30 November 2019, Amsterdam

To the Executive Board of the 2020 Arenberg-Coimbra Group Prize.

By means of the following application, I would like to express my interest in the 2020 Arenberg-Coimbra Group Prize. In the past year, I have graduated cum laude from the University of Leiden with a degree in Bio-Pharmaceutical Sciences. In the course of this program I was fortunate to partake in the Erasmus student exchange program which allowed me to complete a 6-month research internship at the University of Uppsala. During my stay in Uppsala I worked at the department of Pharmacometrics, which focuses on the development of mathematical models to evaluate drug treatments and explore alternative approaches to enhance treatment outcomes. The experience taught me a number of valuable analytical methods and introduced me to an incredible group of friends and colleagues in the field of Pharmaceutical Sciences. My time at the University of Uppsala has been invaluable for my future career and, hopefully, will bring long-term benefits to patient care. In the following letter I will highlight the prominent impact the Erasmus exchange has had on my academic experience by explaining the main aim of my research, underlining the direct consequences for clinical practice and bringing forward the pivotal role of the exchange in the project completion and my future academic direction.

The focus of my research project was the drug sunitinib in the treatment of gastro-intestinal stromal tumors (GIST). The therapeutic indication of sunitinib in GIST has existed for more than a decade and the drug is frequently prescribed by oncologists in specialized centers. Despite the considerable therapeutic benefit found in patients with GIST, treatment with sunitinib can give rise to various troublesome adverse effects such as high blood pressure, a dampened immune system and blistering of the hands and feet. In addition, clinicians are often faced with the challenge of suboptimal tumor responses. Because of the high differences in the degree to which patients develop both beneficial and adverse effects from the standard

sunitinib dose, it has been proposed that the dose should become individualized based on certain biomarkers. Alternatively, different treatment schedules have been proposed to reduce adversity and increase treatment benefit. Unfortunately, there are no studies that systematically compare these strategies with one another, and at the present moment clinicians lack the scientific base required to make therapeutic adjustments for their patients. For my research project, we aimed to utilize mathematical models to simulate the influence of each strategy on treatment outcomes within the GIST patient population.

Based on the results several preliminary conclusions were generated. With respect to alternative treatment schedules, we found that continuous daily dosing of sunitinib results in higher overall survival, while the development of adverse effects remained equal to other dosing regimens. This supports the current notion, wherein many hospitals have shifted from the label-recommended intermediate dosing schedule to the continuous dosing schedules due to often more beneficial outcomes. Changing the recommended dosing schedule would mean that patients would receive a more suitable regimen from the point of treatment initiation, after which individual dose adjustments could be made based on biomarkers to further optimize outcome. For this latter, we investigated the possibility of using plasma concentration, blood pressure, blood cell count or the marker sVEGFR-3 to guide dose adjustments. Based on our analyses, we found that cell-count and sVEGFR-3 increased overall survival without raising the risk for additional adverse events. In addition, we developed a clinical sampling schedule that could be used by clinicals to calculate what dose should be given to which patient.

The results of the project are impactful for several reasons. Firstly, the project compares the various dose strategies that have been brought forward over the years and compares them with each other in a systematic manner in order to allow for objective comparisons. Secondly, the results demonstrate that biomarkers such as cell-count and sVEGFR-3 provide enhanced treatment outcomes compared to other biomarkers. This is significant, as most oncological centers have mainly focused on drug concentrations to individualize sunitinib dose. The research outcomes could therefore provide a basis to investigate the alternative biomarkers. Because the models

together were able to simulate the patient population in a 'holistic manner', taking into account both adverse effects, survival and relevant clinical values, the direct transactability of the findings to clinical applications is maximized. This was further accomplished by consulting both clinical guidelines and hospital-based clinicians in order to further optimize the models to adhere to current practices. Lastly, the project provides a conceptual framework to explore alternative biomarkers and dosing methods from a clinical and patient-centered point of view. The importance of such an approach resides in the fact that there are more than 20 additional drugs similar to sunitinib, most with multiple treatment indications. The abovementioned approach could therefore serve as a method to evaluate different dosing strategies for each drug and therapeutic indication.

The course to the completion of the project required an interdisciplinary approach and was therefore heavily supported by the aid of different specialists from both the medical and pharmaceutical field. Experts from both the Netherlands and Sweden were involved in order to increase the applicability on an international level. Due to the innovative nature and the direct impact on clinical practice the work was rewarded with the 2019 Morra-Nijbakker price. In addition, the project was selected for an oral presentation at the congress for pharmacometrics (PAGE 2018) and the conference in clinical oncology (ICPAD 2018). In many aspects, these incredible opportunities would not have occurred without the Erasmus exchange program and the experiences that have occurred from this. Working at the Department of Pharmacometrics in Uppsala allowed me to be in close contact with the leading scientists in the field of model-based drug development, in addition to granting me access to the Department's learning material. Because of this support, I was able to make a steep learning curve that allowed me to finalize the project in 6 months. In addition, the international community and the strong network at the department have allowed for connections that increased the impact of the project and generated the interest of clinicians over multiple countries.

Spending a semester in Sweden has been beneficial for my academic and personal development. Being a medical student in the Netherlands I have learned the healthcare and insurance system from a Dutch perspective. During my time in

Uppsala I was introduced to the healthcare system in Sweden, which in several cases differs greatly from the Dutch one. Understanding the differences in organization and customs has made me aware of opportunities to improve current medical practices. In addition, learning the Swedish language will be of extreme relevance for my future residence in Uppsala and the collaboration with the Swedish researchers.

Taking everything into consideration, I truly believe that the exchange semester at the University of Uppsala has been a pivotal component of my academic experience and has had an immense impact on my future career direction. In the coming years I will continue the course I initiated, as a MD/PhD student at the University of Amsterdam and the University of Uppsala. Hopefully, this international and interdisciplinary combination will give rise to innovative solutions for improving therapies of current anticancer drugs. Based on my experiences during the exchange program, my aim in to further establish collaborations between clinicians and pharmacologists in order to achieve this goal. I hope that this letter will serve as an example of how the exchange program between Coimbra Group Universities can give rise to solutions that meet patient's needs and improve collaborations between working scientists.

Thank you for your consideration.

Warm regards,
Maddalena Centanni