Preliminary results of a prospective pilot study using CD8 ImmunoPET imaging to evaluate the immune response to radiation therapy (ELIXR)

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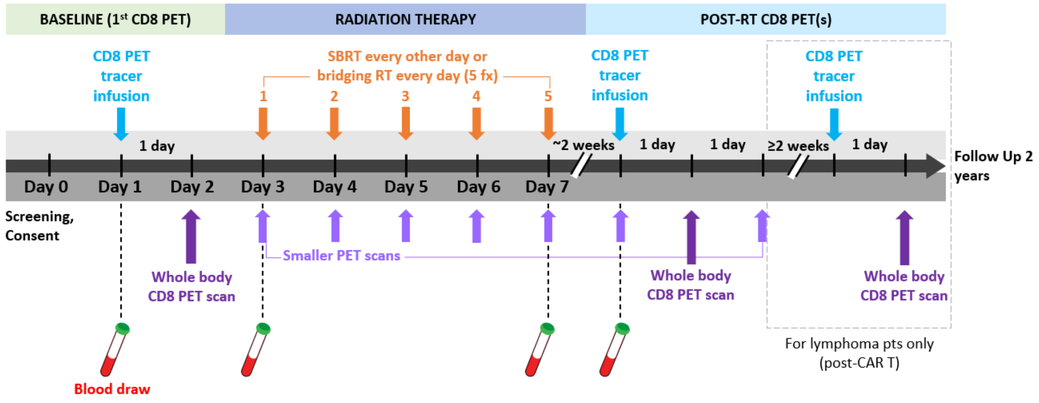
BACKGROUND

- Radiation therapy (RT) may produce immunomodulatory effects that can synergize with immunotherapy, but the immune response to radiation within the heterogeneous tumor microenvironment is poorly understood.
- Tumor accumulation of cancer-killing cytotoxic CD8+ T cells is correlated with response and survival.
- ^{89}Zr-Df-crefmirlimab is a radiolabeled CD8-specific minibody that can image CD8+ T cell distribution throughout entire tumors and the whole body.
- Optimal scans occur at 24 hours post-infusion, but the half-life of the tracer agent (~3 days) enables scans to be taken at multiple timepoints up to one-week post-infusion
- Our pilot study (NCT05371132) uses ^{89}Zr-Df-crefmirlimab to assess intratumoral changes in CD8+ T cell activity during and after RT.
- Here, we present the results of our first four patients.

METHODS

- Eligible patients have no change in systemic treatment within 2 months prior to RT and no splenic disorders.
- Patients receive a 1 mCi dose of ^{89}Zr-Df-crefmirlimab before and 1-2 weeks after a 5-fraction RT course.
- Each dose is followed by a whole-body positron emission tomography (PET) scan, and each radiation fraction is followed by a smaller PET in the region of interest.
- Lymphoma patients enrolled receive RT as bridging before chimeric antigen receptor (CAR) T cell therapy.



- Lymphoma patients receive a 3rd tracer infusion and scan post-CAR T.
- Maximum standardized uptake values (SUV_{max}) of lesions are extracted from all tumors, both target and non-target, in each CD8 ImmunoPET scan.

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RESULTS

- 3 metastatic renal cell carcinoma (mRCC) patients and 1 diffuse large B cell lymphoma (DLBCL) patient have completed treatment.
- Median age 64 years (range 61-65).
- The mRCC patients (P1-P3) received stereotactic body RT (SBRT; 30-40 Gy in 5 fractions, dose painted based on proximity to OARs) to one metastatic site.
- The DLBCL patient (P4) received RT (20-25 Gy in 5 fractions) to two lesions in the legs, as bridging to CAR T cell therapy. Treatment intent was palliative, and this patient had 12 other lesions in the legs that were not treated with RT.
- No toxicities attributable to ^{89}Zr-Df-crefmirlimab were observed.
- Mean peak increase in SUV_{max} of the target lesion in P1-3 was 14.5±8.1.
- Mean size reduction by longest diameter of P1-3 was 36.3%±20.2%.
- In P1, a normal lymph node saw an unusual 4.4 increase in SUV_{max} post-RT. 8 months later this was found to have developed into a lesion (Fig. 1).

Table 1. Change in CD8 ImmunoPET SUV_{max} of treated lesions and response.

	Treated lesion site	Concurrent Therapy	Baseline SUV_{max}	Peak SUV_{max}	Timepoint of peak activity	Response to date
P1	Lung	XL092	1.3	5.2	4th RT fraction	47% decrease
P2	Right shoulder	Cabozantinib	6.8	19.0	Post-RT	13% decrease
P3	Subcarinal lymph node	Nivolumab	6.8	19.4	4th RT fraction	49% decrease
P4	Left leg	None	0.8	2.0	4th RT fraction	Resolved
	Right leg		1.4	4.1	5th RT fraction	Resolved

Figure 1. Images showing a hilar lymph node that displayed notable increase in CD8 PET SUV_{max} post-radiation, which developed into a metastasis 8 months later.

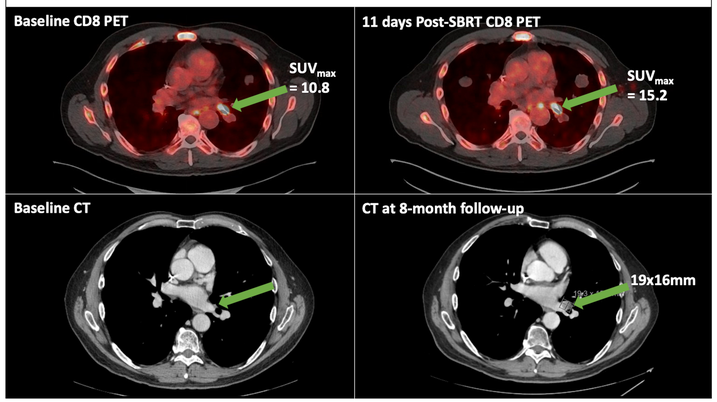
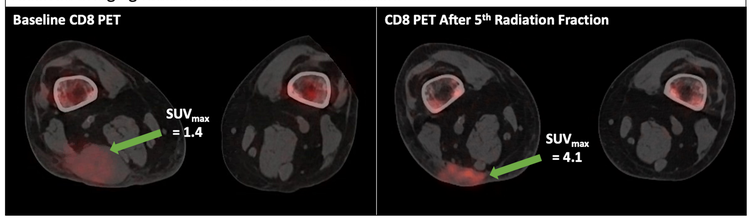


Figure 2. CD8 PET imaging of the irradiated lesion in the right leg of a lymphoma patient who received bridging radiation before CAR T cell infusion.



- In P4, peak increase in SUV_{max} was 1.2 and 2.7 in the left and right leg target lesions, respectively (Fig. 2).
- Two non-target lesions proximal to the left leg target lesion that received ~1% of the dose achieved an increase in CD8 PET SUV_{max} of 1.2 and 1.7 during radiation. Both resolved post-RT pre-CAR T.
- CD8 ImmunoPET taken 7 days post-CAR T infusion did not demonstrate any significant CD8 PET signal.
- All lesions resolved by day 30 post-CAR T on FDG PET imaging.

CONCLUSION

- The use of ^{89}Zr-Df-crefmirlimab to assess the immune response to radiation with serial inter-fraction CD8 ImmunoPET is safe and feasible.
- Increase in intratumoral CD8+ T cell activity was observed during RT in mRCC and lymphoma patients.
- Follow-up may reveal the prognostic implications of visualizing the immunogenic effects of radiation using CD8 ImmunoPET.