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Abstract CT128: RADIANT: A window of opportunity trial exploring preoperative immunomodulatory radiotherapy and durvalumab prior to radical cystectomy in patients with cisplatin-ineligible muscle-invasive bladder carcinoma

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Cancer Res (2025) 85 (8_Supplement_2): CT128.

https://doi.org/10.1158/1538-7445.AM2025-CT128

Abstract

Background:

Ionizing radiotherapy (RT) can potentially enhance anti-tumour responses to immune checkpoint inhibitors. In doses of 6-9Gy/fraction, RT releases free cytosolic DNA which upregulates cyclic GMP-AMP synthase pathways (cGAS-STING) and increases tumor infiltrating CD8+ T-lymphocytes, inflammatory cytokines, programmed-death ligand 1 (PD-L1) expression, and antigen presentation. However >12Gy/fraction RT may paradoxically upregulate TREX1, degrade cytosolic DNA and lead to immunosuppression. We conducted a WOO trial to explore an immunomodulating dose of RT with anti-PD-L1 in patients with MIBC.

Methods:

Eligible patients had histologically confirmed urothelial carcinoma AJCC stage T2-T4aN0, planned for radical cystectomy, ECOG PS 0-2, and ineligible or refused neoadjuvant cisplatin-based chemotherapy. Patients received a single 8-Gy fraction of RT to bladder followed 4 days later by durvalumab 1500mg IV q3week x3. Cystectomy was performed 7-35 days after last durvalumab. Primary endpoint was pathological complete response (pCR: ypT0N0). Secondary endpoints were safety, pathological response (pCR: ypTisN0), recurrence-free survival, overall survival, and tumor/blood correlatives. Transurethral resection of bladder tumor (TURBT) and cystectomy samples were profiled using the Oncomine Comprehensive Assay Plus (DNA), Ion AmpliSeq (RNA), and GeoMx Digital Spatial Profiling (protein).

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Results:

14 patients were enrolled with clinical stage T2 (n=9), T3 (n=3), and T4 (n=2). 5 (36%) had multifocal disease, 7 (50%) had associated carcinoma in situ, 4 (29%) had prior intravesicular therapy, and 11 (79%) had optimal TURBT prior to cystectomy. All patients received 8Gy RT and 3 cycles of durvalumab. Durvalumab-related grade 1-2 adverse events (AE) were hypothyroidism (2), fatigue (1), shoulder pain (1), alkaline phosphatase increase (1), AST elevation (1), and pruritis (1). RT related grade 1-2 AEs were fatigue (2), dysuria (2), and rash (1). There were no related grade 3+ adverse events or surgical delays due to RT or durvalumab. PCR was obtained in 7/14 (50%); PR was demonstrated in 8/14 (57%) and more likely to occur in patients with multifocal disease and optimal TURBT. Luminal TCGA subtype, DNA damage repair gene alterations and high tumor mutational burden (≥10 mut/Mb) were enriched in PR (75%, 50% and 50% respectively) compared with non-PR (33%, 17%, and 33%). The 12 and 18-month landmark survival for PR vs non-PR was 83.3 vs 62.5% and 83.3 vs 31.5% respectively.

Conclusions:

Immune modulating doses of RT and durvalumab were associated with a high pCR and PR rates with excellent tolerability. Further exploration of hypofractionated bladder RT schemes with anti-PD-L1 are warranted.

Citation Format:

Megan Hopkins, Deepak Dinakaran, Aly-Khan A. Lalani, Naveen S. Basappa, Melissa Huynh, Drashti Jain, Vida Talebian, Marc Walsh, Gregory R. Pond, Ricardo Ferandes, Ilias Cagiannos, Scott Morgan, Mark Corkum, Dominick Bosse, Martin N. Reaume, Ana-Alicia Beltran-Bless, Christina Canil, Melanie Spears, Michael Ong. RADIANT: A window of opportunity trial exploring preoperative immunomodulatory radiotherapy and durvalumab prior to radical cystectomy in patients with cisplatin-ineligible muscle-invasive bladder carcinoma [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 CT128.

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

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