Title

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Journal

Cancer Research, 82(12_Supplement)

ISSN

0008-5472

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Publication Date

2022-06-15

DOI

10.1158/1538-7445.am2022-6307

Volume 82, Issue 12_Supplement
15 June 2022

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POSTER PRESENTATIONS - PROFFERED ABSTRACTS | JUNE 15 2022

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Cancer Res (2022) 82 (12_Supplement): 6307.
https://doi.org/10.1158/1538-7445.AM2022-6307

Abstract

Glioblastoma multiforme (GBM) is the most common as well as one of the most malignant types of brain cancer. Despite progress in development of novel therapies for the treatment of GBM, it remains largely incurable with a poor prognosis and a very low life expectancy. Recent studies have shown that oleandrin, a unique cardiac glycoside from Nerium oleander, as well as defined extract (PBI-05204) that contains this molecule, inhibit growth of human glioblastoma, and modulate glioblastoma patient-derived stem cell-renewal properties. The present study aimed to investigate the radiosensitization of PBI-05204 in glioblastoma using both in vitro and in vivo cancer models as well as to explore the potential mechanism of actions in GBM. The radiosensitizing effect of PBI-05204 was assessed against human GBM U87MG, U251, T98G and A172 cell lines as well as their relevant xenograft and orthotopic models. The induction of apoptosis, DNA damage and repair of DNA double strand breaks were assessed with determination of caspase 3 and 9 protein expression, DNA laddering, protein expression of rH2AX, Ku70, DNA-PKcs, and RAD51 as well as a Comet Assay. PBI-05204 treatment leads to an increased in vitro sensitivity of GBM cells, including U87MG, U251, T98G and A172 cells, to radiotherapy (RT) in which the main mechanisms are the transition from autophagy to apoptosis and enhanced DNA damage evidenced by increased expression of γH2AX. Additionally, relative increased expression of Ku70, DNA-PKcs and RAD51 due to RT were reduced by PBI-05204 in U87MG and U251 cells, suggesting PBI-05204 lessened RT mediated DNA repair. PBI-05204 significantly enhanced the RT mediated inhibition of tumor growth by 4.7-, 2.1- and 2.2-fold in U87MG, U251 and T98G xenograft models, respectively. The combination of RT and PBI-05204 showed a significantly enhancement of disease-free survival to 103.0 ± 63.2 days compared to the control group ($p < 0.001$) which was 3-fold longer than that of RT only group. Collectively, these results reveal that PBI-05204 enhances antitumor activity of RT in preclinical/murine models of human GBM. Given the fact that PBI-05204 has already been examined in Phase I and II clinical trials for cancer patients, its efficacy when combined with standard-of-care radiotherapy regimens in GBM should be explored in future clinical trials of this difficult to treat brain cancer.

Citation Format: Alessandro Colapietro, Peiying Yang, Alessandra Rosetti, Andrea Mancini, Flora Vital, Stefano Martellucci, Francesco Marampon, Vincenzo Mattei, Giovanni Luca Gravina, Robert Newman, Claudio Festuccia. The botanical drug PBI-05204, a supercritical CO_2 extract of Nerium oleander, augments the antitumor efficacy of radiotherapy in treatment of human glioblastoma [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; Cancer Res 2022;82(12_Suppl):Abstract nr 6307.

Online ISSN 1538-7445 **Print ISSN** 0008-5472