Lady Garden Foundation report December 2023



2023 Lady Garden Foundation achievements



9 innovative research projects currently taking place at The Royal Marsden



3 exciting research projects approved by the Scientific Committee in November and due to start in 2024



1 Highly Specialist Counselling Psychologist to support patients through their cancer journey



1 Consulting Room within the state-of-the-art Oak Cancer Centre



1 Professorship awarded to Lady Garden Foundation funded researcher, Professor Susana Banerjee



Dear Lady Garden Foundation,

Thank you very much for your continued commitment to improving the lives of gynaecological cancer patients through your support of The Royal Marsden Cancer Charity. I am very pleased to update you on the work you have funded at The Royal Marsden over the past year.

2023 has been another exciting year with your busy events calendar and engaging campaigns. We were delighted to support the Lady Garden Family Challenge in April and the fantastically pink Langan's lunch in September, two very popular and successful events. Your brand-new carol concert

event will take place later this December, and we're sure it will be a very special evening for all those in attendance. You called for the change of the archaic name of the virgin speculum, during your cervical cancer awareness week campaign, which is an important step in helping to remove unhelpful taboos around women's health. During Gynaecological Cancer Awareness Month in September, you visited universities across the country to raise awareness of the five gynaecological cancers and their symptoms among younger women.

This year saw your continued funding of projects spanning many areas of gynaecological cancer research. You are supporting the next generation of researchers by funding Andreia Fernandes' Pre-Doctoral Fellowship. She hopes to improve the follow-up experience of women treated for gynaecological cancer by taking patients' lived experiences into account. Lady Garden Foundation funding also helped enable the opening of the Oak Cancer Centre in Sutton, which we were delighted to celebrate with Lady Garden Foundation representatives in June this year. Exciting progress has also taken place in the projects you approved for funding last July. Dr Ben O'Leary and Dr Susan Lalondrelle opened the gynaecological arm of the ORIGINS-Gynae study in May 2023 and eagerly anticipate the recruitment of the first patient. Professor Banerjee's work in PARP inhibitor resistance is also progressing well, with sample analysis due to commence imminently. You can read about these projects and more in the pages ahead.

You will also remember that in October we celebrated the news that Professor Susana Banerjee was awarded the title of Professor by the Institute of Cancer Research. We are thrilled for her and grateful to all members of the Lady Garden Foundation committee for your commitment to Professor Banerjee's work over the past nine years.

The third Lady Garden Foundation Scientific Committee meeting was held in November, with three high quality research proposals approved for funding. You are supporting new projects led by Dr Angela George and Dr Katherine Vroobel, Professor Amy Berrington and Professor Susana Banerjee, and Dr Susan Lalondrelle.

Thank you once again for your unwavering support of gynaecological cancer research at The Royal Marsden. You are improving the lives of cancer patients at The Royal Marsden, across the UK and worldwide.

With kindest regards,

McDualy

Antonia Dalmahoy Managing Director, The Royal Marsden Cancer Charity

Projects approved for funding in November 2023 and funded from October 2023

Following the third meeting of the Lady Garden Foundation Scientific Committee in November, three high quality research proposals were approved for funding. Thank you very much for making these projects possible. We are pleased to summarise these below.

Carcinogenesis of endometriosis and development of endometriosisassociated ovarian cancer

Led by Dr Angela George and Dr Katherine Vroobel

Some individuals with endometriosis will go on to develop aggressive ovarian cancers within the endometriosis. These tumours are generally multifocal, with very high rates of relapse and new primary tumours in the remaining endometriosis. Recent research into the role of inflammation and cancer has suggested several mutations and molecular signatures may be present in other proinflammatory conditions that can induce cancers.

The team will undertake genomic sequencing to look for biomarkers to indicate those at higher risk of developing ovarian cancer. This could allow earlier detection; or more aggressive management of the endometriosis to prevent subsequent cancer.

The impact of lifestyle before and after diagnosis on survival from ovarian cancer

Led by Professor Amy Berrington and Professor Susana Banerjee

Currently, little is known as to whether lifestyle can improve ovarian cancer survival. This study will examine this question for ovarian cancer using the unique data from the UK Generations Study. In this nationwide prospective study 113,000 women completed multiple questionnaires before and after their cancer diagnoses. 602 cases of ovarian cancer were identified and 200 have died of the disease. The team will provide evidence-based recommendations for lifestyle modifications that can improve patient prognosis and survival.

Adaptive personalised radiotherapy for gynaecological cancers

Led by Dr Susan Lalondrelle

This project will develop new protocols and trials for the delivery of online adaptive radiotherapy (oART) for gynaecological cancer patients, providing an individualised radiotherapy plan each day of treatment. A Clinical Research Fellow will study the improvements in the accuracy of treatment delivery and the reduction in side effects gained with this approach. They will also implement clinical studies through a national competency and training programme to support the rollout of this technique to other centres, to benefit gynaecological cancer patients around the UK.

Highly Specialist Counselling Psychologist

This year, LGF committed to fund a Highly Specialist Counselling Psychologist post. The Royal Marsden's Psychological Support Service provides support to patients and their families throughout their treatment at The Royal Marsden. The service is essential to ensuring that the mental health of patients is treated alongside their physical conditions, reinforcing the hospital's commitment to providing holistic care.

This highly specialised role, which is undertaken by psychologist Holly North, focuses on coordinating the inpatient psychological support for patients and their families across the hospital. Holly supports inpatients with numerous matters including adjustment following surgery, side effects of cancer and treatment, talking to children, and supporting individuals whose mental health may be impacting on their ability to engage with their cancer care or treatment.

The role supports all patients who need it and ensures the most vulnerable patient groups can access cancer care and treatment.

Holly said, "My role, and the wider psychology team are crucial in improving the quality of life and experience for our cancer patients. I am very proud to be able to contribute to this vital work and look forward to being able to continue helping patients through their cancer diagnosis and treatment."

Update on projects approved for funding in July 2022

Seeking genomic insights into radiotherapy-resistant gynaecological squamous cell cancers: ORIGINS-Gynae

ORIGINS is a multi-centre sample collection study which will allow organoid (a 3D miniaturised and simplified version of an organ that mimics its key functions and shows realistic micro-anatomy) generation and molecular analysis of tumours. Gynae cancer is one arm of the study, the others being head and neck cancer, prostate cancer, and colorectal cancer.

Thanks to funding from Lady Garden Foundation, ORIGINS-Gynae aims to explore whether cervical, vaginal and vulval cancers which recur after radiotherapy, have specific changes in DNA that could be used to identify patients at a higher risk of relapse, or provide insights into why particular cancers cannot be cured by radiotherapy. Through ORIGINS-Gynae, researchers aim to complete paired molecular analysis for tumours before and after radiotherapy.

As a result of the study, the organoid models generated could also be used by the wider research community to explore gynae squamous cell cancer biology.

ORIGINS-Gynae opened in May 2023. The team are awaiting recruitment of the first patient and are in close contact with the surgical team.

Within the laboratory, good progress has been made. The team have undertaken further validation of a custom next-generation sequencing assay, designed to assess human papillomavirus (HPV) in cancers. The study continues to focus on HPV+ cancer cells initially, as HPV features in many gynaecological cancers so is important to consider in the analyses. The assay is working well and can identify how HPV is integrated into the genome of cancers. This has been tested on a cell line and nongynaecological HPV-related tumours collected outside the ORIGINS-Gynae study. It has also Dr Ben O'Leary, Clinical Scientist and Honorary Consultant Clinical Oncologist, one of the leads of ORIGINS-Gynae



been tested by analysing the plasma of a patient with cervical cancer, and successfully identified the presence of cancer-derived HPV in the blood. This is promising and suggests that the team will have success using this approach in the ORIGINS-Gynae study when patients have been recruited.

The team have also begun work on a different test for HPV, using a technique called 'digital PCR'. Digital PCR splits the sample into tiny microsamples. Therefore, instead of essentially looking for a needle in a haystack, the new test allows for the detection of HPV down to single copies of DNA. This is in the early stages but showing promising results so far.

The ORIGINS-Gynae team are also collaborating closely other teams who have an interest in HPV. This includes the head and neck cancer team, who are interested in using these assays to examine HPV and its relevance to cancer genomics and radiotherapy response, and the investigators of the PLATO trial, a radiotherapy study in anal cancer, another disease related to HPV infection.

Fat Tissue Grafting to Treat Symptoms of Vaginal Stenosis in Women with Gynaecological Cancer

Cervical cancer and its associated treatments, especially radiotherapy, can cause several changes in the vagina such as narrowing, shortening, dryness and bleeding, known as vaginal stenosis. Consequently, women can experience significant pain during sex, loss of sexual pleasure and some women become unable to have sex. This can, in turn, cause sexual avoidance, relationship problems, feelings of low self-esteem, isolation and difficulties initiating new relationships.

In 2021, a new technique called 'Fat Tissue Grafting' was used in one patient with severe vaginal stenosis after radiotherapy treatment for advanced cervical cancer, by the Gynaecological and Plastic Surgical teams at The Royal Marsden. This technique uses fat tissue that is removed from other parts of the body – usually thighs, belly, and buttocks – by liposuction. The fat tissue is prepared and injected into the vagina area to generate more elasticity and improve the quality of the vaginal tissue. As a result of the procedure, the patient now reports reduction in vaginal bleeding and pain experienced, and a noticeable improvement in the size of the vagina allowing for penetrative sex.

Fat grafting has successfully been used for some years to rectify the cosmetic and functional consequences of Breast and Head and Neck Cancer treatments but the Gynaecological team believe it has never been used before in Gynaecology-oncology.

The experience of the patient mentioned above motivated the Gynaecological and Plastic surgical teams to conduct a feasibility study, looking in detail at the experience of a small number of women receiving this new treatment.

Progress-to-date

The study is launching imminently – the team are at the final ethics approval stage, which has taken longer than anticipated.

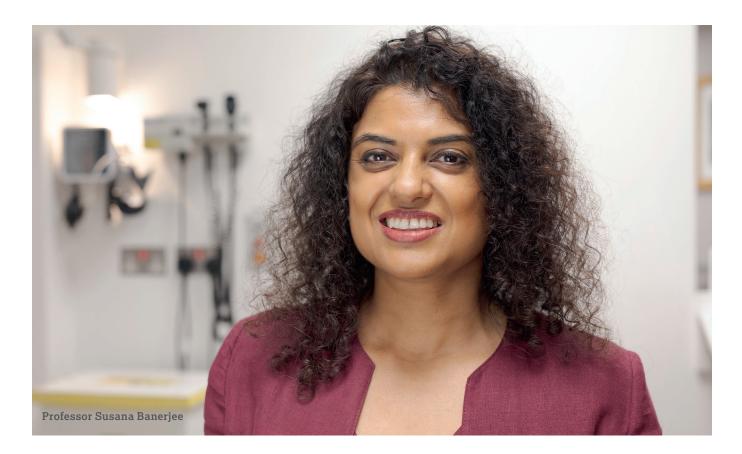
Next steps

The trial will recruit eight patients, six of whom have been approached and are interested. Patients will receive three fat tissue grafting procedures at three-month intervals. Patients will receive three fat tissue grafting procedures at three-month intervals. Biopsies will be taken at each procedure to assess improvement of the vaginal wall. Participants will also receive a pelvic MRI scan and be seen in the surgical gynaecological clinic. They will also be asked to fill in questionnaires at several points throughout the study and invited to join a virtual focus group, where an experienced nurse researcher will be able to capture qualitative data. Women receiving this treatment will follow a supportive rehabilitation programme. Symptoms and mental health scores pre- and post-treatment will be compared to help measure the effect that fat grafting has had on women's symptoms and lives.

The team hopes that the results of this feasibility study will be presented at national and international gynaecological oncology and plastics surgery conferences. They also aim to publish in peer reviewed journals. If the study is successful, they also plan to set up a larger, multicentre study, to look at reproducibility of the outcomes. This study serves as an excellent example of how cross-discipline work focused on patients' needs can produce groundbreaking solutions to complex clinical issues.

Ms Marielle Nobbenhuis is leading the Fat Tissue Grafting to Treat Symptoms of Vaginal Stenosis in Women with Gynaecological Cancer study





Assessing the reasons for PARP inhibitor resistance in some women with ovarian cancer

PARP inhibitors, such as the drug niraparib, have transformed the care of women worldwide with newlydiagnosed and recurrent ovarian cancer, helping to increase remission rates. However, they do not work for all women with ovarian cancer and for some, resistance can develop, causing the cancer to worsen or return.

Circulating tumour DNA sequencing, known as 'liquid biopsies' – simple blood tests that can be used to help find cancer – provide a convenient and noninvasive way to assess and monitor the development of PARP inhibitor resistance in patients.

This trial, led by Professor Banerjee, is collecting blood and tumour samples from women with newly diagnosed, or relapsed ovarian cancer, who are being treated with niraparib and are enrolled in The Royal Marsden sponsored Monitor-UK study. It is using a targeted sequencing gene panel developed by the Institute of Cancer Research and The Royal Marsden to detect mutations or changes in specific genes known to be implicated in the development of PARP inhibitor resistance.

Progress to-date

The Monitor-UK study is progressing very well. Recruitment will finish early, in May 2024, as the team will have successfully reached the target number of patients enrolled, and sample collection is well underway.

Next steps

Sample analysis is due to commence in July 2024.

Update on projects funded from February 2022

Pre-Doctoral Fellowship – 'Development of a safe and personalised follow-up approach for women with gynaecological cancer'

Andreia Fernandes, Lead Nurse for Gynae-oncology at The Royal Marsden is undertaking this Pre-Doctoral Fellowship, thanks to funding from the Lady Garden Foundation. The Fellowship Programme enables participants to develop their research skills and produce the necessary data to springboard onto a National Institute for Health Research (NIHR) Clinical Doctoral Research Fellowship (CDRF) or another appropriate scheme, to undertake their doctorate.

Andreia began her Fellowship in April 2022, and anticipates completing it within the next few months. The Fellowship has taken slightly longer than initially expected due to increased clinical demand, resulting in less time for Andreia to focus on her research work. Andreia is currently finishing her draft research paper for publication, and with support from her supervisory team, she is finalising the research question she will use for her PhD. Professor Susanne Cruickshank, Strategic Lead for Applied Health Research at The Royal Marsden, will continue to be on of Andreia's supervisory team when she starts her PhD in March 2024.

During her Fellowship, Andreia reviewed and appraised existing published literature and found that allocating women to models of follow-up care is based on risk of recurrence and the resources available to deliver this care. She found that both 'patient choice' and a framework to guide clinicians based on individual need were both absent from this process.

Andreia has developed her research skills by using the Vitae Researcher Development Framework. This sets out the wide-ranging knowledge, intellectual abilities, techniques, as well as the personal qualities, knowledge, and skills to work with others and ensure the wider impact of research.

Andreia was also keen to use the Fellowship to expand her expertise in working with patients and members of the public in research. She joined the Equality, Diversity, and Inclusion Patient & Public Contributors Group at The Royal Marsden. The work



of this group addresses inclusion, equality, diversity and equity in membership and patient and public involvement in clinical services, and research across The Royal Marsden and the ICR. This opportunity enabled her to have more interaction with patient and public groups, and build a collegial network in this subject area, that will help shape her future research.

Andreia is passionate about the care received by gynaecological cancer patients. She hopes to be able to influence national policy and develop a safe and personalised approach to follow-up care for women who have been treated for gynaecological cancers.

Andreia is extremely grateful for the opportunity given by the Lady Garden Foundation to undertake the Pre-Doctoral Fellowship, and she looks forward to completing her Fellowship in the coming months, and taking what she has learnt during the Fellowship into her PhD research.

Update on projects approved for funding in March 2021

TROPICCANA trial

The TROPICCANA (Treatment Response In Cervix Cancer Assessed by circulating HPV DNA) trial will test whether a simple blood test can be used to detect cervical cancer persistence or recurrence after treatment with chemo-radiation. The team will test the hypothesis that if no circulating HPV DNA (HPV being the virus associated with 90% of all cervical cancer) is detectable three months after treatment is completed, this will show that treatment has been successful. The researchers will also study if circulating HPV DNA is re-detected when a patient relapses.

As a multi-centre trial using a novel approach to HPV DNA analysis in cervical cancer, TROPICCANA has faced some delays. A new multi-centre trial can be complex in its set up and this has taken longer than initially anticipated. Dr Lalondrelle is pleased to confirm that six centres across the UK have now signed up for the trial – UCLA, Guys and St Thomas', Glasgow, Taunton, Bath and Manchester and they are ready to begin recruitment at the end of January 2024.

In addition to the complex nature of the setup of this trial, Dr Lalondrelle has also faced delays at The Royal Marsden due to capacity issues within the trials team. This meant that the project needed to be temporarily paused as the team completed ongoing work. We are pleased to report that the trials team have now resumed this project and once recruitment opens at the end of January, they expect to make good progress in line with the original timeframe.

Dr Lalondrelle is looking forward to recruitment opening in the New Year. The project remains novel, with exciting potential to be able to use a simple blood test to monitor patients for response to treatment and to use it as a tool to predict relapse. We look forward to updating you on this project as it develops.

Incorporating advanced machine learning methodologies into radiotherapy planning for gynaecological cancer (AMLART)

Artificial intelligence has great potential to improve radiotherapy treatment. The current process of directing radiotherapy to the target area involves manually drawing around tumours on a CT scan to differentiate them from healthy tissue and organs. This is very time-consuming and results in variation – multiple clinicians manually contouring might have different judgments on where the tumour ends due to image quality or because the tumour is hard to reach. This is known as delineation uncertainty.

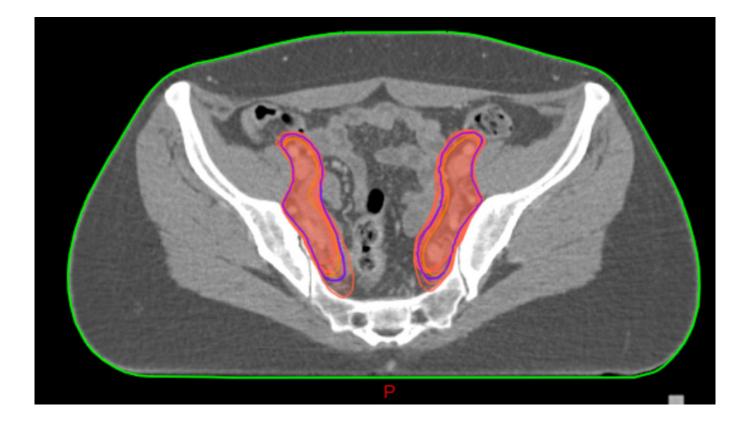
Machine Learning (ML) models have shown promising results for improving contouring accuracy for delineation (called auto-contouring). However, this being a pioneering area of research, very little has been done to evaluate and integrate these methods safely and accurately into the radiotherapy planning process.

This AMLART study investigates how to develop and safely implement machine learning models into cervical cancer radiotherapy treatment. It will assess training and validation metrics and explore novel approaches to account for delineation uncertainty. It aims to improve accuracy in radiotherapy and ultimately improve the overall quality of treatment for patients.

Progress to-date

Dr Katherine MacKay commenced as a clinical research fellow, under the guidance of Dr Alexandra Taylor, in September 2021 and she has now completed the planned two years on the AMLART project, thanks to the funding received from Lady Garden Foundation.

The past 12 months have seen significant advances in the project. Dr MacKay and the team used the ML model and the training data completed in the first year of the project to produce auto-contours on scans of people who had previously been treated. They then trained five Royal Marsden clinicians to contour according to the specific manual contour protocol,



developed in the first year of the project. This was necessary as the data used to train the ML model was just Dr MacKay's manual contouring, which doesn't account for delineation uncertainty. The manual contouring from the five clinicians highlighted the level of variation between observers (inter-observer variation), and even the variation by the same clinician if they repeat the process independently (intra-observer variation).

The above CT scan of pelvic lymph nodes shows the manual contouring (orange), and the ML auto-contour (purple). The various orange outlines indicate the delineation uncertainty.

The range given by the manual delineation uncertainty suggests that when assessing the efficacy of the ML model, we should be checking whether the auto-contours fall into the manual range, rather than if they match a baseline.

The team have now calculated the delineation uncertainties produced by manual contouring, and are in the process of comparing that to the auto-contours produced from the training data.

A systematic review of the assessment metrics used for auto-contouring has now been completed and was published in February 2023. This paper showed that there is a lack of consensus on how to best assess auto-contouring systems, and proposed an evaluation method for each stage of auto-contouring model development and implementation. A proposed method for qualitative assessment of auto-contours has been developed and tested using 20 observers to score multiple auto-contours. The final results are currently being evaluated, with initial results showing considerable inter-observer and intraobserver variation in the scoring of auto-contours.

Next steps

Dr MacKay is now in the process of finalising her thesis and has submitted two abstracts to the European Society for Therapeutic Radiology and Oncology (ESTRO) 2024 scientific programme.

As a result of the team's experience in this project, they are now leading on a national Royal College of Radiologists (RCR) guidance document for clinicians on ML auto-contouring in radiotherapy. They are also working with the National Institute for Health and Care Excellence (NICE) and NHS England on national initiatives for assessing this technology. This has been drafted and the team aim to complete this early next year. This is all thanks to your support.

Furthermore, the funding from Lady Garden Foundation for Dr MacKay to undertake this project has helped develop a young researcher in this new and evolving field. She is now a member of the Royal College of Radiologists (RCR) Artificial Intelligence working group, and lead the auto-contouring workshop at the RCR Annual conference in October 2023. Fam so grateful to Lady Garden Foundation for giving me this opportunity to pursue research in this exciting new area of AI and Machine Learning. The research we've been able to undertake shows huge promise in improving radiotherapy treatment for patients with cervical cancer.

Dr MacKay



The next stage of this project will evaluate how artificial intelligence can be used to incorporate these delineation uncertainties into novel approaches to radiotherapy planning. The team are pleased to share that they have been successful in obtaining an ICR PhD fellowship to continue the work from this project. They are also applying for the funding for a dedicated computer scientist to support this work.

Predicting treatment benefit in low grade serous ovarian cancer (LGSOC) – tumour and liquid biopsy mutation analysis

Low grade serous ovarian cancer, a rare type of ovarian cancer, often affecting younger women, does not respond well to standard chemotherapy and further research is urgently needed to develop more effective treatments. Professor Banerjee is seeking to determine whether mutations in a gene named KRAS, and others, can be detected in the blood of patients with LGSOC, to help identify which patients will benefit from treatment. Lady Garden Foundation is funding the blood and tumour sample analysis.

Progress to-date

Initial analysis of blood and tumour samples to try and detect KRAS mutations began in March 2022. This is now complete; there are no official results yet, but initial findings are exciting and have the potential to influence the RAMP201 and 301 trials.

The international phase 2 RAMP-201 study, led by Professor Banerjee, is trialling avutometinib alone and in combination with defactinib for patients with LGSOC. The drugs are designed to block signals that encourage cancer cells to grow.

Results were presented at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting in June 2023, and showed that the drug combination could be nearly twice as effective as the next best treatment. Responses to the drug combination were particularly promising in those with a mutation in a gene called KRAS.

RAMP-301 is a phase 3 follow-up confirmatory trial, aiming to evaluate the efficacy and safety of avutometinib and defactinib versus standard of care (SOC) chemotherapy and hormonal therapy in patients with recurrent LGSOC.

Next steps

The findings from the ctDNA analysis are being written up, and will be submitted for presentation at an international conference. We look forward to sharing the full results with you.

Update on other projects

The Oak Cancer Centre



We were delighted to officially open the Oak Cancer Centre in June this year. The Royal Marsden Cancer Charity would like to thank Lady Garden Foundation for their commitment and support, which helped us to raise over £70 million in our biggest-ever fundraising appeal.

His Royal Highness Prince William, Prince of Wales, President of The Royal Marsden, visited Sutton to officially open the Oak Cancer Centre. His Royal Highness met patients and staff to hear about how the state-of-the-art facilities will enable The Royal Marsden to achieve even more for people with cancer, immediately and for decades to come. He praised the remarkable generosity of donors who made the Oak Cancer Centre possible.



We were delighted to welcome Lady Garden Foundation representatives Jenny Halpern Prince and Tamara Beckwith Veroni to the official opening of the Oak Cancer

Centre. Lady Garden Foundation generously donated £100,000 to fund a consulting room in the Outpatient Department, pictured left.

Thanks to your support, The Royal Marsden is now uniquely positioned to drive forward innovative research with global impact and deliver the highest standard of modern cancer care, long into the future.

ATARI Trial

The groundbreaking ATARI trial led by Professor Banerjee, aims to revolutionise treatment options for women with rare, relapsed or advanced gynaecological cancers. The trial is part-funded by Lady Garden Foundation and also by pharmaceutical firm AstraZeneca.

Progress to-date

The trial recruited patients from across the UK (London, Manchester, Edinburgh, Glasgow and Bath) and in France and Canada.

Professor Banerjee presented trial results at the ESMO Gynaecological Cancers Congress in February 2023. Results showed that that some patients benefited from this targeted therapy approach with a drug called ceralasertib. The team are currently working on identifying which patients may benefit. The trial is the first of its kind to target tumours that have a faulty DNA repair gene known as ARID1A.

Next steps

Analysis of blood and tumour samples is almost complete. Professor Banerjee and her team are preparing a manuscript to submit soon, and are considering further presentations on ATARI for 2024.

The ATARI trial will now see two new cohorts opening (four and five) by the end of the year. These will focus on women with endometrial cancer who have undergone immunotherapy, and whose cancer has worsened, trialling ATR inhibitor therapy and immunotherapy. This will be a novel, first of its kind study.

We are hugely grateful to the funding from Lady Garden Foundation, which has been absolutely crucial to the success of the ATARI trial.



Thank you

The Lady Garden Foundation is a passionate advocate for women's health, and we are incredibly grateful for all that you do to improve the lives of women diagnosed with gynaecological cancer at The Royal Marsden and beyond. Following the recent Scientific Committee meeting, you have expanded the Lady Garden Foundation's research portfolio and from January 2024, there will be nine active research projects at the hospital which will be made possible thanks to your funding. With this commitment, you are driving forward the change required to develop better treatment options for women across the world.

You have also continued your support of The Royal Marsden's psychological support service, thanks to another successful ladies lunch in September. The service is essential in ensuring the mental health of patients is treated alongside their physical condition. This is now an incredibly important part of any treatment journey, thank you for your support of this area. We were also delighted to welcome you to the Oak Cancer Centre for its official opening in June. As an incredibly special occasion for the hospital and the Charity, we were so pleased that you were able to join us to celebrate this important milestone in the history of The Royal Marsden.

We are so proud to work alongside you. As you approach your 10th year of fundraising, we are extremely excited to see what new breakthroughs your funding will bring. Thank you to all the Lady Garden Foundation co-founders, trustees, committee members and supporters for your inspirational support of women affected by gynaecological cancers.

