MUNI

COMMENTARY TO HABILITATION THESIS[1]

Background and state of the art

Multiple myeloma (MM) is a heterogeneous hematologic malignancy with major advances in diagnostics and therapy over the last two decades. A subset of patients develops extraosseous multiple myeloma (EMM) involvement, characterized by plasmacytomas arising outside the bone marrow niche. This phenotype, encompassing paraskeletal lesions contiguous with bone structures and true extramedullary plasmacytomas in soft tissues or visceral organs, represents a biologically distinct and particularly aggressive manifestation of the disease. While the availability of novel imaging modalities such as whole-body MRI and FDG-PET/CT has improved the detection of plasmacytomas, their biology and treatment responses remain insufficiently understood.

Recent research has underscored the central role of genomic complexity, clonal evolution, and immune escape in driving EMM. Recurrent alterations of chromosome 1 (gain(1q21), del(1p32)), MAPK pathway mutations (KRAS, BRAF), and loss of tumor suppressor genes such as TP53 or RB1 define a molecular profile associated with extramedullary spread and treatment resistance. In parallel, EMM is marked by profound remodeling of the tumor microenvironment, loss of adhesion molecules, and downregulation of therapeutic targets (e.g., CD38, BCMA), collectively contributing to immune evasion and refractoriness to standard therapies. Consequently, patients with EMM continue to experience dismal outcomes even in the era of immunotherapy.

Aims of the work

The habilitation thesis aimed to comprehensively address the clinical, molecular, and therapeutic aspects of EMM by:

1. Defining the prognostic impact of paraskeletal versus extramedullary plasmacytomas.
2. Identifying genetic aberrations and molecular predictors associated with extramedullary spread.
3. Evaluating clinical outcomes and mechanisms of resistance in patients with EMM, including in the context of novel immunotherapies.
4. Integrating clinical and translational data to improve risk stratification and guide the development of therapeutic strategies for this high-risk subgroup.

Methods

The thesis is based on a structured body of publications combining clinical analyses with translational research. Clinical cohorts from national registries and institutional databases were evaluated to determine incidence, prognosis, and treatment outcomes of patients with plasmacytomas. Molecular investigations included cytogenetic analyses by interphase FISH and targeted next-generation sequencing, with parallel evaluation of bone marrow and plasmacytoma tissue. Imaging data from advanced modalities (FDG-PET/CT, whole-body MRI) were integrated into clinical analyses, while correlative studies explored immunophenotypic characteristics and tumor–microenvironment interactions. Together, this multidisciplinary approach provided both population-level evidence and mechanistic insights into the biology of EMM.

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[1] The commentary must correspond to standard expectations in the field and must include a brief characteristic of the investigated matter, objectives of the work, employed methodologies, obtained results and, in case of co-authored works, a passage characterising the applicant's contribution in terms of both quality and content.

Results
The analyses confirmed that paraskeletal plasmacytomas diagnosed at baseline do not adversely affect prognosis once corrected for disease stage and tumor burden, aligning their outcome with standard intramedullary disease. In sharp contrast, extramedullary plasmacytomas, whether present at diagnosis or emerging at relapse, were consistently associated with inferior survival. Secondary EMM in particular exhibited treatment resistance, with median overall survival measured in months despite modern therapies.
Genomic profiling identified recurrent early events predisposing to extramedullary spread, including gain(1q21), del(1p32), and MAPK pathway mutations. These aberrations were frequently shared between paired bone marrow and plasmacytoma samples, underscoring early clonal divergence as a hallmark of extramedullary transformation. Importantly, loss of surface molecules such as CD38 and BCMA explained refractoriness to monoclonal and bispecific antibodies, while immune profiling revealed exhausted T cells and paucity of NK cells in plasmacytomas.
Clinical outcome analyses documented limited efficacy of both proteasome inhibitors and IMiDs, as well as reduced benefit from daratumumab and teclistamab in the extramedullary setting. Encouraging signals were observed with BCMA-directed CAR-T cells, particularly when tumor burden was reduced before administration, and emerging dual-targeted strategies (e.g., BCMA + GPRC5D) seems promising for overcoming resistance.

Conclusions
This habilitation thesis establishes EMM as a distinct clinical and biological entity within the MM spectrum. It demonstrates that while paraskeletal lesions do not adversely affect prognosis, true extramedullary plasmacytomas herald a high-risk phenotype characterized by aggressive biology, poor outcomes, and resistance to current therapies. The work identifies key genetic drivers and highlights the urgent need for novel therapeutic concepts.
Despite substantial progress, EMM remains an area of unmet medical need. Future improvements are likely to arise from integration of molecular diagnostics, advanced imaging, and next-generation immunotherapies targeting multiple antigens. By combining large-scale clinical analyses with molecular studies, this thesis contributes to both the understanding and recognition of EMM as a crucial challenge in contemporary hematology, providing a platform for translational and clinical innovation aimed at improving the prognosis of this particularly vulnerable group of patients.

[1][2] **STORK, Martin**, Sabina SEVCIKOVA, Jiri MINARIK, Petra KRHOVSKA, Jakub RADOCHA, Lenka POSPISILOVA, Lucie BROZOVA, Jiri JARKOVSKY, Ivan SPICKA, Jan STRAUB, Petr PAVLICEK, Alexandra JUNGOVA, Tomas JELINEK, Viera SANDECKA, Vladimir MAISNAR, Roman HAJEK and Ludek POUR. Identification of patients at high risk of secondary extramedullary multiple myeloma development. *British Journal Of Haematology* [online]. 2022, **196**(4), 954–962. ISSN 1365-2141. Available at: doi:10.1111/bjh.17925

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
90	NA	95	95

[2] **STORK, Martin**, Eva ONDROUSKOVA, Michaela BOHUNOVA, Ivanna BOICHUK, Dominik FRIC, Zdenek ADAM, Marta KREJCI, Viera SANDECKA, Zdenka KNECHTOVA, Lenka RADOVA, Zuzana JELINKOVA, Tatana ADLEROVA, Milan KRTICKA, Vladimir NEKUDA, Marek BORSKY, Sabina SEVCIKOVA, Marie JAROSOVA and Ludek POUR. Del(1p32) is an early and high-risk event in multiple myeloma patients with extraosseous disease. *Blood Cancer Journal* [online]. 2024, **14**(1, Article 146). ISSN 2044-5385. Available at: doi:10.1038/s41408-024-01131-6

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	NA	95	95

[3] **STORK, Martin**, Sabina SEVCIKOVA, Tomas JELINEK, Jiri MINARIK, Jakub RADOCHA, Tomas PIKA, Lenka POSPISILOVA, Ivan SPICKA, Jan STRAUB, Petr PAVLICEK, Alexandra JUNGOVA, Zdenka KNECHTOVA, Viera SANDECKA, Vladimir MAISNAR, Roman HAJEK and Ludek POUR. Unexpected Heterogeneity of Newly Diagnosed Multiple Myeloma Patients with Plasmacytomas. *Biomedicines* [online]. 2022, **10**(10, Article 2535). ISSN 2227-9059. Available at: doi:10.3390/biomedicines10102535

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
90	NA	95	95

[4] **STORK, Martin**, Ivan SPICKA, Jakub RADOCHA, Jiri MINARIK, Tomas JELINEK, Alexandra JUNGOVA, Petr PAVLICEK, Lenka POSPISILOVA, Frantisek SEDLAK, Jan STRAUB, Tomas PIKA, Zdenka KNECHTOVA, Anna FIDRICHOVA, Ivanna BOICHUK, Sabina SEVCIKOVA, Vladimir MAISNAR, Roman HAJEK and Ludek POUR. Daratumumab with lenalidomide and dexamethasone in relapsed or refractory multiple

[2] Bibliographic record of a published scientific result, which is part of the habilitation thesis.

myeloma patients - real world evidence analysis. *Annals Of Hematology* [online]. 2023, **102**(6), 1501–1511. ISSN 1432-0584. Available at: doi:10.1007/s00277-023-05188-4

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
80	NA	95	95

[5] STORK, Martin, Jakub RADOCHA, Jana MIHALYOVA, Ivan SPICKA, Tomas PIKA, Alexandra JUNGOVA, Ivanna BOICHUK, Klara MENSIKOVA, Jan STRAUB, Frantisek SEDLAK, Jiri MINARIK, Petra KRHOVSKA, Denisa NOVAKOVA, Michaela HORNAKOVA, Zdenka KNECHTOVA, Nela SENDLEROVA, Tereza DEKOJOVA, Vladimir MAISNAR, Tomas JELINEK, Roman HAJEK and Ludek POUR. De-escalated Teclistamab dosing in relapsed/refractory multiple myeloma: Czech myeloma group real-world evidence analysis. *Annals Of Hematology* [online]. 2025. **104**(8), 4141-4147. ISSN 1432-0584. Available at: doi:10.1007/s00277-025-06529-1

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
80	NA	100	95