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605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

Targeted DNA Damage Boost with Loncastuximab Tesirine in Combination with PARP Inhibitors in Diffuse Large B-Cell Lymphoma

Stefania Fusani[1], *Alessandra Rossi*[2], *Saveria Mazzara*[3], *Elena Baiardi*[2], *Stefania Orecchioni*[4], *Giovanna Talarico*[4], *Paolo Falvo*[5], *Francesca Zammarchi, PhD*[6], *Patrick Van Berkel, PhD*[7], *Stefano A. Pileri, MDPhD*[8], *Francesco Bertolini, MD PhD*[9], *Corrado Tarella*[10], *Enrico Derenzini, MD*[10,11]

[1] Oncohematology Division, IEO European Institute of Oncology, European Institute of Oncology, Milano, Italy
[2] European Institute of Oncology IRCCS, Milan, ITA
[3] Eruopean Institute of Oncology, (IEO), Milan, ITA
[4] European Institute of oncology, Milano, Italy
[5] European Institute of Oncology, Milan, ITA
[6] ADC Therapeutics, London, GBR
[7] ADC Therapeutics Ltd, London, United Kingdom
[8] Division of Hematopathology, Istituto Europeo di Oncologia, Milano, Italy
[9] European Institute of Oncology, Milano, ITA
[10] Oncohematology Division, IEO European Institute of Oncology IRCCS, Milan, Italy
[11] Department of Health Sciences, University of Milan, Milan, Italy

MYC-over expressing lymphomas display inherent resistance to standard chemoimmunotherapy regimens and are characterised by genomic instability and constitutive activation of the DNA damage response (DDR) pathway.
Loncastuximab tesirine (Lonca) is an antibody-drug conjugate directed against CD19, a surface antigen broadly expressed in B-cell malignancies. Upon CD19 binding, Lonca induces DNA damage by delivering a pyrrolobenzodiazepine dimer-based, DNA crosslinking warhead into target cells. Here we hypothesised that DDR inhibition could enhance DNA damage induced by Lonca in CD19-positive lymphoma cells. Since MYC-overexpressing cells mainly rely on PARP activity to attenuate endogenous MYC-induced replicative stress, we combined Lonca with Talazoparib (an FDA-approved PARP inhibitor), in a panel of 12 DLBCL cell lines (7 with MYC-rearrangement), and *in vivo* in a MYC/BCL-2-rearranged DLBCL PDX model.
Lonca and Talazoparib showed significant antiproliferative activity in a dose and time dependent manner in most cell lines at clinically achievable concentrations. The highest sensitivity to both compounds was observed in a BRCA2 mutant cell line (DOHH2). These data are in line with the known synthetic lethality between *BRCA* mutations and platinum derivatives and PARP inhibitors. The addition of Talazoparib significantly enhanced the antiproliferative effects of Lonca in DLBCL cell lines irrespective of *MYC/BCL2* rearrangements and *TP53* genomic alterations. Of note, the highest efficacy of the combination was observed in MYC-rearranged and MYC-overexpressing cell lines. The combination of Lonca and Talazo sinergistically increased DNA damage as evaluated by comet assay, induced enhanced cell death and caused specific changes in cell cycle dynamics. Enhanced apoptosis was confirmed by Annexin/PI staining and caspase 3/7 cleavage, assessed by caspase Glo assay and Western Blot analyses. As previously shown (Fusani et al., ASH 2021), while Lonca and Talazoparib affected cell cycle inducing G2/M phase arrest, the combination specifically increased the percentage of cells arrested in the BrdU negative S phase of cell cycle. Upon combined treatment, we observed increased DDR activation with the evaluation of several DDR biomarkers such as phospho(p)-ATM, pCHK2 ^{Thr68}, pCHK1 ^{Ser345}, gH2AX. To better understand the molecular mechanism underlying this synergistic interaction, we performed RNA-Seq analysis in two representative cell lines (OCI-LY18 and SUDHL5). Interestingly while Lonca did not cause significant changes in gene expression profiling (GEP) after 24 hours of incubation, the combination resulted in specific GEP changes such as down-regulation of histone H2B and aurora kinase A (AURKA), genes mainly involved in S and G2/M transition of the cell cycle. Similar results were obtained by combining Talazoparib and different PARP inhibitors with the alkylating agent cisplatin, indicating a class effect.
The synergistic interaction of Lonca and Talazoparib was further confirmed *in vivo* in a MYC/BCL-2 double hit PDX model.

As previously shown (Fusani et al., ASH 2021), Lonca/Talazoparib combination did not result in enhanced DNA damage induction in PBMC-derived B cells from healthy donors. Importantly, PBMC-derived T cells from healthy donors did not show any sign of DNA damage accumulation upon exposure to Lonca, Talazoparib and the combination.
These data provide the rationale for future therapeutic strategies based on selective induction of DNA damage in neoplastic B cells in combination with DDR inhibition in aggressive MYC-positive B cell lymphoma.

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