2023 APPLE
The 13th Asia-Pacific Primary Liver Cancer Expert Meeting
Novel Insights into the Evolution of Liver Cancer Management
July 6-8, 2023 | Grand InterContinental Seoul Parnas, Seoul, Korea

Olaparib contributes to radiation induced primary and abscopal tumor control by activating STING-dependent innate immune response

Genwen Chen PhD, Danxue Zheng MD, Shisuo Du PhD and Zhaochong Zeng PhD

Department of Radiation Oncology, Zhongshan Hospital, Fudan University, Shanghai, China, 200032

E-mail: gwchen15@fudan.edu.cn

Background/Aim

- HCC has a poor prognosis and limited treatment options, such as surgery, TACE, and sorafenib, highlighting the need for new therapies.
- PARP inhibitors show promise in cancers with BRCA mutations, but their efficacy in HCC is limited, particularly in patients without BRCA mutations.
- Radiation therapy, including SBRT, is effective in local control of advanced HCC, and combining it with PARP inhibitors may enhance DNA damage and improve treatment outcomes.
- The cGAS-STING pathway plays a crucial role in radiation-induced antitumor immune response, and the combination of radiation therapy and immune checkpoint inhibition has increased the occurrence of the abscopal effect, but the role of PARP inhibitors in this process is not well understood.

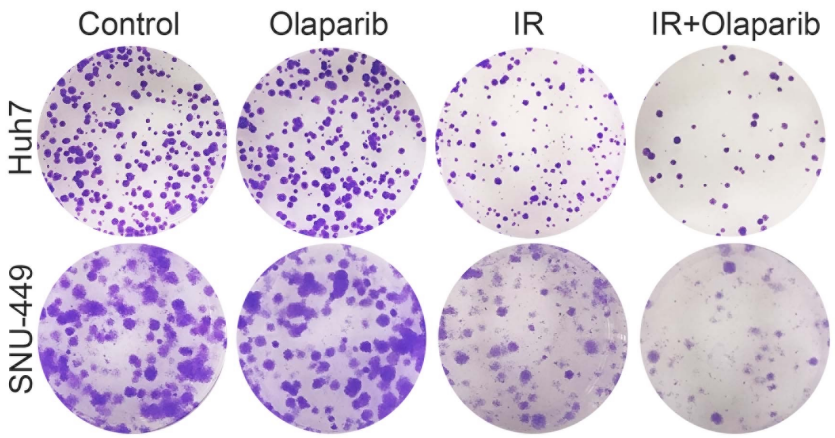
Methods

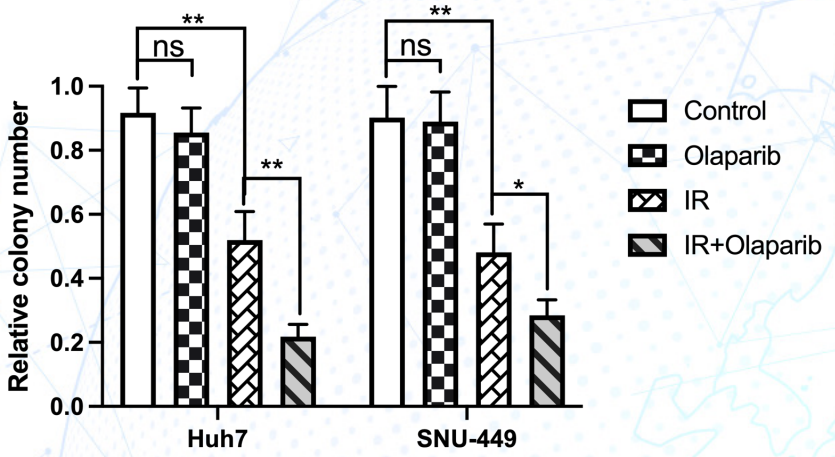
- HCC cells were treated with irradiation with or without olaparib and DNA damage and cell proliferation were analyzed.

- Immune deficient, immune competent, and cGAS knockout mice underwent X-ray irradiation of 24 Gy in three fractions were used to investigate the roles of olaparib, irradiation and anti-CTLA4 on tumor growth and tumor microenvironment.

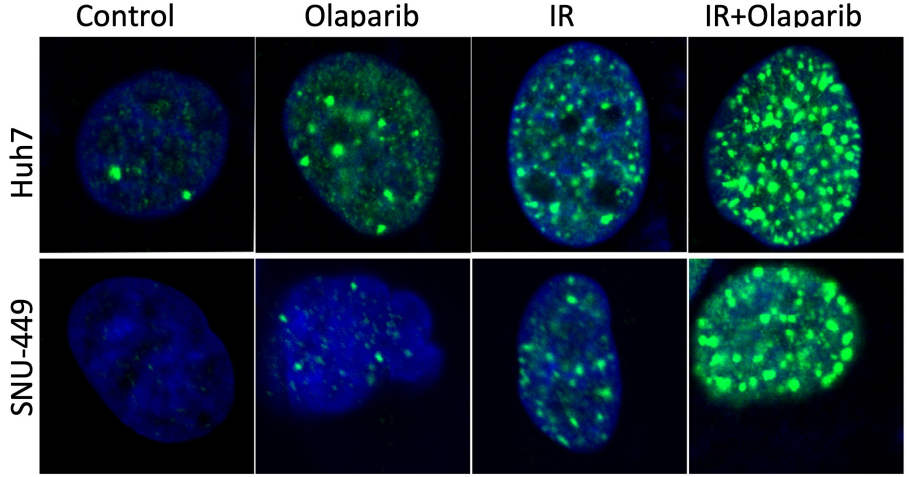
Results Olaparib sensitized HCC cells to irradiation

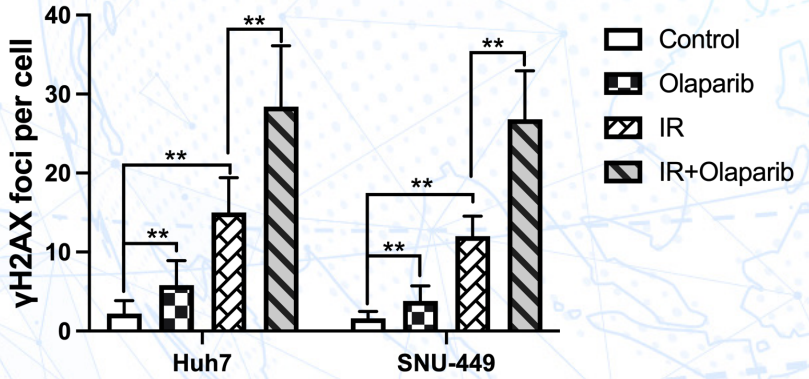
A





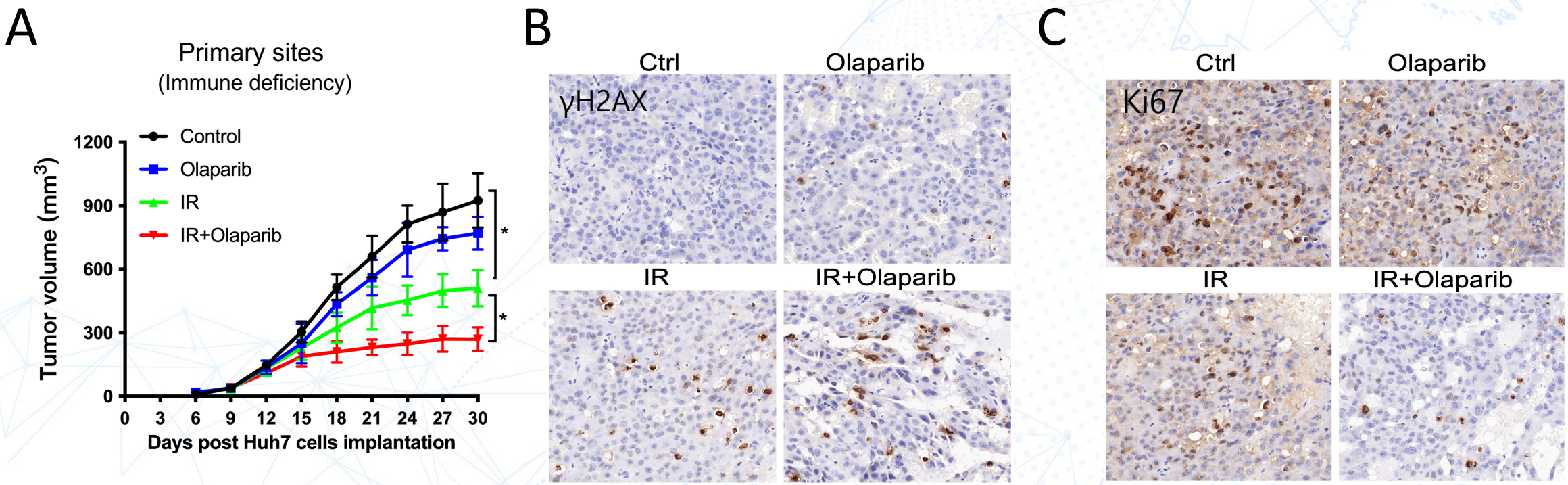
B





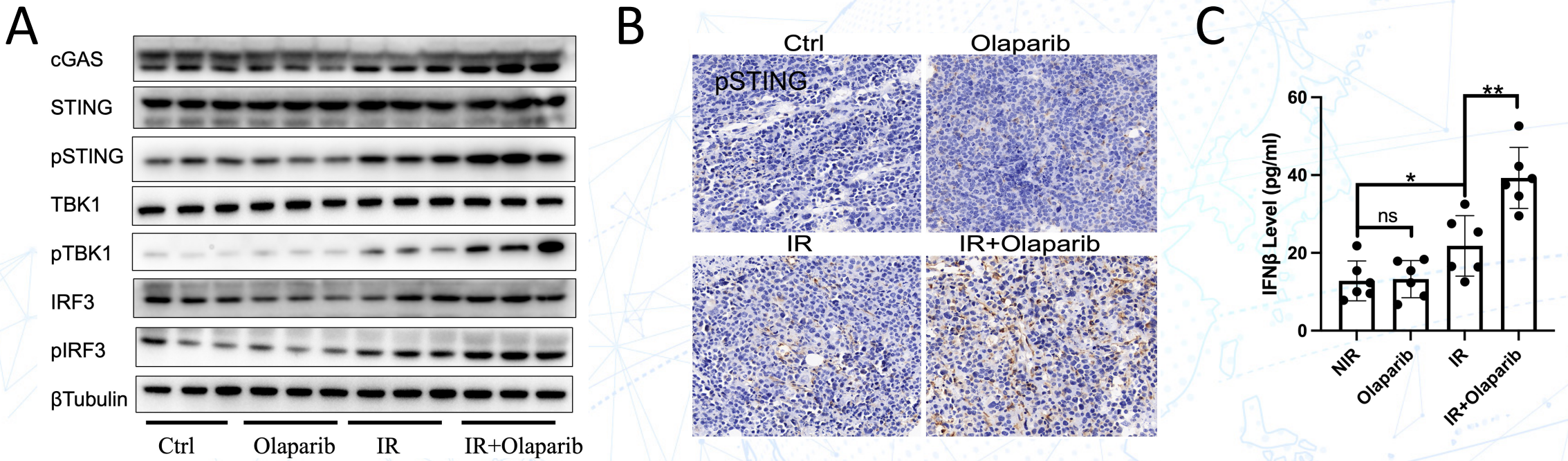
(A) Representative images of the colony formation assay in Huh7 and SNU-449 cells treated with olaparib, 4 Gy irradiation and the combination. Quantitation of the colony number is indicated on the right. (B) Representative γH2AX-positive foci treated with olaparib, 2 Gy irradiation and the combination in Huh7 and SNU-449 cells (scale bar, 10 μm). Quantitation of the γH2AX foci is indicated on the right. (*P <.05; #P <.01; ns, no significance)

Olaparib augments irradiation-induced DNA damage in vivo



(A) Growth curves from Huh7 tumors in immune deficient mice treated with olaparib, IR and the combination. (B) Representative immunochemistry images and quantitation of γH2AX staining in Huh7 tumor tissues in mice treated with olaparib, IR and the combination. (F) Representative immunochemistry images and quantitation of Ki67 staining in Huh7 tumor tissues in mice treated with olaparib, IR and the combination. (magnification × 200). ($^{\#}P$ <.01)

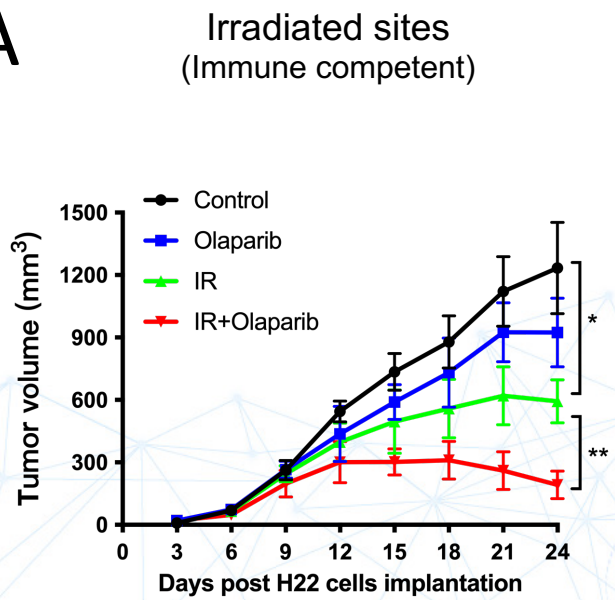
Olaparib combination with RT activates cGAS-STING-mediated Type I IFN



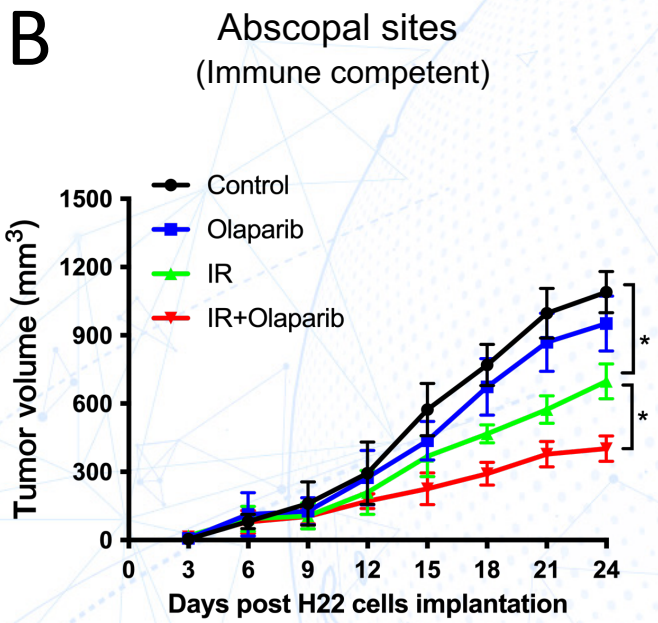
(A) Western blot of cGAS-STING-IRF3 signaling in primary H22 tumor tissues in mice treated with olaparib, IR and the combination. (B) Representative immunochemistry images phosphor-STING staining in primary H22 tumor tissues in mice treated with olaparib, IR and the combination (magnification × 200). (C) IFNβ levels in mice treated with olaparib, IR and the combination. (*P <.05; #P <.01; ns, no significance)

cGAS-STING signaling is required for radiotherapy-driven and olaparib-enhanced primary and abscopal responses

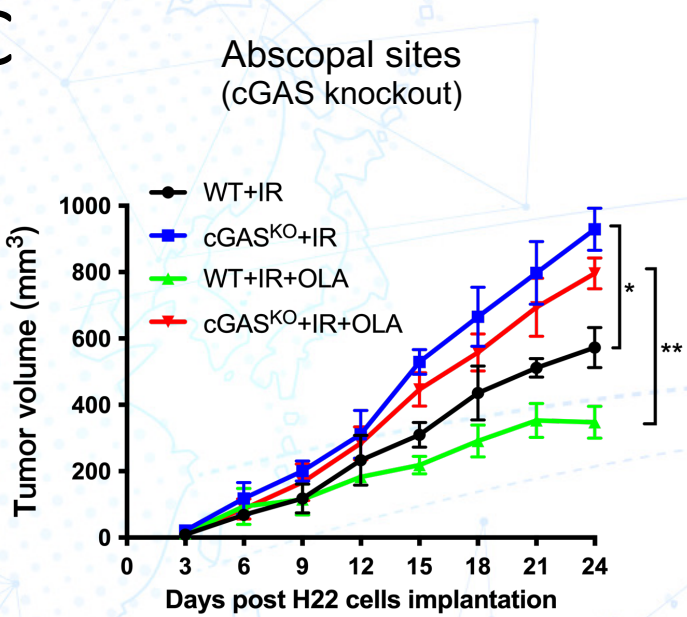
A



B

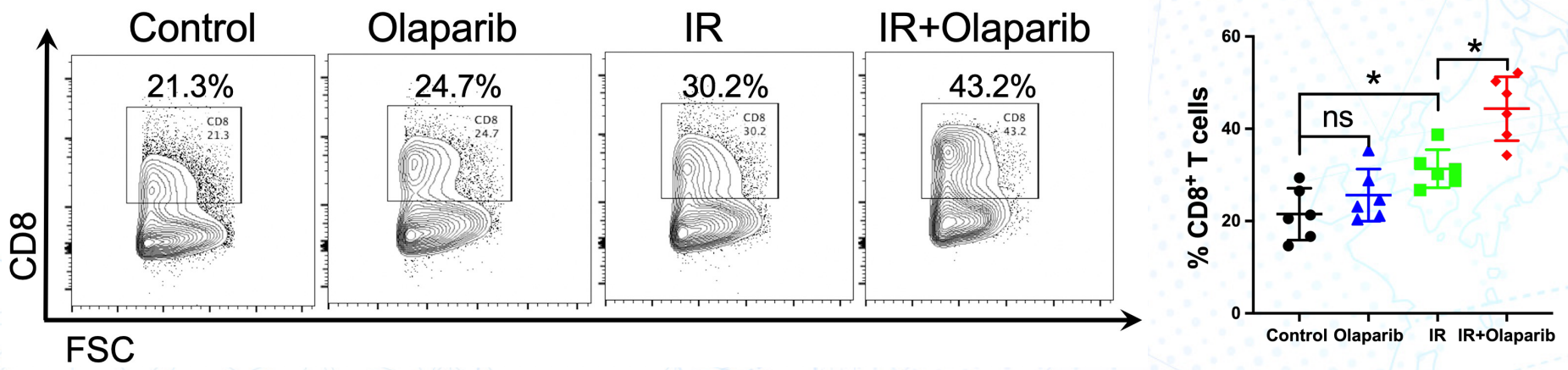


C



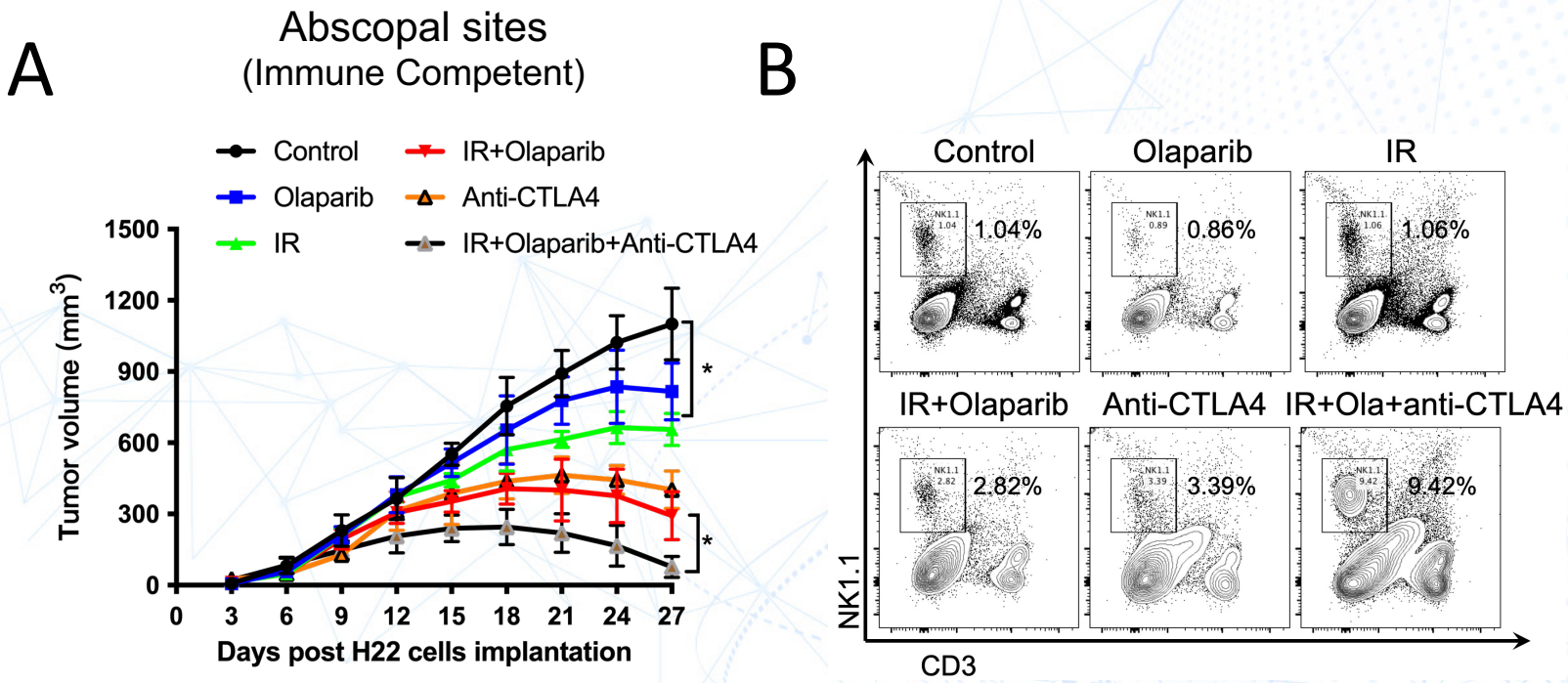
(A) Growth curves from primary (A) and abscopal (B) H22 tumors in immune competent mice treated with olaparib, IR and the combination. (C) Growth curves from abscopal H22 tumors in immunocompetent and cGAS KO mice treated with olaparib, IR and the combination. (*P <.05; #P <.01)

STING activation reprograms the immune microenvironment in the abscopal tumor



FACS analysis of infiltrating CD8+ cytotoxic T cells after treatment with olaparib, IR and the combination. (*P <.05; #P <.01; ns, no significance).

Olaparib impacts immune exhaustion following radioimmunotherapy



(A) Growth curves from abscopal H22 tumors in immune competent mice treated with olaparib, IR, anti-CTLA4, and the combination. (B) FACS analysis of infiltrating NK cells from abscopal H22 tumors after treatment with olaparib, IR, anti-CTLA4, and the combination. (*P <.05; #P <.01; ns, no significance)

Conclusions

Combination therapy with PARP inhibitors and radiotherapy contributes to local (primary) and systemic (abscopal) tumor control and enhance responsiveness of HCC to immunotherapy through inducing DNA damage and boosting innate immune response.