Clinical Cancer Research

615 Chestnut Street

Philadelphia, PA 19106-4404

Re: Activated anti-tumor immune infiltrates are associated with improved survival in p53 abnormal endometrial carcinoma

Aug 23, 2024

Dear editor,

It is with great enthusiasm that we submit our research article: “**Activated anti-tumor immune infiltrates are associated with improved survival in p53 abnormal endometrial carcinoma**” for publication in Clinical Cancer Research. Our work provides a timely and in-depth view of the immune landscape of p53-mutated endometrial carcinoma, the most aggressive molecular subtype of endometrial cancer.

We studied 256 treatment-naive tumors, one of the largest cohorts of this cancer type to date, with multiplex immunofluorescence and guided artificial intelligence analysis, showing that approximately 50% of tumors are extensively infiltrated by tumor-infiltrating lymphocytes. These extensively infiltrated tumors express markers of active anti-tumor immunity and are associated with longer overall, progression-free and disease-specific survival in multimodal analysis. We show that these tumors upregulate immunomodulatory molecules (PD-1, PD-L1 and IDO-1), making them prime targets for immune checkpoint inhibitors. Our results contextualize the findings of recent clinical trials (RUBY, GYO18/KEYNOTE-868) that have demonstrated the benefit of immunotherapy in both mismatch repair-deficient and mismatch repair-proficient endometrial cancers. Additionally, we integrated immune profiling with sequencing and immunohistochemical-based measurements of HER2 amplification and homologous recombination deficiency, the targets of HER2 and PARP inhibitors, respectively. We show that the immune-hot phenotype is independent of HER2 and homologous recombination status.

We anticipate that our research will be of high interest for clinicians who treat gynecological malignancies, and researchers and clinicians interested in cancer immunotherapy. Our results will help set the groundwork for personalized targeted therapies using immunotherapy, HER2 targeted therapies, and PARP inhibition in endometrial carcinoma based on immune infiltrate and molecular characterization.

We suggest the following reviewers would be suitably qualified to assess our work:

* Dr. Katherine Fuh, UCSF (gynecologic cancers, immunotherapy, targeted therapy)
* Dr. Matthew Powell, Washington University in St Louis (gynecologic cancers, immunotherapy clinical trials)
* Dr. Casey Cosgrove, OHSU (gynecologic cancers, targeted therapy)
* Dr. Britt Erickson, University of Minnesota (gynecologic cancers, clinical trials)

On behalf of our co-authors, we thank you for your consideration and look forward to hearing back from you in due course. Please do not hesitate to contact us should you require additional information or materials.

Sincerely,



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