Original article

Description of the EuroTARGET cohort: A European collaborative project on TArgeted therapy in renal cell cancer—GEnetic- and tumor-related biomarkers for response and toxicity

Loes F.M. van der Zanden, Ph.D.[a],[1], Sita H. Vermeulen, Ph.D.[a],[1], Arna Oskarsdottir, M.Sc.[b],
Jake S.F. Maurits, M.Sc.[a], Meta H.M. Diekstra, M.Pharm.[c], Valentin Ambert, M.D.[d],
Anne Cambon-Thomsen, M.D., D.R., C.N.R.S.[e], Daniel Castellano[f], Achim Fritsch, R.Ph.[g],
Jesus Garcia Donas, M.D., Ph.D.[h], Rosa Guarch Troyas, M.D.[i], Henk-Jan Guchelaar, Pharm.D., Ph.D.[c],
Arndt Hartmann, M.D.[j], Christina Hulsbergen-van de Kaa, M.D., Ph.D.[k], Ulrich Jaehde, Ph.D.[g],
Kerstin Junker, Ph.D.[l], Anna Martinez-Cardus, Ph.D.[m], Gisli Masson, Ph.D.[b],
Jeannette Oosterwijk-Wakka, Ph.D.[n], Marius T. Radu, M.D.[d], Thorunn Rafnar, Ph.D.[b],
Cristina Rodriguez-Antona, Ph.D.[o], Max Roessler, Ph.D.[p], Rob Ruijtenbeek, Ph.D.[q],
Kari Stefansson, M.D., Ph.D.[b],[r], Anne Warren, M.B.B.S., M.Sc., F.R.C.Path.[s],
Lodewyk Wessels, Ph.D.[t], Tim Eisen, F.R.C.P., Ph.D.[u], Lambertus A.L.M. Kiemeney, Ph.D.[a],*,[2],
Egbert Oosterwijk, Ph.D.[n],[2]

[a] Radboud University Medical Center, Radboud Institute for Health Sciences, Nijmegen, The Netherlands
[b] deCODE Genetics/Amgen, Reykjavik, Iceland
[c] Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands
[d] University of Medicine and Pharmacy Carol Davila, Bucuresti, Romania, Bucuresti, Romania
[e] Epidemiology and analyses in public health, Joint Unit 1027, Institut National de la Santé et de la Recherche Médicale (INSERM), Université Toulouse III Paul Sabatier, Faculty of Medicine, Toulouse, France
[f] Medical Oncology Department, Hospital Universitario 12 de Octubre, I + 12 Research Institute, (CiberOnc), Madrid, Spain
[g] Institute of Pharmacy, Clinical Pharmacy, University of Bonn, Bonn, Germany
[h] Medical Oncology, HM Hospitales—Centro Integral Oncológico HM Clara Campal, Madrid, Spain
[i] Anatomía Patológica, Complejo Hospitalario de Navarra, Pamplona, Spain
[j] Department of Pathology, University Erlangen-Nürnberg, Erlangen, Germany
[k] Department of Pathology, Radboud University Medical Center, Radboud Institute for Molecular Life Sciences, Nijmegen, The Netherlands
[l] Clinic of Urology and Paediatric Urology, Saarland University, Homburg, Germany
[m] Cancer Epigenetics and Biology Program, Bellvitge Biomedical Research Institute, Barcelona, Catalonia, Spain
[n] Radboud University Medical Center, Radboud Institute for Molecular Life Sciences, Nijmegen, The Netherlands
[o] Hereditary Endorine Cancer Group, Spanish National Cancer Research Centre (CNIO) and Biomedical Network on Rare Diseases (CIBERER), Madrid, Spain
[p] CESAR central office, CESAR Central European Society for Anticancer Drug Research-EWIV, Vienna, Austria
[q] PamGene International B.V., 's-Hertogenbosch, The Netherlands
[r] Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavík, Iceland
[s] Department of Histopathology, Cambridge University Hospitals NHS Foundation Trust, Cambridge Biomedical Campus, Cambridge, UK
[t] Department of Molecular Carcinogenesis, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[u] Department of Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge Biomedical Campus, Cambridge, UK

[1] Shared first authorship.
[2] Shared last authorship.
* Corresponding author. Tel.: +31-24-361-3745.
E-mail address: Bart.Kiemeney@radboudumc.nl
(Lambertus A.L.M. Kiemeney).

Abstract

Objective: For patients with metastatic renal cell cancer (mRCC), treatment choice is mainly based on clinical parameters. With many treatments available and the limited response to treatment and associated toxicities, there is much interest in identifying better biomarkers for personalized treatment. EuroTARGET aims to identify and characterize host- and tumor-related biomarkers for prediction of response to tyrosine kinase inhibitor therapy in mRCC. Here, we describe the EuroTARGET mRCC patient cohort.

Methods and materials: EuroTARGET is a European collaborative project designed as an observational study for which patients with mRCC were recruited prospectively in 62 centers. In addition, 462 patients with mRCC from previous studies were included. Detailed clinical information (baseline and follow-up) from all patients was entered in web-based case record forms. Blood was collected for germline DNA and pharmacokinetic/pharmacodynamic analyses and, where available, fresh-frozen tumor material was collected to perform tumor DNA, RNA, kinome, and methylome analyses.

Results: In total, 1,210 patients with mRCC were included. Of these, 920 received a tyrosine kinase inhibitor as first-line targeted treatment (sunitinib [N = 713, 78%], sorafenib [N = 41, 4%], or pazopanib [N = 166, 18%]) and had at least 6 months of outcome assessment (median follow-up 15.3 months [interquartile range: 8.5–30.2 months]). Germline DNA samples were available from 824 of these patients, fresh-frozen tumor material from 142 patients, fresh-frozen normal kidney tissue from 95 patients, and tissue microarrays created from formalin-fixed paraffin-embedded tumor material from 247 patients. Of the 920 patients, germline DNA variant chip data were successfully generated for 811 patients (Illumina HumanOmniExpress BeadChip). For 80 patients, next-generation exome sequencing of germline and tumor DNA was performed, tumor RNA sequencing was performed for 124 patients, kinome activity measured and processed for 121 patients (PamChip), and methylome data (Illumina Infinium HumanMethylation450 BeadChip) were created for 116 RCC tissues (and 23 normal kidney tissues). For 73 out of the 920 patients, all platform data types were generated. In addition, 40 patients were included in a pharmacokinetic/pharmacodynamic phase IV substudy.

Conclusions: Analysis of EuroTARGET cohort data will contribute to personalization of therapy for patients with mRCC. The extensive clinical data and multiplatform EuroTARGET data will be freely available. © 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Metastatic renal cell carcinoma; Therapy response; Tyrosine kinase inhibitor; Biomarker; Transcriptomics; Genomics

1. Introduction

With more than 121,000 newly diagnosed patients and 52,000 deaths each year, kidney cancer is the seventh most common cancer in Europe [1]. Further, 90% of all kidney cancers are renal-cell carcinomas (RCC). The prognosis of RCC is highly dependent on stage. Surgery is effective for the 70% to 80% of patients with localized disease, leading to 5-year relative survival rates of more than 70% [2]. However, ∼25% of patients have metastatic RCC (mRCC) at first diagnosis, and ∼25% of patients with localized disease develop metastases after surgery [3,4].

Until the arrival of tyrosine kinase inhibitors (TKIs), treatment options in mRCC were limited, and 5-year relative survival was only 5% to 10%. Randomized clinical trials showed that TKI agents, directly targeting tumorigenic and angiogenic pathways (reviewed in [5]), significantly improved the outcomes of these patients [6]. Several first-line TKI treatment options are now available, such as sunitinib, pazopanib, or bevacizumab plus interferon-alpha [6]. Most patients experience disease stabilization or response for a median of ∼12 months [7]. However, TKI treatment is extremely expensive (sunitinib was estimated in the UK to cost £71,462 per quality adjusted life year gained [8]), 15% to 20% of patients experience immediate disease progression despite treatment [7], nearly all patients eventually become resistant, and toxicity is common and leads to dose reduction. In addition, first-line treatment options for patients with mRCC will likely increase in coming years (including immune checkpoint inhibition) [9]. There is, hence,

much interest in tools for prediction of individual therapy response and acquired resistance to TKIs to optimize treatment outcome while reducing unnecessary drug use and expenses, and improving human health and quality of life.

Currently, treatment choice in mRCC is based on risk grouping of patients by clinical parameters such as the patient's performance status, and serum biochemical measurements, and histological features of the tumor [10]. A comparison study into several clinical risk grouping models, including that of the International Metastastic Renal Cell Carcinoma Database Consortium [11] and the Memorial Sloan Kettering Cancer Center (MSKCC) [12], showed modest discriminatory values for survival (area under the receiver operating curve ∼0.66) and indicated that addition of tumor-specific or patient-specific biomarkers is likely required for the improvement of the accuracy of these models [13].

Advances in high-throughput technologies have paved the way to personalized medicine using biomarkers. For mRCC, potential prognostic molecular biomarkers such as *PBRM1*, *BAP1*, and *KDM5C* tumor mutations [14]; IL8 [15], VEGF, and PlGF levels [16]; *ABCB1* and *VEGFR-3* germline polymorphisms [17]; and miRNA levels have been identified [18,19]. However, there are no validated biomarkers yet that can guide personalization of therapy in patients with mRCC.

In this framework EuroTARGET was initiated, a "European collaborative project on TArgeted therapy in Renal cell cancer: GEnetic and Tumor-related biomarkers for response and toxicity." The overarching goal of this