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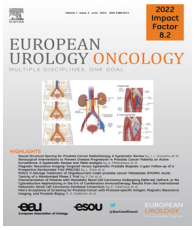

European Association of Urology

Pembrolizumab with Chemoradiation as Treatment for Muscle-invasive Bladder Cancer: Analysis of Safety and Efficacy of the PCR-MIB Phase 2 Clinical Trial (ANZUP 1502)

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Article info

Article history:
Received 25 May 2023
Received in Revised form
7 September 2023
Accepted 20 September 2023
Available online 7 October 2023

Associate Editor:
Morgan Rouprêt

Keywords:
Immunotherapy
Bladder cancer
Chemoradiation

Abstract

Background: Radiation may improve the efficacy of immune checkpoint inhibition. This study investigates the combination of pembrolizumab and chemoradiation (CRT) for muscle-invasive bladder cancer (MIBC).
Objective: To assess the feasibility and safety of pembrolizumab combined with CRT for MIBC.
Design, setting, and participants: A single-arm phase 2 trial was performed with 28 participants having cT2-T4aN0M0 MIBC (Eastern Cooperative Oncology Group performance status 0–1; estimated glomerular filtration rate ≥40 ml/min; no contraindications to pembrolizumab) suitable for CRT.
Intervention: Whole bladder radiation therapy (RT; 64 Gy in 32 daily fractions, over 6.5 wk, combined with cisplatin (35 mg/m^2 intravenously [IV] weekly, six doses) and pembrolizumab (200 mg IV q3 weeks, seven doses), both starting with RT. Surveillance cystoscopy/biopsy and computerised tomography scans performed 12 and 24 wk after CRT.
Outcome measurements and statistical analysis: The primary endpoint was feasibility, determined by a prespecified satisfactory low rate of grade 3 or worse nonurinary toxicity or completion of planned CRT according to defined parameters. Secondary endpoints were complete cystoscopic response, locoregional progression-free survival (LRPFS), distant metastasis-free survival (DMFS), and overall survival (OS).
Results and limitations: Twenty-eight patients were enrolled with a 31-mo median follow-up. Six had Grade >3 nonurinary adverse events during/within 12 wk after treatment; three had more than one cisplatin dose reduction. The 24-wk post-CRT complete response (CR) rate was 88%. Eight patients developed metastatic disease, and three had nonmetastatic progression. The DMFS at 2 yr is 78% (95% confidence interval [CI] 54–

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https://doi.org/10.1016/j.euo.2023.09.011

90%), with LRPFS at 2 yr of 87% (95% CI 64–96%) and median OS of 39 mo (95% CI 17.1–not evaluable). Limitations are the single-arm design and sample size.
Conclusions: Combining pembrolizumab with CRT for MIBC was feasible, with manageable toxicity and promising CR rates.
Patient summary: Immunotherapy treats nonmetastatic/metastatic bladder cancer effectively. We combined pembrolizumab with chemotherapy and radiation to assess its safety and impact on treatment delivery. The combination was feasible with encouraging early activity. Further larger trials are warranted.

1. Introduction

Chemoradiation is a well-established treatment option for nonmetastatic muscle-invasive bladder cancer (MIBC) leading to bladder preservation [1–3]. Although antibodies that block PD1/PD-L1 signalling are active in metastatic urothelial cancer [4,5], with emerging evidence of activity in localised disease [6,7], less is known if there are synergy and safety in combination with chemoradiation. Radiation increases tumour antigen exposure to the immune system and alters the immune microenvironment by increasing cytokine levels, recruiting dendritic cells, and priming CD8 + cells [8–10]. In vitro and in vivo studies report synergy in combining immunotherapy agents with radiation [11–14]. Beyond case reports on abscopal effects of radiation and immunotherapy [15], larger randomised studies such as the PACIFIC trial have reported improved overall survival (OS) in participants receiving the anti–PD-L1 antibody durvalumab after chemoradiation [16], albeit in patients with non–small cell lung carcinoma.

The Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group trial of Pembrolizumab with Chemo-Radiation in Muscle Invasive Bladder cancer (PCR-MIB, ANZUP 1502; NCT02662062) explored the safety and efficacy of adding pembrolizumab to the combination of weekly cisplatin and concurrent radiation treatment in participants undergoing curative treatment for MIBC. Pembrolizumab was continued for a limited 3-mo period of adjuvant treatment after the chemoradiation had been finished. Furthermore, the trial was designed to report on preliminary efficacy and explore potential biomarkers of response and resistance to the trimodality treatment.

2. Patients and methods

PCR-MIB was a phase 1/2 single-arm, multicentre, open-label clinical trial that recruited participants from six hospitals in Australia between 2015 and 2021. Ethics approval was obtained from local institutional review boards, and all participants provided written informed consent.

2.1. Participants

Participants ≥18 yr of age with Eastern Cooperative Oncology Group performance status of 0 or 1, muscle-invasive T2-4a (Nx or N0) bladder cancer, predominant urothelial (>50%) histology, and no evidence of metastatic disease on systemic staging were eligible for the study. Participants with radiological evidence of pelvic lymphadenopathy were not eligible unless a biopsy of the node was negative for malignancy. Participants with bulky T3/T4a tumours deemed unsuitable for definitive chemoradiation were excluded, as were participants with untreated hydronephrosis, and those with extensive or multifocal carcinoma in situ (CIS) or other sites of urothelial carcinoma in the ureter or urethra. Participants must have undergone a maximum transurethral resection of the bladder cancer within 6 wk prior to the start date of chemoradiation. Prior neoadjuvant chemotherapy was not permitted. Participants required adequate haematological, hepatic, and renal organ function (calculated creatinine clearance ≥40 ml/min) and needed to be suitable for weekly cisplatin based on adequate hearing and the absence of pre-existing clinically significant neuropathy. Exclusions included prior pelvic radiation, pregnancy, a history of active autoimmune disease or pneumonitis, or previous treatment with anti-PD1/PD-L1 antibodies.

2.2. Study treatment

Participants received 64 Gy of intensity-modulated radiation therapy (IMRT) or three-dimensional conformal external beam radiation (3DCRT) to the whole bladder in 32 fractions over 6 wk and 2 d. Choice of radiation was permissible provided that three or more fields were employed for 3DCRT and IMRT techniques. The clinical target volume (CTV) had to include the whole bladder, the tumour bed region, the proximal urethra, and, in the male patient, if there was involvement of the bladder neck and/or prostatic fossa, the entire prostatic urethra. Patients who had a previous prostatectomy and bladder neck involvement required the urethra covered for a distance of 2 cm distal to the bladder neck. Any extravesical extension (eg, perivesical fat) was to be included in the CTV. Nodal groups including first echelon lymph nodes (obturator) in the immediate vicinity of the bladder were not covered in the radiation field. Unusual anatomical variations (eg, cystoceles and diverticula) were covered, and in cases involving the ureteric orifice, the distal ureter was covered to a distance of 1 cm. Participating institutions were required to submit and pass a credentialing case for approval prior to the commencement of therapy.

Participants received cisplatin 35 mg/m^2 (30 mg/m^2 if creatinine clearance was 40–50 ml/min) intravenously (IV) weekly concurrently with radiation for six doses. Pembrolizumab 200 mg IV commenced concurrently with radiation and was administered every 21 d for seven doses,

continuing until the 12-wk cystoscopy and assessment, resulting in five doses administered after the completion of radiation.

Surveillance assessments included cystoscopy and systemic computerised tomography (CT) imaging, performed 12 and 24 wk after completing chemoradiation to assess response and to evaluate any local recurrence or distant metastatic disease, and predefined intervals for 5 yr. A biopsy of the tumour bed to document a response was required at the 12- and 24-wk cystoscopies. Adverse events, according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, were documented at each visit during treatment and follow-up.

2.3. Outcomes

The primary objective was to determine the safety and feasibility of adding pembrolizumab to chemoradiation, measured by a satisfactorily low rate of unacceptable toxicity events during and within 12 wk of study treatment. Unacceptable toxicity events were defined by the occurrence of any of the following: (1) grade 3 or worse adverse events (excluding grade 3 or 4 urinary adverse events), (2) cisplatin withheld for two or more doses, (3) cisplatin withheld or reduced such that <66% of the intended total cisplatin dose is delivered, (4) radiation delivery extending beyond >7 wk, or (5) any single pembrolizumab dose being delayed for >6 wk (multiple dose delays were aggregated).

The secondary objectives were to evaluate the activity of the addition of pembrolizumab to chemoradiation based on the complete response (CR) rate, defined as a complete clinical response on cystoscopic biopsy at 12 and 24 wk after chemoradiation without radiological evidence of metastatic disease. OS, distant metastasis-free survival (DMFS), and local disease-free survival were also characterised. Local recurrence was defined as recurrence in the bladder or nodal recurrence in the pelvis. Exploratory objectives of the trial were related to the tumour, urine, and blood-based biomarkers of response and are not presented here.

2.4. Statistical analysis

A Simon two-stage design was used, with an initial evaluation of safety outcomes in the first stage conducted after ten participants received treatment, with the trial to halt if more than five participants experienced unacceptable toxicity. A further 20 participants were then planned to be recruited to complete the second stage of the trial, with all participants included in the assessment of the primary and secondary outcomes. A predefined definition of "definitely considered safe" was defined as <30% of participants experiencing unacceptable toxicity, with the definition of "definitely considered unsafe" defined as >50% of participants experiencing unacceptable toxicity. Power calculations estimated that this was achievable with a total of 30 participants. Binary proportions for unacceptable toxicity and CR rate and their 95% confidence intervals (CIs) were provided using the Clopper-Pearson [17] method. Survival endpoints were characterised using Kaplan-Meier curves. All statistical analyses were performed in R version 4.0.3. An independent data safety management committee reviewed the interim safety data regularly to ensure participant safety.

Drug and funding for this research were provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), Australia. The trial was sponsored by the ANZUP Cancer Trials Group and conducted independently by investigators, with the funders having no role in the trial design, data collection, analysis, or interpretation.

3. Results

Between June 2016 and November 2021, 28 of the planned 30 participants were recruited at six Australian centres. PCR-MIB was closed early due to slow accrual and competing studies. One participant completed chemoradiation and received two doses of pembrolizumab, but withdrew from study follow-up and was not evaluable for efficacy or adverse events beyond this point.

Baseline characteristics of the participants are shown in Table 1. Most participants (25/28, 89%) had pure transitional cell urothelial carcinoma. All participants completed their planned course of 64 Gy/32 fractions of radiation (Table 2). Four patients had more than one cisplatin dose omitted due to adverse events; however, the mean relative dose of cisplatin was 92% of the planned dose. The mean relative dose of the planned dose of pembrolizumab was 97%.

Nine participants (32%, 95% CI 16–52%) experienced a predefined unacceptable toxicity event within 12 wk of treatment completion (Table 3). Two of these nine patients

Table 1 – Baseline characteristics

		Total (n = 28)
Age (yr), median (range)		72 (58–86)
Sex, n (%)	Male	26 (93)
	Female	2 (7)
ECOG, n (%)	0	18 (64)
	1	10 (36)
Histology, n (%)	Transitional cell/urothelial	25 (89)
	Mixed transitional/nontransitional	3 (11)
	Associated CIS	9 (33)
T stage, n (%)	T2	26 (89)
	T3	2 (11)
Prior BCG, n (%)		2 (7)

BCG = bacillus Calmette-Guérin vaccine; CIS = carcinoma in situ; ECOG = Eastern Cooperative Oncology Group Performance Status.

Table 2 – Treatment delivered

		Total (n = 28)
Radiation technique, n (%)	Inverse planned IMRT	16 (57)
	VMAT	7 (25)
	3D-RT	4 (14)
	Other	1 (4)
Radiation delivery time, n (%)	≤7 wk	25 (89)
	>7 wk	3 (11)
Relative mean dose intensity (% of planned dose)	Cisplatin	92%
	Pembrolizumab	97%

3D-RT = three-dimensional conformal radiation therapy; IMRT = intensity-modulated radiation therapy; VMAT = volumetric arc therapy.

Table 3 – Unacceptable toxicity

Pt	Description of toxicity	Category of unacceptable toxicity			
		Adverse event ≥G3	Cisplatin ≥2 dose omissions	Radiation >7 wk	Pembrolizumab >6 wk delay
1	G3 haematuria	×			
2	G3 haematuria	×		×	
3	G3 hypertension	×			
4	COVID-19		×		
5	Congestive cardiac failure		×		
6	Cisplatin infusion reaction		×		
7	G5 respiratory failure/COPD	×	×	×	×
8	G3 colitis (irAE)	×			
9	G3 polymyalgia (irAE)	×			

COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; irAE = immune-related adverse event; Pt = patient.

experienced adverse events that met more than one prespecified definition for unacceptable toxicity, with one of these patients dying from respiratory failure with exacerbation of underlying obstructive airways disease.

Only two participants developed immune-related toxicities that met the definition for unacceptable toxicity. One participant experienced grade 3 colitis and one experienced grade 3 polymyalgia within 12 wk of treatment completion.

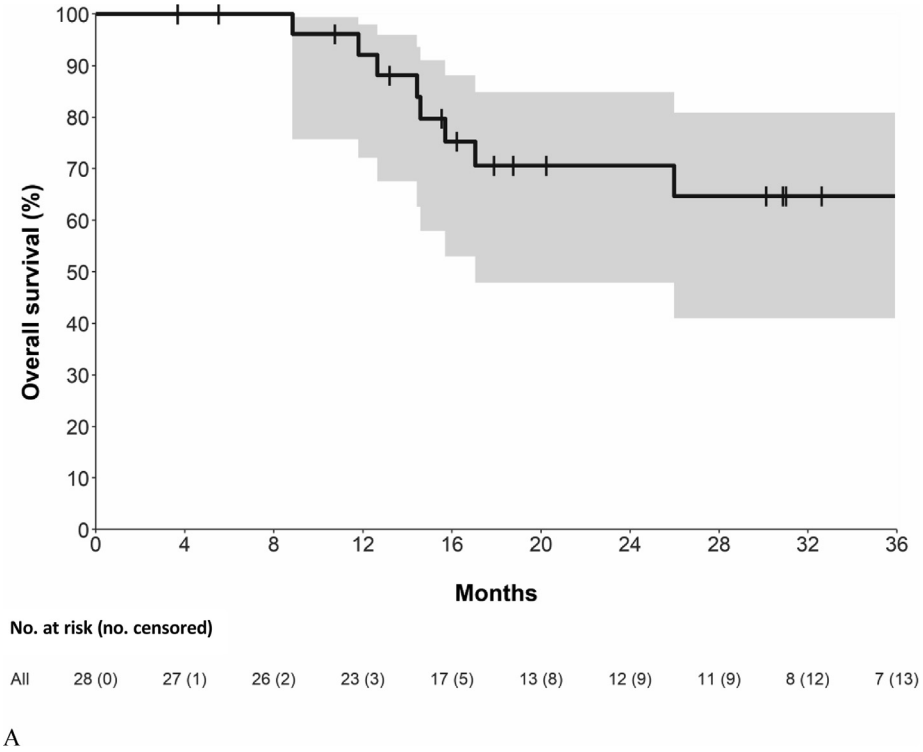
An additional two participants experienced grade 3–4 toxicity within 12 wk of completing treatment; however, both these patients had progressed with incurable disease at this time and were excluded from the analysis given that

Table 4 – Common Terminology Criteria of Adverse Events (by worst grade) [a]

CTCAE event term	CTCAE grade					Total (n = 28), n (%)
	1	2	3	4	5	
Respiratory failure	0	0	0	0	1	1 (4)
Sepsis (after cystectomy for locoregional PD)	0	0	0	1	0	1 (4)
Cystitis noninfective	3	1	3	0	0	7 (26)
Haematuria	9	0	2	0	0	11 (41)
Anaemia	1	2	1	0	0	4 (15)
Hypertension	0	1	1	0	0	2 (7)
Gastrointestinal disorders—colitis	0	0	1	0	0	1 (4)
Infusion-related reaction	0	0	1	0	0	1 (4)
Kidney infection	0	0	1	0	0	1 (4)
Polymyalgia rheumatica (musculoskeletal—other)	0	0	1	0	0	1 (4)
Neutrophil count decreased	0	0	1	0	0	1 (4)
Urinary tract infection	0	0	1	0	0	1 (4)
Urinary tract obstruction	0	0	1	0	0	1 (4)
Fatigue	14	5	0	0	0	19 (70)
Diarrhoea	10	4	0	0	0	14 (52)
Fever	1	4	0	0	0	5 (19)
Hypothyroidism	1	4	0	0	0	5 (19)
Constipation	7	3	0	0	0	10 (37)
Urinary frequency	13	3	0	0	0	16 (57)
Chills	2	2	0	0	0	4 (15)
Dyspnoea	1	2	0	0	0	3 (11)
Rash maculopapular	8	1	0	0	0	9 (33)
Oedema limbs	3	1	0	0	0	4 (15)
Platelet count decreased	3	1	0	0	0	4 (15)
Fall	2	1	0	0	0	3 (11)
Urinary incontinence	2	1	0	0	0	3 (11)
Nausea	6	0	0	0	0	6 (22)
Alanine aminotransferase increased	4	0	0	0	0	4 (15)
Urinary tract pain	4	0	0	0	0	4 (15)
Dry skin	3	0	0	0	0	3 (11)
Gastro-oesophageal reflux disease	3	0	0	0	0	3 (11)
Insomnia	3	0	0	0	0	3 (11)
Paraesthesia	3	0	0	0	0	3 (11)
Tinnitus	3	0	0	0	0	3 (11)
Urinary urgency	3	0	0	0	0	3 (11)
Abdominal pain	2	0	0	0	0	2 (7)
Cough	2	0	0	0	0	2 (7)
Creatinine increased	2	0	0	0	0	2 (7)
Headache	2	0	0	0	0	2 (7)
Hyperthyroidism	2	0	0	0	0	2 (7)
Mucositis oral	2	0	0	0	0	2 (7)
Weight loss	2	0	0	0	0	2 (7)
Any adverse event [a]	7	9	10	2	1	28 (100)

CTCAE = Common Terminology Criteria of Adverse Events; PD = progressive disease.
[a] Inclusive of all CTCAE G1 events occurring in more than one patient.

the toxicities were also deemed to be due to subsequent therapies. One of these participants experienced grade 3 anaemia secondary to palliative chemotherapy following development of metastatic disease, and the other had grade 4 sepsis following cystectomy, which was performed after locoregional progression with pelvic nodal metastases.



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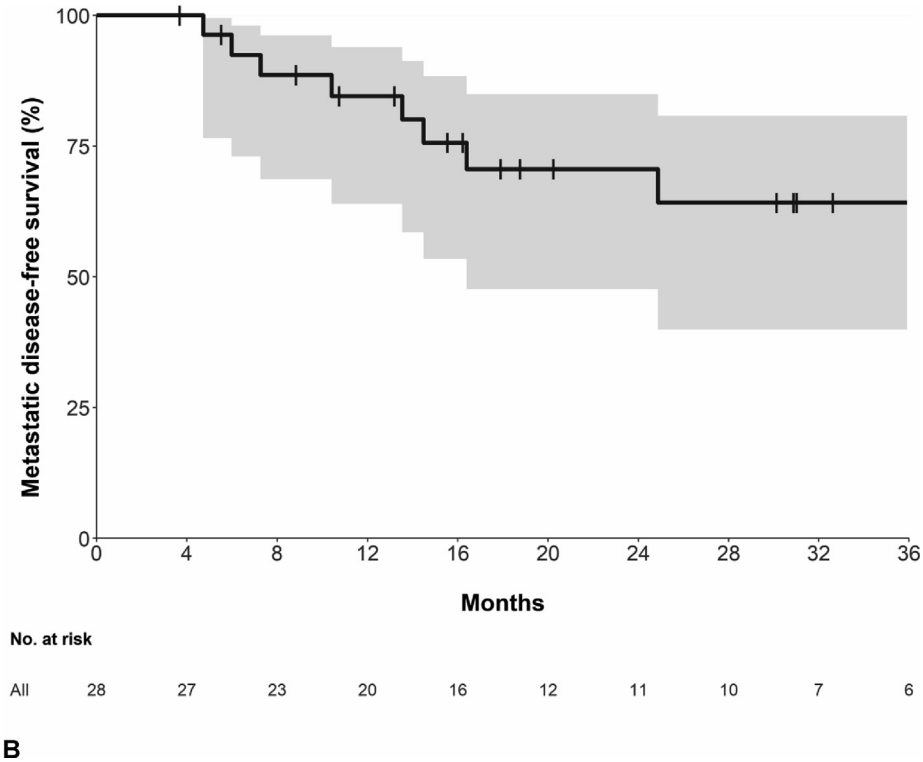

B

Fig. 1 – (A) Overall survival. (B) Distant metastatic disease-free survival. (C) Locoregional progression-free survival. Grey indicates 95% CI. CI = confidence interval.

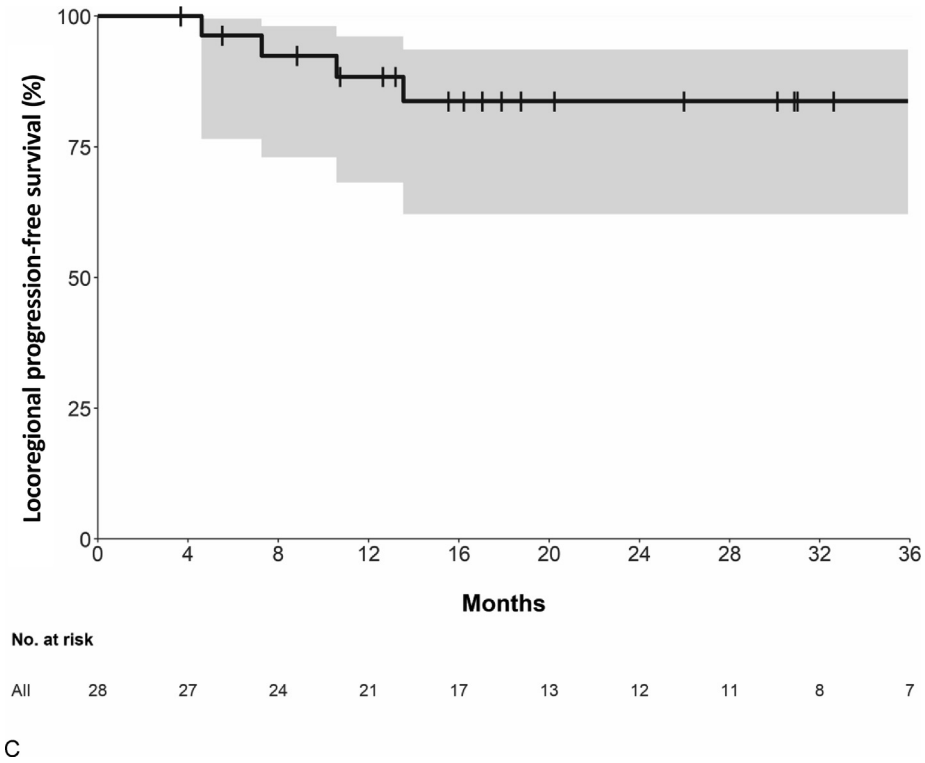

Fig. 1 (*continued*)

Although another participant developed grade 3 autoimmune nephritis, this occurred beyond 12 wk and did not classify as an unacceptable toxicity per protocol definition.

In total, 11 of 28 participants (39%) experienced grade 3–4 toxicity. The two most common grade 3–4 adverse events were cystitis (3/28) and haematuria (2/28). Other common adverse events are shown in Table 4.

By week 19, 19 out of 21 evaluable patients (90%, 95% CI 70–99%) achieved a cystoscopic CR. At week 31, the best overall response was CR in 23/26 (88%, 95% CI 70–98%) and progressive disease in 3/26 (12%, 95% CI 2–30%) of evaluable participants—two participants had experienced initial locoregional nodal disease progression and another had developed distant metastatic disease. Two participants were not evaluable for secondary response endpoints: one participant withdrew consent and one participant died from infective exacerbation of their pre-existing chronic airways disease.

After a median follow-up of 31 mo, the median OS time is 39 mo (95% CI 17%–not evaluable). The estimated OS and DMFS at 12 mo were 92% (95% CI 72–98%) and 85% (95% CI 64–94%), respectively (Fig. 1A and 1B). LRPFS was estimated at 88% at 12 mo (95% CI 68-98%; Fig. 1C). The sites of progression are shown in Table 5.

4. Discussion

The PCR-MIB trial found that pembrolizumab with cisplatin-based chemoradiation for MIBC is feasible and results in activity justifying further research. All participants completed their radiation course with a 92% mean dose intensity of cisplatin. No participants had significant interruption to chemoradiation due to immune-related adverse events. CR was documented in 88% of participants by 31 wk, with a median OS of 39 mo.

Evidence of the efficacy and toxicity of combining immunotherapy with radiation in urothelial cancer is evolving. A small number of studies have reported toxicity data from prospective trials of immunotherapy with conventional chemoradiation schedules in MIBC [18–21]. Balar et al [18] reported outcomes from the treatment of 54 participants receiving gemcitabine twice weekly and whole bladder radiation of 52 Gy in 20 fractions, with pembrolizumab given IV every 3 wk for a total of four doses, beginning 2–3 wk prior to radiation. Treatment was tolerable, with a grade 3–4 adverse event rate of 31% and a grade 3–4 immune-related adverse event rate of 7%. Additionally, concurrent nivolumab and ipilimumab appeared tolerable when administered with chemoradiation in another study [20]. In contrast, Marcq et al [19] terminated their study early due to higher-than-expected immune toxicity participants treated with atezolizumab and chemoradiation. Additionally, the PLUMMB trial, with concurrent pembrolizumab and radiation to the bladder (36 Gy in six fractions) was stopped early due to toxicity, but this may relate to the extreme hypofractionation of radiation and the inclusion of patients with either locally advanced or metastatic disease [22].

The combination of pembrolizumab and chemoradiation could not be formally declared safe in PCR-MIB based on not having met the requirement for unacceptable toxicity of <30%. Nine of 28 participants (32%) experienced a predefined "unacceptable toxicity", below the prespecified mar-

Table 5 – Sites of metastatic/locoregional progressive disease (PD)

Patient	Bladder/upper tract	Nodal site	Metastatic site
1			Pulmonary mets
2			Abdominal LN
3			Abdominal LN
4		Unilateral iliac lymph nodes (N2)	Abdominal LN subsequently *
5			Liver mets
6			Abdominal LN *
7		Unilateral iliac lymph nodes (N2)	Peritoneal mets subsequently
8			Liver mets, abdominal LN
9	Bladder pTa		
10	Bladder pTis		
11	Upper tract high-grade pTa		

LN = lymph node; mets = metastases.

gin of 50% required to consider the regimen unsafe. The novel endpoint of unacceptable toxicity was chosen to capture synergistic immune-oncology (IO) toxicities not captured by the CTCAE criteria, excluding probable radiation-related adverse events that are common, such as cystitis (Table 4). The definition and threshold were chosen prospectively for rigour, but led inevitably to non-IO toxicity influencing the endpoint and limiting the strength of any conclusion. While two participants developed serious toxicity related to immunotherapy contributing to this endpoint (grade 3 polymyalgia and grade 3 colitis), the other high-grade toxicities were related to coronavirus disease 2019, cardiac failure, chronic obstructive pulmonary disease, sepsis with neutropenia, hypertension, and haematuria. Some of these likely represent pre-existing comorbid conditions or chemotherapy-related toxicity rather than toxicity from the pembrolizumab. Chemoradiation alone has similar toxicity (26–36% grade 3–4 adverse events) to PCR-MIB [1,23]. Large randomised trials of the addition of immunotherapy to chemoradiation [21,24,25] will better assess this issue.

The 88% CR rate at 6 mo in PCR-MIB is encouraging, but evaluation is limited by the follow-up duration, trial's small size, and relative favourable population of 89% T2 tumours. The following chemoradiation is similar to the 12-wk CR rate of 87% reported in the only other trial of pembrolizumab with chemoradiation [18]. Trials of chemoradiation alone reported not dissimilar CR rates between 70% and 80% [23,26], and a trial of chemoradiation with cetuximab documented a CR rate of 90% at 6 mo [27]. Disappointingly, 8/28 (29%) participants on PCR-MIB developed metastatic disease. Positron emission tomography/CT staging of patients was not required and may have improved case selection, given that several patients relapsed with either pelvic or abdominal lymphadenopathy. More work is required to assess what early efficacy signals can predict longer-term outcomes in future trials. The recent failure of pembrolizumab to improve disease-free survival (DFS) and OS when combined with chemoradiation in head and neck cancer highlights the need to explore the biomarkers of response and synergy [28]. Simple biomarkers such as PD-L1 expression have been uninformative in similar trials [18].

Other limitations to PCR-MIB include the lack of use of longer-term radiation-specific toxicity assessment tools and participant quality-of-life endpoints, reflecting limited trial resources. PCR-MIB and similar-sized trials are limited in answering essential questions regarding the optimum timing of immunotherapy administration, duration of adjuvant immunotherapy required, and preferred chemotherapy partner. Data from Checkmate 274 support the use of adjuvant nivolumab to reduce the risk of recurrence in patients with high-risk urothelial cancer after cystectomy, but PCR-MIB and other similar studies have utilised shorter periods of adjuvant treatment and alternative anti-PD1 or PD-L1 antibodies [29]. The optimum chemotherapy partner to combine with pembrolizumab with radiation is also uncertain. While there is already variability in clinical practice between the choice of 5-fluorouracil plus mitomycin, cisplatin, and gemcitabine, there is also uncertainty about which agents may be synergistic or at least additive with immunotherapy. Notably, there was no evidence of synergy between the platinum/gemcitabine chemotherapy and the PD1/PD-L1 antibody backbone in either KEYNOTE-361 (pembrolizumab) or IMvigor130 (atezolizumab) [30,31]. Notably, recent trials of neoadjuvant immunotherapy approaches to MIBC have not reported convincing increases in the pathological response rates, compared with immunotherapy alone when the immunotherapy has been combined with chemotherapy [6,7,32–35]. Further study is required to understand the optimum chemotherapy and immunotherapy combination [36]. Larger randomised trials of chemoradiation with immunotherapy such as KEYNOTE-992 and INTACT permit different chemotherapy backbones and will better delineate optimum combination therapies [24]. Work is also required to explore the optimal radiation fields when using concurrent immunotherapy as preclinical models report elective nodal irradiation decreasing immunotherapy effectiveness and reducing antigen-specific T cells and epitope spreading [37].

5. Conclusions

In summary, PCR-MIB suggests that pembrolizumab is feasible to combine with chemoradiation in MIBC, with a promising early signal of efficacy. There were limited severe immune-related adverse events, and all participants completed radiation without significant interruption. Future trials will better define any longer-term DFS and OS benefits from the approach.

Author contributions: Andrew Weickhardt had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Drafting of the manuscript: Weickhardt, Hayne, Conduit, Davis, Hayne.

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Obtaining funding: Weickhardt, Foroudi, Hayne.
Administrative, technical, or material support: Weickhardt, Xie, Tran, Davis.
Supervision: Weickhardt, McJannett, Davis.
Other: None.
Consulting: MSD, Astellas, Pfizer, Merck, Ipsen, Astra-Zeneca, BMS Honoraria: MSD, BMS Research Grants: MSD, BMS.

Financial disclosures: Andrew Weickhardt certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** Drug and funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), Australia. Data was collected independently of the pharmaceutical company which did not have access to the data, but provided review and approval of the manuscript. Ian Davis is supported in part by an NHMRC Investigator Grant (2016274).

***Acknowledgements*:** PCR-MIB is a collaborative investigator-initiated trial led by ANZUP in collaboration with the Centre of Biostatistics and Clinical Trials who provided central study coordination. We thank the patients, the principal investigators and study coordinators at the participating centres across Australia for their commitment to the PCR-MIB study.

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