CANCER RESEARCH

POSTER PRESENTATIONS - PROFFERED ABSTRACTS | APRIL 04 2023

Abstract 6129: The proapoptotic peptide PEP-010 is efficient on several models of different tumor origins and it can be monitored by pharmacodynamic biomarker candidates in clinical practice

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Cancer Res (2023) 83 (7_Supplement): 6129.

https://doi.org/10.1158/1538-7445.AM2023-6129

Abstract

In cancer cells, the proapoptotic proteins caspase-9 and PP2A interaction prevents them to play their role in apoptosis. PEP-010, a drug candidate developed by PEP-Therapy, a French Biotech company, is a proapoptotic peptide targeting and disrupting this interaction leading to restoration of the apoptotic cascade. PEP-010 is an innovative bifunctional peptide. It penetrates into cells thanks to its cell penetrating part and specifically disrupts the caspase-9/PP2A interaction thanks to its interfering part. PEP-010 is currently in Phase I a/b multicenter clinical trial for the treatment of advanced solid tumors.To the aim of screening different potential therapeutic targets, to investigate the molecular mechanism-of-action of PEP-010 and to identify potential pharmacodynamic biomarkers, we have tested PEP-010 efficacy on several cell models of different tumor origins. By the Annexin V/Propidium Iodide staining and flow cytometry analysis, we found that PEP-010 induces apoptosis in most of the tested models. One possible mechanism-of-action is an involvement of the PP2A which, once released by PEP-010, could regulate expression and/or activity of different intracellular factors leading to caspases activation and cell death.The identification of the major molecular features involved in PEP-010 mechanism-of-action, were instrumental to identify different pharmacodynamic biomarker candidates (e.g. active caspase-3). Hence, such biomarkers could be useful in clinical practice to monitor the effect of PEP-010 at molecular level. We have compared specific features related to the mechanism-of-action of PEP-010 in sensitive (MDA-MB-231, IGROV1) and not sensitive cell models of different tumor origins and in tissue sections derived from Patient-Derived Xenografts models of breast cancer treated or not with PEP-010. Widely used techniques as immunofluorescent staining and immunohistochemistry were employed, making these results easily transferable in clinical routine.Taken together, our pre-clinical data showed the potential of PEP-010 as an anti-cancer peptide on a wide variety of malignancies and enabled the identification of pharmacodynamic biomarker candidates, important to ease the clinical development.

Citation Format: Rayan Farhat, Laura Dadon, F Nemati, A Rebollo, D Decaudin, Joelle Wiels, Catherine Brenner, Diego Germini. The proapoptotic peptide PEP-010 is efficient on several models of different tumor origins and it can be monitored by pharmacodynamic biomarker candidates in clinical practice. [abstract].

In: Proceedings of the American Association for Cancer Research Annual Meeting 2023; Part 1 (Regular and Invited Abstracts); 2023 Apr 14-19; Orlando, FL. Philadelphia (PA): AACR; Cancer Res 2023;83(7_Suppl):Abstract nr 6129.