610 IMMUNORAD: A STRATIFIED PHASE II TRIAL OF IMAGE GUIDED HYPOFRACTIONATED RADIOTHERAPY WITH CONCURRENT NELFINAVIR & PD-1 INHIBITION IN ADVANCED MELANOMA, LUNG CANCER & RENAL CELL CARCINOMA

[1]Peter H Goff*, [2]Kelsey K Baker, [2]Sylvia M Lee, [1,2]Scott S Tykodi, [2]Shailender Bhatia, [1]Jing Zeng, [2]Mary Redman, [1,2]Ramesh Rengan. [1]*University of Washington, Seattle, WA, USA*; [2]*Fred Hutchinson Cancer Center, Seattle, WA, USA*

Background Resistance to immune checkpoint inhibitors (ICIs) is a persistent challenge in treating advanced malignancies. Our preclinical data showed that nelfinavir (NFV), an HIV protease and Ras-PI3K-Akt pathway inhibitor, augments tumor response to ICIs. We hypothesized that NFV will synergize with concurrent hypofractionated radiotherapy (HRT) and ICIs.

Methods We conducted a phase II trial of concurrent NFV (1250mg PO BID), HRT (8Gy x3) and nivolumab in ICI-naïve (ICI-N) or ICI-refractory (ICI-R) patients with melanoma (MEL), renal cell carcinoma (RCC) or non-small cell lung cancer (NSCLC) (6 cohorts total). The primary endpoint was investigator-assessed objective response rate (ORR), per RECIST 1.1, in unirradiated lesions. Secondary endpoints included overall survival (OS), progression-free survival (PFS), and toxicity. Patients receiving $\geq$1 dose of NFV, ICI and RT were eligible for efficacy analyses. Patients receiving NFV or ICI were assessed for toxicity.

Results Twenty patients (8-MEL, 11-RCC, 1-NSCLC; 15/20 (75%) ICI-R), 30% female with median age 59.4 years (range: 30.5 – 73.8), enrolled before the trial was suspended due to toxicity. Irradiated lesions included lung, liver, bone, soft tissue, nodal and other visceral metastases. Out of 17 evaluable patients, 2 (11.8%) patients had an objective response, 1 partial response (MEL ICI-R) and 1 complete response (MEL ICI-N). Six-month PFS rates were 25% (2/8) for ICI-R RCC and 40% (2/5) for ICI-R melanoma, with 3 ICI-R patients having prolonged disease control lasting 10.4, 15.5 and 15.7 months, respectively.

Most common clinical AEs were grade 1–2 diarrhea (70%), fatigue (40%) or nausea (30%). Three clinical grade 3 AEs were observed (2 arthralgia, 1 hyperglycemia). Eight patients (40%) had grade 2–4 immune-mediated AST/ALT elevation requiring steroids.

Conclusions PI3K/Akt-pathway inhibition with NFV, HRT & ICI resulted in higher-than-anticipated hepatotoxicity. Immune-correlate studies will investigate if toxicity is related to immune activation. Formal evaluation of clinical efficacy was compromised by toxicity-related treatment discontinuation.

Trial Registration ClinicalTrials.gov ID: NCT03050060

Ethics Approval This study was approved by the Fred Hutchinson Cancer Center's IRB (9712).

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