

HABILITATION THESIS REVIEWER'S REPORT

Masaryk University	
Faculty of Medicine	
Procedure field	
Applicant	MUDr. Daniela Žáčková, Ph.D.
Applicant's home unit, institution	Department of Internal Medicine, Hematology and Oncology
Habilitation thesis	Chronic myeloid leukemia: from long-term treatment to its permanent withdrawal
Reviewer	Prof. Thomas Lion, MD, PhD, MSc
Reviewer's home unit, institution	St. Anna Children's Cancer Research Institute, Vienna, Austria

It is my pleasure and a privilege to review the habilitation thesis of MUDr. Daniela Zackova, PhD, because I have had the opportunity to attend several of her scientific presentations at international meetings over the past years, and I am therefore fully aware of her expertise and her achievements in the field of chronic myeloid leukemia.

The candidate has an impressive publication record of more than 40 peer-reviewed articles listed in the NIH National Library of Medicine (PubMed), on several of which she appears as first or senior author. The list of her publications includes papers in prestigious international journals, such as Leukemia, Haematologica, American Journal of Hematology, British Journal of Haematology, Oncotarget or Experimental Hematology.

Regarding the habilitation thesis itself, I should mention that I am able to read Czech, thus enabling me to appreciate the entire contents, but it is considerably easier for me to write my comments in English. The thesis is based on a detailed and comprehensive introduction to the topic followed by a series of publications pertaining to various aspects of therapy in CML patients. The papers address a number of important topics, which include the establishment of a patient database compiling detailed real-life data on clinical responses to TKI therapy. The database termed INFINITY is a large and comprehensive collection of a broad spectrum of clinically relevant data, and received both national and international recognition by its inclusion

in the European CML registry supported by the European LeukemiaNet (ELN). The candidate performed a comparison of data derived from the registry to results obtained in diverse clinical studies, with a particular focus on the efficacy and tolerability of the first-generation TKI imatinib, provided as first-line therapy, as well as that of dasatinib as second-line therapy in patients revealing resistance or intolerance to imatinib. The data confirmed the excellent efficacy and tolerability of first-line treatment with imatinib observed outside the setting of clinical studies at specialized centers in the Czech Republic. Moreover, innovative parameters assessing the long-term responsiveness to the TKI were established and successfully presented to the scientific community. The use of dasatinib as second-line therapy was also reported to display good efficacy and safety outside clinical study settings, at least in patients who were still in chronic phase of CML.

Furthermore, the candidate addressed the mechanisms of resistance to TKIs, both related and unrelated to the BCR-ABL1 fusion gene, and emphasized the fact that the phenomenon of resistance is a multifactorial process, which cannot be fully elucidated in a substantial proportion of patients by currently available technical approaches. In the context of response to treatment, the crucial importance of adherence to the prescribed TKI therapy is highlighted. Another interesting topic investigated by the candidate was a systematic analysis of the BCR-ABL1 interactome as an important basis for targeted therapies aiming at complete eradication of the disease. Additionally, a number of papers included in the thesis assessed the causes of TKI intolerance and metabolic issues related to treatment with nilotinib, including particularly the impairment of glucose tolerance and its impact on treatment-associated vascular complications.

In the summary section of the thesis, the candidate recapitulates the important findings and insights that emanated from her clinical research and offers an outline of her interesting future activities in the field.

Dr.Zackova is a nationally and internationally recognized expert in hemato-oncology, and my overall assessment of her current habilitation thesis is excellent. She has made important contributions in the field of chronic myeloid leukemia, which has been the main focus of her research and clinical interest. I am therefore convinced that she is highly qualified for the academic promotion she is applying for.

Reviewer's questions for the habilitation thesis defence

1. Do you believe that the documentation of early molecular response during the first three months of TKI therapy is of clinical relevance and, if so, how would you see the potential therapeutic consequences?
2. What is your personal opinion regarding the optimal duration of TKI treatment and the depth of molecular response in CML patients prior to an attempt of treatment cessation?
3. What is your preferred indication and dosing regimen for the use of ponatinib?
4. What is your assessment of the potential strengths and weaknesses of asciminib, applied either as a single agent or in combination with other TKIs?
5. Do you think that the presence of low-level mutations (detectable by NGS, but below the detection limit of Sanger sequencing) has a prognostic impact, and how could they affect the diagnostic and therapeutic approaches?
6. What is the role of compound mutations in different phases of CML and the current/future treatment options?
7. How will the relatively recent insights into the prognostic role of additional chromosomal abnormalities (ACAs) at diagnosis or during the course of therapy impact the diagnostic and treatment strategies in the future?
8. What is your personal vision of future treatment strategies for CML on the path to cure?

Conclusion

The habilitation thesis entitled “Chronic myeloid leukemia: from long-term treatment to its permanent withdrawal” by MUDr. Daniela Žáčková, Ph.D. fulfils the requirements expected of a habilitation thesis in the field of **Oncology**.

Vienna, 20 May, 2021

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