



**NATIONAL CANCER INSTITUTE**  
**Center for Cancer Research**

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Dear Members of the Biotechnology Discipline Council:

I was appointed by the Biotechnology Discipline Council of the University of Gdańsk – Poland as an external reviewer of the Doctoral Thesis entitled: “**Dissecting the mechanism and functional landscape of cancer PD1 signalling in osteosarcoma**” authored by **Katarzyna Dziubek, MSc**. The doctoral dissertation meets the requirements set for doctoral dissertations by The Higher Education and Science Act dated 20 July 2018 (Polish Journal of Laws of 2018; item 1668, as amended). In this letter, please find my complete assessment of her work, in which I wish to convey my enthusiastic support for her findings. I have reviewed the Doctoral Thesis in its entirety, and find the work innovative, well-constructed, and cogently presented by Mrs. Dziubek. My evaluation of her work is positive. My assessment contains the following points:

1) The doctoral dissertation presents an overview of the complex challenges of cancer immunotherapy, with specific focus on immune checkpoint inhibitors (ICIs) and the limited understanding of why and how some patients do not generate a satisfactory clinical response to such therapies. The Thesis document contains a well-referenced and clearly presented overview of the major players of the immune system and how specific signaling mechanisms and pathways function in health and disease. From this section, it is clear that Mrs. Dziubek possesses a high level of knowledge and mastery of the published literature, which is key to the granting of a doctoral degree in this research area. Further, the clinical problem and the main scientific questions, which form the basis of her work, regarding how PD-1 may be acting as a tumor suppressor in osteosarcoma are clearly conveyed. To this point, the phenomenon of ‘hyperprogressive disease’ after ICI therapy is a largely unexplored area of cancer immunotherapy research, and has significant implications for the field.

2) The Thesis document provides abundant evidence that Mrs. Dziubek has demonstrable ability in independently conducting scientific investigations, commensurate with an individual applying for granting a doctoral degree. Her goals are to explore the PD-1 interactome through a variety of scientific and experimental techniques with the human U2OS cell line to more fully define the implications of PD-1 blockade and explore novel ICI combinatorial therapies. Mrs. Dziubek clearly presents the limitations and challenges of each technique and provides a balanced, appropriate interpretation of the data generated therein.

3) The doctoral dissertation constitutes an original solution to a scientific problem, through the main findings that PD-1 appears to be acting as a tumor suppressor in osteosarcoma, although the work is limited to observations within a single human cell line (U2OS). As pointed out in the document, additional work will be needed to determine if this phenomenon can be documented in other experimental systems and/or patient-derived materials or data.

Further, the novel findings that AXL appears to be a novel PD-1 binding partner is indeed exciting and provides new information to support combinatorial approaches that could be tested in relevant animal models. To this point, Mrs. Dziubek presents a project which is funded by the Preludium research grant 2022/45/N/NZ1/02699, in which she plans to carry out additional comparative research in canine osteosarcoma. In this work, she describes how she will mine canine data and conduct experiments using the Chick Chorioallantoic Membrane (CAM) assay to determine the impact of PD-1 expression on the metastatic properties of canine and human osteosarcoma cell lines. If I may offer an additional opinion on this plan, it may be to include some murine metastasis modelling to allow interrogation of tumor cell-lung microenvironmental interactions to complement the CAM assay. This data will provide the necessary footing upon which additional studies of PD-1 signaling can be conducted in pet dogs with osteosarcoma in the future and provide critical insight into the role of PD-1 in this devastating disease.

Therefore, I am applying to the Council of the Biotechnology Discipline for admission of **Mrs. Katarzyna Dziubek**, MSc to further stages of the doctoral procedure. Please contact me using the information below if additional information or opinion is needed for this decision.

Sincerely yours,



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