS provides the full suite of specialised oncology and haematology services at the NUH Medical Centre at Kent Ridge, Singapore, including those by the NCIS Chemotherapy Centre, NCIS Radiotherapy Centre and NCIS Cellular Therapy Centre.

NCIS also offers cancer services at other hospitals in Singapore:
• NCIS Cancer & Blood Clinic @ Ng Teng Fong General Hospital
• NCIS Radiotherapy Centre @ Tan Tock Seng Hospital
• NCIS Radiotherapy Clinic @ Khoo Teck Puat Hospital

To bring cancer care even closer to our patients, our NCIS on the Go programme delivers a range of cancer services at clinics within the community for their convenience.

For more information, please visit www.ncis.com.sg.

About the National University of Singapore

The National University of Singapore (NUS) is Singapore’s flagship university, which offers a global approach to education, research and entrepreneurship, with a focus on Asian perspectives and expertise. We have 15 colleges, faculties and schools across three campuses in Singapore, with more than 40,000 students from 100 countries enriching our vibrant and diverse campus community. We have also established more than 20 NUS Overseas Colleges entrepreneurial hubs around the world.

Our multidisciplinary and real-world approach to education, research and entrepreneurship enables us to work closely with industry, governments and academia to address crucial and complex issues relevant to Asia and the world. Researchers in our faculties, research centres of excellence, corporate labs and more than 30

university-level research institutes focus on themes that include energy; environmental and urban sustainability; treatment and prevention of diseases; active ageing; advanced materials; risk management and resilience of financial systems; Asian studies; and Smart Nation capabilities such as artificial intelligence, data science, operations research and cybersecurity.

For more information on NUS, please visit nus.edu.sg.

About the Cancer Science Institute of Singapore (CSI Singapore)

The Cancer Science Institute of Singapore (CSI Singapore) is a University Research Institute at the National University of Singapore (NUS). Officially launched on 15 October 2008, CSI Singapore aims to position Singapore as a global-leader in the field of Biomedical Sciences. Its mission is to better understand the causes of human cancer across Asia, and thereby improve its detection, treatment and prevention for the benefit of the patients. The CSI Singapore's outstanding researchers and excellent scientific facilities create an energetic environment for ground-breaking research and world-class training. The CSI Singapore is internationally recognized for its innovative research on the biology of cancers prevalent in Asia, and for taking new methods for cancer treatment from the laboratory to the clinic. Through its local and global partnerships, the CSI Singapore works with leading minds from multiple scientific and clinical disciplines, both in academia and in industry.

For more information on CSI Singapore, visit https://csi.nus.edu.sg/

About the National Medical Research Council (NMRC)

The NMRC was established in 1994 to oversee research funding from the Ministry of Health and support the development and advancement of biomedical research in Singapore, particularly in the public healthcare clusters and medical schools. NMRC engages in research strategy and planning, provides funding to support competitive research grants and core research enablers, and is responsible for the development of clinician scientists through awards and fellowships. The council's work is supported by the NMRC Office which is part of MOH Holdings Pte Ltd. Through its management of the various funding initiatives, NMRC promotes healthcare research in Singapore, for better health and economic outcomes.