ESMO Clinical Research Fellowship

(May 2021 – May 2022)

Aljosja Rogiers

FINAL REPORT

Host Institute: The Royal Marsden NHS Foundation Trust, London, United Kingdom
Mentor: Dr Samra Turajlic
Project title: A prospective observational study to identify a composite biomarker for prediction and early detection of immunotherapy-related adverse events (irAEs)
Home Institute: Melanoma Institute Australia, Sydney, Australia

Introduction

Immune checkpoints are regulators that are essential to modulate physiological immune responses and maintain self-tolerance. Monoclonal antibodies that disrupt this interaction have revolutionised the treatment of a range of cancer types (Pardoll, 2012). However, by increasing the activity of the immune system, immune checkpoint inhibitors (CPI) can induce significant immune-related adverse events (irAEs). If diagnosed early, most irAEs are generally well manageable. However, treatment interruptions, diagnostic interventions, hospital admissions and immunosuppression can negatively influence outcomes and quality of life. In rare cases, irAEs can be permanent (diabetes mellitus) or result in significant disability or even death (neurotoxicity or cardiomyopathy).

Rationale and Aim

Biomarkers that predict irAEs or detect subclinical irAEs would greatly improve patient safety because they would allow for early detection. This could minimise exposure to immunosuppressive agents and may prevent irreversible toxicity. These biomarkers would also improve decision making, especially in the adjuvant setting to better inform the risk-benefit discussion with patients. Furthermore, a better understanding of pathogenesis of irAEs could pave the way for targeted toxicity treatments and personalised management.

Experimental design

We designed a prospective observational cohort study at The Royal Marsden NHS Foundation Trust: EXACT (Understanding immunE-related toXicities by multifACeT Profiling). Over a 36 month period, we aim to recruit 200 patients who will start treatment with anti-PD-1-based immunotherapy. The primary objective is to determine the proportion of patients who experience irAEs during treatment with CPI. This allows contextualisation in the current landscape of available data. Secondary objectives are (1) to profile biological and clinical characteristics at baseline and during treatment with CPI to predict the development of immunotherapy-related adverse events (irAEs); (2) to determine time to clinical development of irAEs and (3) to determine the proportion of patients experiencing any irAE during long-term follow up, post-treatment. Other outcome measures include the quality-of-life impact on patients enrolled in longitudinal multi-facet disease profiling and in patients who develop irAEs.

Results, Conclusions and Future Perspectives

The study officially opened on the 6th of April 2022 (ClinicalTrials.gov Identifier: NCT05331066). Given that this took place towards the end of my fellowship, it is, at this stage, too early to present results or draw conclusions. However, setting up this project during my fellowship has been an important opportunity for my professional development, which I will further outline in my personal statement.

List of Publications and Presentations Resulting from the Translational Research Project "*A prospective observational study to identify a composite biomarker for prediction and early detection of immunotherapy-related adverse events (irAEs)"*
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List of Publications and Presentations resulting from other projects during the fellowship period (if applicable)
Holmberg CJ, Ny L, Hieken TJ, Block MS, Carr MJ, Sondak VK, Örtenwall C, Katsarelias D, Dimitriou F, Menzies AM, Saw RP, **Rogiers A**, Straker RJ 3rd, Karakousis G, Applewaite R, Pallan L, Han D, Vetto JT, Gyorki DE, Tie EN, Vitale MG, Ascierto PA, Dummer R, Cohen J, Hui JY, Schachter J, Asher N, Helgadottir H, Chai H, Kroon H, Coventry B, Rothermel LD, Sun J, Carlino MS, Duncan Z, Broman K, Weber J, Lee AY, Berman RS, Teras J, Ollila DW, Long GV, Zager JS, van Akkooi A, Olofsson Bagge R. The efficacy of immune checkpoint blockade for melanoma in-transit with or without nodal metastases - A multicenter cohort study. *Eur J Cancer*. 2022;169:210-222. **Rogiers A***, Lobon I*, Spain L, Turajlic S. The Genetic Evolution of Metastasis. *Cancer Res*. 2022;82:1849-1857. *Contributed equally Fendler A, Shepherd STC, Au L, Wilkinson KA, Wu M, Schmitt AM, Tippu Z, Farag S, **Rogiers A**, Harvey R, Carlyle E, Edmonds K, Del Rosario L, Lingard K, Mangwende M, Holt L, Ahmod H, Korteweg J, Foley T, Barber T, Emslie-Henry A, Caulfield-Lynch N, Byrne F, Shum B, Gerard CL, Deng D, Kjaer S, Song OR, Queval C, Kavanagh C, Wall EC, Carr EJ, Namjou S, Caidan S, Gavrielides M, MacRae JI, Kelly G, Peat K, Kelly D, Murra A, Kelly K, O'Flaherty M, Shea RL, Gardner G, Murray D, Popat S, Yousaf N, Jhanji S, Van As N, Young K, Furness AJS, Pickering L, Beale R, Swanton C; Crick COVID19 consortium, Gandhi S, Gamblin S, Bauer DLV, Kassiotis G, Howell M, Nicholson E, Walker S, Wilkinson RJ, Larkin J, Turajlic S; CAPTURE consortium. Immune responses following third COVID-19 vaccination are reduced in patients with hematological malignancies compared to patients with solid cancer. *Cancer Cell*. 2022;40:438. Fendler A, Shepherd STC, Au L, Wilkinson KA, Wu M, Byrne F, Cerrone M, Schmitt AM, Joharatnam-Hogan N, Shum B, Tippu Z, Rzeniewicz K, Boos LA, Harvey R, Carlyle E, Edmonds K, Del Rosario L, Sarker S, Lingard K, Mangwende M, Holt L, Ahmod H, Korteweg J, Foley T, Bazin J, Gordon W, Barber T, Emslie-Henry A, Xie W, Gerard CL, Deng D, Wall EC, Agua-Doce A, Namjou S, Caidan S, Gavrielides M, MacRae JI, Kelly G, Peat K, Kelly D, Murra A, Kelly K, O'Flaherty M, Dowdie L, Ash N, Gronthoud F, Shea RL, Gardner G, Murray D, Kinnaird F, Cui W, Pascual J, Rodney S, Mencel J, Curtis O, Stephenson C, Robinson A, Oza B, Farag S, Leslie I, **Rogiers A**, Iyengar S, Ethell M, Messiou C, Cunningham D, Chau I, Starling N, Turner N, Welsh L, van As N, Jones RL, Droney J, Banerjee S, Tatham KC, O'Brien M, Harrington K, Bhide S, Okines A, Reid A, Young K, Furness AJS, Pickering L, Swanton C; Crick COVID-19 Consortium, Gandhi S, Gamblin S, Bauer DLV, Kassiotis G, Kumar S, Yousaf N, Jhanji S, Nicholson E, Howell M, Walker S, Wilkinson RJ, Larkin J, Turajlic S; CAPTURE Consortium. Adaptive immunity and neutralizing antibodies against SARS-CoV-2 variants of concern following vaccination in patients with cancer: the CAPTURE study. *Nat Cancer*. 2021;2:1305-1320. Fendler A, Shepherd STC, Au L, Wu M, Harvey R, Schmitt AM, Tippu Z, Shum B, Farag S, **Rogiers A**, Carlyle E, Edmonds K, Del Rosario L, Lingard K, Mangwende M, Holt L, Ahmod H, Korteweg J, Foley T, Barber T, Emslie-Henry A, Caulfield-Lynch N, Byrne F, Deng D, Kjaer S, Song OR, Queval C, Kavanagh C, Wall EC, Carr EJ, Caidan S, Gavrielides M, MacRae JI, Kelly G, Peat K, Kelly D, Murra A, Kelly K, O'Flaherty M, Shea RL, Gardner G, Murray D, Yousaf N, Jhanji S, Tatham K, Cunningham D, Van As N, Young K, Furness AJS, Pickering L, Beale R, Swanton C, Gandhi S, Gamblin S, Bauer DLV, Kassiotis G, Howell M, Nicholson E, Walker S, Larkin J, Turajlic S; CAPTURE consortium. Omicron neutralising antibodies after third COVID-19 vaccine dose in patients with cancer. *Lancet*. 2022;399(10328):905-907. Fendler A, Shepherd STC, Au L, Wilkinson KA, Wu M, Schmitt AM, Tippu Z, Farag S, **Rogiers A**, Harvey R, Carlyle E, Edmonds K, Del Rosario L, Lingard K, Mangwende M, Holt L, Ahmod H, Korteweg J, Foley T, Barber T, Emslie-Henry A, Caulfield-Lynch N, Byrne F, Shum B, Gerard CL, Deng D, Kjaer S, Song OR, Queval C, Kavanagh C, Wall EC, Carr EJ,

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Selection of Courses and Workshops Attended During the Fellowship

IHC-GCP refresher course
Human Tissue Act training

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Personal Statement

This fellowship helped me in my professional development in numerous ways.

I was embedded in a clinical trials team with a dedicated senior clinical trial coordinator. Together we outlined (1) the current landscape and available data, (2) rationale and hypothesis, (3) study design and objectives, (4) methodology, (5) patient population, (6) inclusion/exclusion criteria, (7) guidance for adverse and serious adverse event reporting, (8) statistical considerations, (9) financial and legal considerations and (10) ethical conduct.

This project, in a broader sense, allowed me to familiarise myself with the regulatory environment in the UK including the Committee for Clinical Research (CCR), Research Ethics Committee (REC) and Health Research Authority (HRA). A better understanding of the regulatory structure of the UK will facilitate future collaborations across countries.

I had the opportunity to interact with experts at The Francis Crick Institute to enhance my understanding of translational research and laboratory techniques in the context of immunology and immunotherapy.

Given the ongoing COVID-19 pandemic, I could also participate and contribute to time-sensitive studies that improved our understanding of the COVID-19 immune response in cancer patients. These efforts led to publications that were used in national and international vaccination recommendations.

This experience in the UK, after working in Belgium and Australia, improved my understanding of organisational culture, effective workspaces and communication within hospitals and clinical trial teams.

The need to combine patient care responsibilities with clinical research was instrumental in gaining insights in time management and helped me to better define career trajectories.

The EXACT study is now open at The Royal Marsden with current and future fellows taking over the study. This study will contribute to the safety of patients treated with immune checkpoint inhibitors. I wish current and future fellows all the very best!

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SIGNATURES	
Award Recipient full name	***Signature and Date***
Aljosja Rogiers	14 July 2022

Research Mentor full name	***Signature and Date***
Samra Turajlic	14 July 2022

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