Commentary

Background. Tyrosine kinase inhibitors (TKI) introduction into chronic myeloid leukemia (CML) therapy dramatically improved patients' prognosis with overall survival becoming similar to that of global population. Despite controlled and successful treatment discontinuation attempts with the aim of treatment-free remission (TFR) achievement, life-long TKI therapy is inevitable and thus challenging for vast majority of patients. Treatment efficacy and safety data are usually derived from clinical trials; however, their extrapolation into every-day clinical practice has been complicated not only due to selection bias but also following the fact that particularly long-term efficacy measurements are often inadequate. Resistance to and/or intolerance of TKI therapy has been an issue for nonnegligible patients group, and is further hampered by unknown etiopathogenesis as well as uncertain clinical significance. Non-adherence, a confirmed factor leading to TKI treatment resistance, has been potentiated by the lack of relevant information provided by physicians as well as insufficient management of side effects. Crucial role of physician-patient interaction has been acknowledged also in the context of TFR.

Aims. This habilitation thesis has been divided into four themes or objectives reflecting CML therapy optimization challenges outlined above. Objective 1 – to create detailed and comprehensive database of CML patients treated with TKI in every-day clinical practice. Objective 2 – to systematically perform data-analyses and compare our results to those obtained from clinical trials. Objective 3 – to investigate possible mechanisms of resistance to TKI or their intolerance with the aim to manage them successfully eventually. Objective 4 – to empower patients awareness and adherence since they have a significant impact on treatment efficacy.

Methods. In this habilitation thesis, an applicant took an opportunity given by the Medical Faculty of Masaryk University to collect previously published works and completed them with commentary.

Results. As an objective No. 1 fulfilment, one of the largest non-commercial and parametrically plentiful database worldwide was created and also implemented into the European CML Registry shortly after its development. Collected data were used both for analyses in the frame of international cooperation and for our own projects with results published in virtually only impacted journals. Regarding objective No. 2, we confirmed TKI treatment very good efficacy and acceptable toxicity in the frame of centralised specialized haematological care, however at the same time we found established efficacy assessment tools insufficient and heterogenous among published analyses. Our newly proposed parameter called alternative treatment-free survival (ATFS) was accepted by the panel of experts as a part of official international guidelines for clinical trials results statistical assessment, and our modification of current leukemia-free survival (CLFS) reflected particular drug position in clinical practice more properly than conventional survival analyses. During TKI resistance possible mechanisms research (Objective No. 3) we revealed

some analytic and interpretation inconsistency eliminating use of established parameters such as hOCT1, ABCB-1 or plasmatic and intracellular imatinib concentrations for treatment outcome prediction. By confirmation of CD26 marker as a reliable tool for leukemia stem cells identification, and thanks to the Bcr-Abl interactom structure and dynamics elucidation we moved a step forward to an ambitious goal to cure from leukemia completely. Our group for the first time clarified the mechanism of impaired glucose tolerance caused by rapidly evolving tissue insulin resistance and compensatory hyperinsulinemia, which at least partially explain also promptly developing dyslipidemia and probably also peripheral arterial occlusions emergence as a serious adverse effect of nilotinib treatment. Thanks to extensive educational activity targeted not only to the patients and their relatives but also to broader health care community, which has been realised by multiple ways with both national and international coverage (Objective No. 4), an applicant significantly contributed to all participants' awareness, motivation and adherence as a crucial prerequisite both for therapy and its instructed discontinuation.

Summary. In summary, we fulfilled all the objectives set up previously, as was documented by our own results published in fairly cited articles in impacted journals. Our contribution to CML patient therapy optimization has been further amplified with our academic multicentre trial HALF (NCT04147533), evaluating efficacy and safety of TKI withdrawal after previous two-step dose reduction, led by our Department where an applicant plays a role of study concept co-author, principal investigator and national coordinator.

In total, 21 publications including reviews, research articles, and books or book chapters were chosen to corroborate the thesis objectives fulfilment. The applicant contribution to these publications is summarized in the following tables with special attention to the conceptualization of the study, project administration, data curation and manuscript preparation.

Note: (-) means "not applicable" and concerns review articles, books and book chapters.

1. **ŽÁČKOVÁ, D**. Chronická myeloidní leukemie v roce 2015. *Onkologie* (Czech Republic). 2015, 9(3), 119–122.
   Document Type: Article

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
-	-	-	**100**

2. **ŽÁČKOVÁ, Daniela**. Problematika chronické myeloidní leukemie u seniorů. In: Hana KUBEŠOVÁ a Igor KISS. *Geriatrická onkologie*. 1. vyd. Praha: Mladá fronta, 2015, s. 257–265. ISBN 978-80-204-3738-9.

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)

-	-	-	**100**

3. **ŽÁČKOVÁ, D.,** E. FABER, K. INDRÁK, P. ROHOŇ, H. KLAMOVA, K. MACHOVÁ POLÁKOVÁ, M. KARAS, O. ČERNÁ, I. SKOUMALOVÁ, P. BĚLOHLÁVKOVÁ, P. ŽÁK, Z. RÁČIL a J. MAYER. Chronická myeloidní leukemie. In: Jiří MAYER, ed. *Léčebné postupy v hematologii: doporučení České hematologické společnosti České lékařské společnosti Jana Evangelisty Purkyně.* 1. vyd. Praha: Česká hematologická společnost České lékařské společnosti J.E. Purkyně, 2016, s. 79–99. ISBN 978-80-260-9718-1.

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
-	-	-	**80**

4. **ŽÁČKOVÁ, Daniela**. Chronická myeloidní leukemie. In: Tomáš BÜCHLER. *Speciální onkologie*. 2. aktual. a dopl. vyd. Praha: Maxdorf, 2020, s. 185–191. ISBN 978-80-7345-651-1.

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
-	-	-	**100**

5. **ŽÁČKOVÁ, Daniela.** Chronická myeloidní leukemie - je možné terapii ukončit? *Postgraduální medicína: odborný časopis pro lékaře.* 2020, 22(1), 36–45. ISSN 1212-4184.
Document Type: Article

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
-	-	-	**100**

6. HOFFMANN, V.S., M. BACCARANI, J. HASFORD, F. CASTAGNETTI, F. DI RAIMONDO, L.F. CASADO, A. TURKINA, **D. ZACKOVA**, G. OSSENKOPPELE, A. ZARITSKEY, M. HÖGLUND, B. SIMONSSON, K. INDRAK, Z. SNINSKA, T. SACHA, R. CLARK, A. BOGDANOVIC, A. HELLMANN, L. GRISKEVICIUS, G. SCHUBERT-FRITSCHLE, D. SERTIC, J. GUILHOT, S. LEJNIECE, I. ZUPAN, S. BURGSTALLER, P. KOSKENVESA, H. EVERAUS, P. COSTEAS, D. LINDOERFER, G. ROSTI, S. SAUSSELE, A. HOCHHAUS a R. HEHLMANN. Treatment and outcome of 2904 CML patients from the EUTOS population-based registry. *Leukemia* [online]. 2017, 31(3), 593–601. Dostupné z: doi:10.1038/leu.2016.246
Document Type: Article; (IF = 10,023; Category JCR: ONCOLOGY Q1, HEMATOLOGY Q1)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
10	**20**	**20**	**10**

7. **ZACKOVA, Daniela*** ***(corresponding author)****, Hana KLAMOVA, Ladislav DUSEK, Jan MUZIK, Katerina MACHOVA POLAKOVA, Jana MORAVCOVA, Tomas JURCEK, Dana DVORAKOVA, Zdenek RACIL, Zdenek POSPISIL, Alexandra OLTOVA, Kyra MICHALOVA, Jana BREZINOVA, Filip RAZGA, Michael DOUBEK, Petr CETKOVSKY, Marek TRNENY a Jiri MAYER. Imatinib as the first-line treatment of patients with chronic myeloid leukemia diagnosed in the chronic phase: Can we compare real life data to the results from clinical trials? *American Journal of Hematology* [online]. 2011, 86(3), 318–321. ISSN 0361-8609. Dostupné z: doi:10.1002/ajh.21942
   Document Type: Letter; (IF = 4,671; Category JCR: HEMATOLOGY Q1)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
80	**50**	**50**	**80**

8. PAVLIK, Tomas, Eva JANOUSOVA, Jiri MAYER, Karel INDRAK, Marie JAROSOVA, Hana KLAMOVA, **Daniela ZACKOVA**, Jaroslava VOGLOVA, Edgar FABER, Michal KARAS, Katerina MACHOVA POLAKOVA, Zdenek RACIL, Eva DEMECKOVA, Ludmila DEMITROVICOVA, Elena TOTHOVA, Juraj CHUDEJ, Imrich MARKULJAK, Eduard CMUNT, Tomas KOZAK, Jan MUZIK a Ladislav DUSEK. Current survival measures reliably reflect modern sequential treatment in CML: Correlation with prognostic stratifications. *American Journal of Hematology* [online]. 2013, 88(9), 790–797. ISSN 0361-8609. Dostupné z: doi:10.1002/ajh.23508
   Document Type: Letter; (IF = 3,477; Category JCR: HEMATOLOGY Q1)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
20	**20**	**30**	**10**

9. **ZACKOVA, Daniela*** ***(corresponding author)*,*** Hana KLAMOVA, Jan MUZIK, Eduard CMUNT, Zdenek RACIL, Katerina MACHOVA POLAKOVA, Dana DVORAKOVA, Tomas JURCEK, Filip RAZGA, Petr CETKOVSKY, Ladislav DUSEK a Jiri MAYER. Efficacy and tolerance of dasatinib after imatinib failure or intolerance for patients with chronic myeloid leukemia treated in three different hospitals compare well with results achievable in formal clinical trials. *Leukemia & Lymphoma* [online]. 2013, 54(10), 2310–2313. ISSN 1042-8194. Dostupné z: doi:10.3109/10428194.2013.772173
   Document Type: Letter; (IF = 2,605; Category JCR: ONCOLOGY Q2)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
80	**50**	**50**	**80**

10. **ZACKOVA, D.*(corresponding author)***, H. KLAMOVA, P. BELOHLAVKOVA, L. STEJSKAL, T. NECASOVA, L. SEMERAD, B. WEINBERGEROVA, D. SRBOVA, J. VOGLOVA, P. CICATKOVA, Z. SUSTKOVA, T. HORNAK, J. BARANOVA, J. PROCHAZKOVA a J. MAYER. Dasatinib treatment long-term results among imatinib-resistant/intolerant patients with chronic phase chronic myeloid leukemia are favorable in daily clinical practice. *Leukemia and Lymphoma* [online]. 2020. Dostupné z: doi:10.1080/10428194.2020.1827242
    Document Type: Article; (v roce 2019 IF = 2,969; Category JCR: HEMATOLOGY Q2, ONCOLOGY Q3)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
80	**50**	**50**	**80**

11. RACIL, Zdenek, Filip RAZGA, Lucie BURESOVA, Tomas JURCEK, Dana DVORAKOVA, **Daniela ZACKOVA**, Shira TIMILSINA, Petr CETKOVSKY a Jiri MAYER. The assessment of human organic cation transporter 1 (hOCT1) mRNA expression in patients with chronic myelogenous leukemia is affected by the proportion of different cells types in the analyzed cell population. *American Journal of Hematology* [online]. 2010, 85(7), 525–528. ISSN 0361-8609. Dostupné z: doi:10.1002/ajh.21722
    Document Type: Letter; (IF = 3,576; Category JCR: HEMATOLOGY Q2)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
10	**20**	**30**	**20**

12. RACIL, Zdenek, Filip RAZGA, Katerina MACHOVA POLAKOVA, Lucie BURESOVA, Vaclava POLIVKOVA, Dana DVORAKOVA, **Daniela ZACKOVA**, Hana KLAMOVA, Petr CETKOVSKY a Jiri MAYER. Assessment of adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) mRNA expression in patients with de novo chronic myelogenous leukemia: the role of different cell types. *Leukemia & Lymphoma* [online]. 2011, 52(2), 331–334. ISSN 1042-8194. Dostupné z: doi:10.3109/10428194.2010.533220
    Document Type: Letter; (IF = 2,580; Category JCR: ONCOLOGY Q2)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
10	**20**	**30**	**20**

13. RACIL, Zdenek, Filip RAZGA, Hana KLAMOVA, Jaroslava VOGLOVA, Petra BELOHLAVKOVA, Ludmila MALASKOVA, David POTESIL, Jan MUZIK, **Daniela ZACKOVA**, Katerina MACHOVA POLAKOVA, Zbynek ZDRAHAL, Jana MALAKOVA, Jiri SUTTNAR, Jan DYR a Jiri MAYER. No clinical evidence for performing trough plasma and intracellular imatinib concentrations

monitoring in patients with chronic myelogenous leukaemia. *Hematological Oncology* [online]. 2014, 32(2), 87–93. ISSN 0278-0232. Dostupné z: doi:10.1002/hon.2091
Document Type: Article; (IF = 3,084; Category JCR: ONCOLOGY Q2)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
10	**20**	**30**	**20**

14. ROMZOVA, Marianna, Dagmar SMITALOVA, Nikola TOM, Tomas JURCEK, Martin CULEN, **Daniela ZACKOVA**, Jiri MAYER a Zdenek RACIL. Novel Illumina-based next generation sequencing approach with one-round amplification provides early and reliable detection of BCR-ABL1 kinase domain mutations in chronic myeloid leukemia. *British Journal of Haematology* [online]. 2020, 189(3), 469–474. ISSN 0007-1048. Dostupné z: doi:10.1111/bjh.16382
Document Type: Article; (v roce 2019 IF = 5,518; Category JCR: HEMATOLOGY Q1)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
10	**20**	**20**	**10**

15. CULEN, Martin, Marek BORSKY, Veronika NEMETHOVA, Filip RAZGA, Jiri SMEJKAL, Tomas JURCEK, Dana DVORAKOVA, **Daniela ZACKOVA**, Barbora WEINBERGEROVA, Lukas SEMERAD, Irina SADOVNIK, Gregor EISENWORT, Harald HERRMANN, Peter VALENT, Jiri MAYER a Zdenek RACIL. Quantitative assessment of the CD26+leukemic stem cell compartment in chronic myeloid leukemia: Patient-subgroups, prognostic impact, and technical aspects. *Oncotarget* [online]. 2016, 7(22), 33016–33024. Dostupné z: doi:10.18632/oncotarget.9108
Document Type: Article; (IF = 5,168; Category JCR: ONCOLOGY Q1)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
10	**20**	**20**	**10**

16. GREGOR, Tomas, Michaela Kunova BOSAKOVA, Alexandru NITA, Sara P. ABRAHAM, Bohumil FAFILEK, Nicole H. CERNOHORSKY, Jan RYNES, Silvie FOLDYNOVA-TRANTIRKOVA, **Daniela ZACKOVA**, Jiri MAYER, Lukas TRANTIREK a Pavel KREJCI. Elucidation of protein interactions necessary for the maintenance of the BCR-ABL signaling complex. *Cellular and Molecular Life Sciences* [online]. 2020, 77(19), 3885–3903. ISSN 1420-682X. Dostupné z: doi:10.1007/s00018-019-03397-7
Document Type: Article; (v roce 2019 IF = 6,496; Category JCR: BIOCHEMISTRY & MOLECULAR BIOLOGY Q1)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)

20	**20**	**20**	**10**

17. RACIL, Zdenek, Filip RAZGA, Jana DRAPALOVA, Lucie BURESOVA, **Daniela ZACKOVA**, Martina PALACKOVA, Lukas SEMERAD, Ludmila MALASKOVA, Martin HALUZIK a Jiri MAYER. Mechanism of impaired glucose metabolism during nilotinib therapy in patients with chronic myelogenous leukemia. *Haematologica* [online]. 2013, 98(10). ISSN 0390-6078. Dostupné z: doi:10.3324/haematol.2013.086355
Document Type: Letter; (IF = 5,868; Category JCR: HEMATOLOGY Q1)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
20	**30**	**30**	**20**

18. RACIL, Zdenek, Eva KORITAKOVA, Tomasz SACHA, Hana KLAMOVA, Petra BELOHLAVKOVA, Edgar FABER, Delphine REA, Ludmila MALASKOVA, Jirina PROCHAZKOVA, **Daniela ZACKOVA**, Jaroslava VOGLOVA, Joanna WACLAW, Petr CETKOVSKY, Pavel ZAK a Jiri MAYER. Insulin resistance is an underlying mechanism of impaired glucose metabolism during nilotinib therapy. *American Journal of Hematology* [online]. 2018, 93(10), E342–E345. ISSN 0361-8609. Dostupné z: doi:10.1002/ajh.25232
Document Type: Letter; (IF = 6,137; Category JCR: HEMATOLOGY Q1)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
20	**30**	**30**	**20**

19. HORNAK, Tomas, Lukas SEMERAD, **Daniela ZACKOVA**, Barbora WEINBERGEROVA, Zuzana SUSTKOVA, Jirina PROCHAZKOVA, Petra BELOHLAVKOVA, Lukas STEJSKAL, Peter ROHON, Edgar FABER, Pavel ZAK, Jiri MAYER a Zdenek RACIL. Analysis of serum lipids, cardiovascular risk, and indication for statin use during nilotinib and imatinib therapy in de novo CML patients - results from real-life prospective study. *Leukemia & Lymphoma* [online]. 2020, 61(2), 494–496. ISSN 1042-8194. Dostupné z: doi:10.1080/10428194.2019.1672054
Document Type: Letter; (v roce 2019 IF = 2,969; Category JCR: HEMATOLOGY Q2, ONCOLOGY Q3)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
20	**40**	**30**	**30**

20. **ŽÁČKOVÁ, Daniela.** *Chronická myeloidní leukemie: informace pro pacienty a jejich blízké.* Brno: Česká leukemická skupina - pro život (CELL), 1. Vydání, 2012. ISBN 978-80-260-1828-5.

Conceptualization of the	Project	Data	Manuscript

study (%)	administration (%)	curation (%)	preparation (%)
-	-	-	**100**

21. SAGLIO, Giuseppe, Giora SHARF, Antonio ALMEIDA, Andrija BOGDANOVIC, Felice BOMBACI, Jelena CUGUROVIC, Nigel DEEKES, Valentin GARCIA-GUTIERREZ, Jan DE JONG, Sarunas NARBUTAS, Peter WESTERWEEL a **Daniela ZACKOVA**. Considerations for Treatment-free Remission in Patients with Chronic Myeloid Leukemia: A Joint Patient-Physician Perspective. *Clinical Lymphoma Myeloma & Leukemia* [online]. 2018, 18(6), 375–379. ISSN 2152-2650. Dostupné z: doi:10.1016/j.clml.2018.04.005
    Document Type: Article (IF = 2,274; Category JCR: ONCOLOGY Q3)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
20	**20**	**20**	**20**