effectively sensitize SCLC cells to ionizing radiation (IR). We further hypothesized that PARP trapping, a cytotoxic mechanism of action distinct from inhibition of the PARP enzyme and the DNA damage response, contributes to radiosensitization by PARP inhibitors.

Materials/Methods: Short-term viability assays and clonogenic survival assays (CSA) were used to assess radiosensitization in six SCLC cell lines. PARP trapping and PARP enzymatic inhibition were analyzed by quantifying the chromatin-bound fraction of PARP1 and the total cell PAR polymer, respectively, using western blot. Doses of veliparib, a weak PARP trapper, and talazoparib, a potent PARP trapper, that had equivalent enzymatic inhibitory activity but differing PARP trapping activity were identified and compared in CSAs. The number of g-H2AX foci induced by veliparib and talazoparib were compared with and without IR using immunofluorescence assays. Talazoparib, IR, and their combination were tested in three patient-derived xenograft (PDX) models, and time for the tumors to grow to 1000 mm^3 was compared using the log-rank test.

Results: Radiosensitization by talazoparib was seen in 5 of 6 cell lines in short term viability assays: one cell line at 0.2 nM (Dose Modification Factor [DMF] 1.56), two cell lines at 2 nM (DMF 1.34 − 1.86), and four cell lines at 20 nM (DMF 1.61 − 2.88). Using CSAs, sensitization to IR was seen in 3 of 3 cell lines, with two cell lines sensitized at 20 nM (DMF 1.40-2.13) and one at 200 nM (DMF 2.20). Doses of 200 nM talazoparib and 1600 nM veliparib similarly inhibited PAR polymerization; however, as expected, talazoparib exhibited greater PARP trapping activity. This dose of veliparib was insufficient for radiosensitization, while the greater PARP trapping observed with 200 nM talazoparib was associated with significant radiosensitization (DMF 3.3). This further correlated with more double-stranded DNA breaks (g-H2AX foci) seen with talazoparib compared to veliparib both in the absence of IR (mean foci per cell: 8.4 DMSO, 19.3 veliparib, 58.7 talazoparib) and with IR (22.4 DMSO, 32.8 veliparib, 75.6 talazoparib). Finally, a dose of 0.2 mg/kg talazoparib in vivo led to statistically significant tumor growth inhibition in combination with IR but not as a single agent in three SCLC PDX models.

Conclusion: PARP inhibition effectively sensitizes SCLC cell lines and PDXs to IR, and PARP trapping correlates with radiosensitization. PARP inhibitors, especially those with high PARP trapping activity, may provide a powerful tool to improve the efficacy of radiation therapy in SCLC.

Author Disclosure: **J.H. Laird**: None. **B.H. Lok**: None. **J. Ma**: None. **A. Bell**: None. **E. De Stanchina**: None. **J. Poirier**: None. **C.M. Rudin**: Consultant; AbbVie, Aveo/Biodesik, Boerhinger Ingelheim, GlaxoSmithKline; FreeToBreathe.

SU_44_2434

Hafnium Oxide Nanoparticles Activated By Radiation Therapy for the Treatment of Solid Tumors

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Purpose/Objective(s): To improve radiotherapy (RT) in terms of tumor response and to reduce irradiation of healthy tissues, innovative therapeutic approaches are needed. In response, NBTXR3, injectable hafnium oxide nanoparticles, was developed for the treatment of solid tumors. Once injected intratumorally, NBTXR3 can deposit high energy within tumors only when activated by an ionizing radiation source, like current standard RTs. Upon activation, the high energy radiation physically kills the tumor cells by triggering DNA damage and cell destruction improving clinical outcomes. Since its first successful clinical evaluation in a completed phase I trial in patients with locally advanced soft tissue sarcoma, NBTXR3 is currently evaluated in numerous indications worldwide (EU, Asia, US).

Materials/Methods: NBTXR3 was the object of numerous in vitro and in vivo tumor models to determine its mechanism of action, performance and biocompatibility profile. Once they were assessed, NBTXR3 entered clinical development and was administered as a single intratumoral (IT) injection activated by RT. NBTXR3 is clinically evaluated in head and neck [NCT01946867; NCT02901483], prostate [NCT02805894], liver [NCT02721056] and rectum cancers [NCT02465593] with the scope of determining the Recommended Dose or observing any Dose Limiting Toxicities (DLTs) in each indication. A phase II/III trial in soft tissue sarcoma (STS) of the trunk and extremities [NCT02379845] is about to be finalized.

Results: Preclinically, in vitro results showed an increase of cancer cells death and in vivo results demonstrated antitumor efficacy with NBTXR3 + RT compared to RT alone. This physical cell killing could open a potential systemic activity through immune response by triggering immunogenic cell death, reinforcing local effect. Clinically, across the 7 clinical trials and 6 indications, NBTXR3 demonstrated an overall positive safety profile. The numerous types of tumors and different body locations involved in these trials confirmed feasibility of IT injection and persistence of NBTXR3 in the tumor, with no leakage in the surrounding healthy tissues. NBTXR3 antitumor activity is currently evaluated in its first phase II/III in patients with STS. Besides, analysis of tumor biopsies collected pre- and post-radiotherapy suggested a release of tumor antigens during cancer cell death and stimulation of local immunological effects.

Conclusion: NBTXR3 have shown promising results in non-clinical studies with marked antitumor efficacy and in clinical development in terms of safety and preliminary evaluations of efficacy. Considering the preliminary results of the 145 patients injected across all clinical trials, these first-in-class nanoparticles have already proven to be an encouraging innovative treatment in various types of tumors.

Author Disclosure: **C. Le Tourneau**: Honoraria; Novartis, Bristol-Myers Squibb. Consultant; Amgen, Bristol-Myers Squibb, Merck Serono, AstraZeneca. Travel Expenses; MSD. **J.O. Thariat**: None. **E. Chajon Rodriguez**: None. **P. Sargos**: None. **C. Le Pechoux**: None. **G. Kantor**: None. **C. Hoffmann**: None. **V. Moreno Garcia**: None. **T. De Baere**: None. **V. Vendrely**: None. **E. Rio**: None. **A. Lecesne**: None. **A. Gronchi**: None. **P.L. Nguyen**: Honoraria; Bayer. Consultant; Nanobiotix, Infinity Pharmaceuticals, GI Windows, Astellas, Augmenix. Advisory Board; Ferring, Medivation, Genome DX, Dendreon. Stock Options; Augmenix; Genitourinary Cancers Symposium. **A.P. Dicker**: Research Grant; Radiation Therapy Oncology Group. Travel Expenses; Prostate Cancer Foundation; Department of Defense. **T.Y. Seiwert**: Honoraria; Amgen, BMS, Jounce, Merck/ MSD. Travel Expenses; BMS, Jounce, Merck/ MSD. **Z. Papai**: None. **P. Rutkowski**: None. **S. Bonvalot**: None.

SU_44_2435

CRISPR Cas9 Mediated Caveolin-1 Knockout Sensitizes Radioresistant Non-Small Cell Lung Cancer

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