ORAL PRESENTATIONS - PROFFERED ABSTRACTS | APRIL 25 2025

Abstract CT132: Phase 2 trial of metastasis directed radiotherapy without systemic therapy (MRWS) for oligometastatic clear cell renal cell carcinoma (ccRCC) and investigation of circulating tumor DNA (ctDNA) as a personalized biomarker FREE

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Cancer Res (2025) 85 (8_Supplement_2): CT132.

https://doi.org/10.1158/1538-7445.AM2025-CT132

Abstract

Background:

Current treatment for frontline ccRCC focuses on systemic therapy doublets. Although effective, such combinations exhibit substantial toxicities and healthcare costs. An underutilized option is MRWS, which may facilitate a prolonged systemic therapy-free interval in select patients. Unfortunately, no reliable prognostic markers exist to select patients for MRWS. Although ctDNA assays may guide patient selection, implementation in ccRCC has proven challenging due to limited ctDNA shedding. Therefore, advanced sequencing and bioinformatic pipelines are needed to enhance ctDNA reliability in ccRCC.

Methods:

This phase 2 single-arm trial (NCT03575611) enrolled patients with oligometastatic ccRCC and up to 5 metastases. All patients had either never received systemic therapy or ceased >1 month earlier. Patients were treated with MRWS, consisting of predominately stereotactic radiation therapy to all sites of disease. Subsequent rounds of MRWS were administered if limited progression was observed. The co-primary endpoints were progression free survival (PFS) and systemic therapy free survival (STFS). For the latter, a median STFS of >24 months (mo) was prespecified as the threshold for success. Individualized ctDNA panels (Myriad Genetics) were created from tumor whole genome sequencing and applied to serial plasma samples. Molecular residual disease (MRD) status was determined based on whether ctDNA was detected (MRD+) or not (MRD-).

Results:

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Between July 2018 to May 2023, 121 oligometastatic ccRCC patients were enrolled. Median follow up was 36 mo (range 13-68 mo). Most patients (72%) had 1 site of metastatic disease and had never received systemic therapy (70%). The median PFS was 18 mo (95% CI: 15-22 mo) and STFS was 34 mo (95% CI: 28-54 mo). The lower bounds of 95% CI of the median STFS exceeded the prespecified 24 mo threshold for success. Two-year PFS and STFS were 40% and 75%, respectively. Median OS was not reached, and 2- and 3-year OS were 94% and 87%, respectively. Eight (7%) patients experienced grade 3+ toxicities at least possibly attributed to MRWS. There were no grade 5 toxicities.MRD+ was detected in 56% of patients at baseline and associated with significantly shorter STFS (HR 2.9, 95% CI 1.4-6.1, P=0.003). Patients who were MRD+ and MRD- at baseline exhibited 27 vs. 54 mo median STFS, respectively. Three months after MRWS, 31% of MRD + patients converted to MRD-. Positive MRD status at 3 month follow up was strongly associated with shorter STFS (HR 4.3, 95% CI 2.0-9.0, P<0.001).

Conclusions:

MRWS exhibited excellent tolerability and facilitated prolonged time off systemic therapy without compromising OS. Our ctDNA approach appears to be a promising baseline prognostic biomarker for STFS and a dynamic marker of MRWS response.

Citation Format:

Chad Tang, Alexander Sherry, Aaron Seo, Kieko Hara, Haesun Choi, Suyu Liu, Xiaowen Sun, Anya Montoya, Ethan Ludmir, Amishi Y. Shah, Eric Jonasch, Amado J. Zurita, Craig Kovitz, Christopher J. Battey, Sarah Ratzel, Giannicola Genovese, Kanishka Sircar, Jose Karam, Nizar Tannir, Pavlos Msaouel. Phase 2 trial of metastasis directed radiotherapy without systemic therapy (MRWS) for oligometastatic clear cell renal cell carcinoma (ccRCC) and investigation of circulating tumor DNA (ctDNA) as a personalized biomarker [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2025; Part 2 (Late-Breaking, Clinical Trial, and Invited Abstracts); 2025 Apr 25-30; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2025;85(8_Suppl_2):Abstract nr CT132.

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Online ISSN 1538-7445 **Print ISSN** 0008-5472

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