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#1002

PEMBROLIZUMAB WITH CHEMORADIOTHERAPY IN MUSCLE INVASIVE BLADDER CANCER
ANALYSIS OF SAFETY AND EFFICACY OF THE PCR-MIB PHASE II CLINICAL TRIAL (ANZUP 1502)

Investigator Initiated Trial
Funding and Pembroizumab From

MSD

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BACKGROUND

Objective response rates to PD-1/PD-L1 inhibitors in metastatic urothelial carcinoma are between 10-30%[1,2] with durable responses >12 months.

Radiation may be synergistic with PD-1/PD-L1 inhibitors[3-4].
Chemotherapy may also be synergistic with PD-1/PD-L1 inhibitors[5-6].

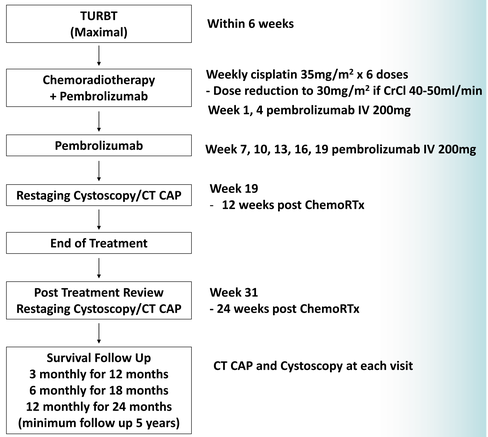
Historical outcomes and survival for chemoradiotherapy[7] in muscle invasive bladder cancer (MIBC)
- **complete response rates (at 12-24 week cystoscopy) ~ 70-85%**
- **2 year disease-free survival of 60-70%, 5 year OS ~ 45-72%**

Historical adverse event rates for chemoradiotherapy[8]:
- **G3/4 AE rates 5-30% ; Radiotherapy discontinuation rate 0-5%**

METHODS

Non randomised phase II trial
Interim safety analysis after first 10 patients presented at ASCO 2020

28 patients treated at 6 Australian centres between July 2017- Nov 2021



KEY INCLUSION/EXCLUSION CRITERIA

Inclusion:
- **T2-T4a, Nx or N0, M0 urothelial carcinoma of the bladder**
- **Maximal TURBT within 7 weeks of planned start date; ECOG 0-1**
- **Planned for curative chemoradiotherapy as definitive treatment**
- **Adequate organ function including Creatinine Clearance >40 ml/min**

Exclusion:
- **concurrent extra-vesical (i.e. urethra, ureter or renal pelvis) urothelial carcinoma of the bladder; Extensive CIS**
- **Bulky T3/T4a tumors unsuitable for curative treatment**
- **Evidence of tumor-related moderate/severe hydronephrosis**
- **Unsuitable for concurrent cisplatin based chemoradiotherapy based on: audiometry/peripheral neuropathy**
- **History of autoimmune disease or pneumonitis**

STATISTICAL CONSIDERATIONS

Primary endpoint of the study is safety
- Considered definitely safe if 'unacceptable toxicity' events <30%, unsafe if >50%

Unacceptable toxicity is defined as:
- **Occurrence of a G3/4 acute toxicity (excluding G3/4 non infective urinary toxicity), either during treatment or within 12 weeks after scheduled completion of treatment, *or***
- **Cisplatin being withheld for ≥ 2 doses *or***
- **Cisplatin doses being withheld or reduced such that <66% of the intended total cisplatin dose is delivered *or***
- **Radiation treatment being delayed > 7 weeks *or***
- **Any single pembrolizumab dose being delayed > 6 weeks**

Secondary endpoints was efficacy
- **Best response at 3 and 6 months post chemoradiation on cystoscopy**
- **Metastatic disease free survival and overall survival**

Exploratory endpoints are related to biomarkers of efficacy - not reported here

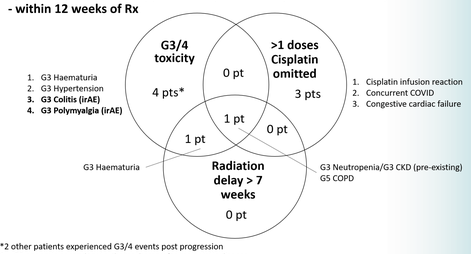
PATIENTS

Characteristic		Total n=28 (%)
Age, median in year (range)		72 (58-86)
Sex, n (%)	Male	26 (93)
	Female	2 (7)
ECOG, n (%)	0	18 (63)
	1	10 (37)
Histology, n (%)	Transitional cell/Urothelial	26 (93)
	Mixed transitional/non-transitional	2 (7)
	Associated CIS	9 (33)
Clinical T stage, n (%)	T2	26 (89)
	T3	2 (11)
Prior BCG, n (%)		2 (7)
Radiotherapy technique used	Inverse planned IMRT	16 (57)
	VMAT	7 (25)
	3D-RT	4(14)
	Other	1(4)

SAFETY

100% patients completed planned radiotherapy
92% mean relative dose intensity cisplatin
97% mean relative dose intensity pembrolizumab

9/28 (32%, 16-52 95% CI) patients experienced a predefined toxicity event - within 12 weeks of Rx



*2 other patients experienced G3/4 events post progression
1. G3 anaemia secondary to chemotherapy for metastatic disease
2. G4 sepsis post cystectomy for locoregional disease

3/28 patients had immune related adverse events requiring steroids
- **G3 colitis**
- **G3 polymyalgia**
- **G3 nephritis**

all occurred >10 weeks post chemo/radiation

11 patients in total experienced G3/4 Adverse Events during Rx and follow up
1 patient died from an exacerbation underling COPD

Adverse Events (all G2-4 AE; G1 >15% AE)	1	2	3	4	Total
Sepsis (post cystectomy for loco-regional PD)	0	0	0	1	1 (4%)
Cystitis Noninfective	3	1	3	0	7 (26%)
Hematuria	9	0	2	0	11 (41%)
Anemia	1	2	1	0	4 (15%)
Hypertension	0	1	1	0	2 (7%)
Gastrointestinal Disorders - Colitis	0	0	1	0	1 (4%)
Infusion Related Reaction	0	0	1	0	1 (4%)
Kidney Infection	0	0	1	0	1 (4%)
Polymyalgia Rheumatica (musculoskeletal – other)	0	0	1	0	1 (4%)
Neutrophil Count Decreased	0	0	1	0	1 (4%)
Urinary Tract Infection	0	0	1	0	1 (4%)
Urinary Tract Obstruction	0	0	1	0	1 (4%)
Fatigue	14	5	0	0	19 (70%)
Diarrhea	10	4	0	0	14 (52%)
Fever	1	4	0	0	5 (19%)
Hypothyroidism	1	4	0	0	5 (19%)
Constipation	7	3	0	0	10 (37%)
Urinary Frequency	13	3	0	0	16 (57%)
Chills	2	2	0	0	4 (15%)
Dyspnea	1	2	0	0	3 (11%)
Rash Maculo-Papular	8	1	0	0	9 (33%)
Edema Limbs	3	1	0	0	4 (15%)
Platelet Count Decreased	3	1	0	0	4 (15%)
Fall	2	1	0	0	3 (11%)
Urinary Incontinence	2	1	0	0	3 (11%)
Nausea	6	0	0	0	6 (22%)
Alanine Aminotransferase Increased	4	0	0	0	4 (15%)
Urinary Tract Pain	4	0	0	0	4 (15%)
Any Adverse Event†	7	9	10	1	27 (100%)

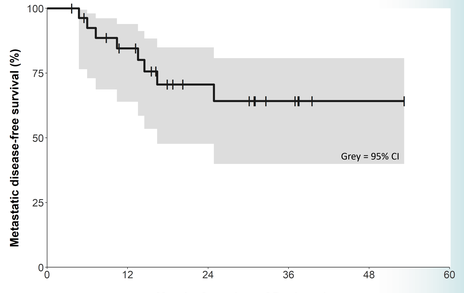
† - Number of patients whose worst AE was grade 1, 2, 3, 4, and Total

EFFICACY

Best Response at Cystoscopy	Week 31 (6m)
Complete Response	23 (88% [70, 98])
Progression	3 (12% [2, 30])

2 non assessable patients: One patient withdrew consent; another ceased treatment due to severe COPD

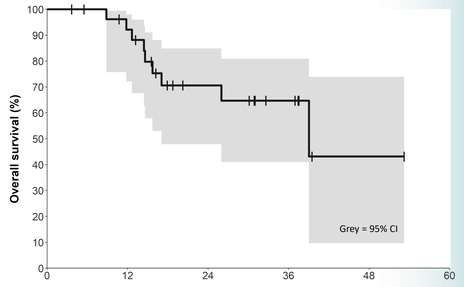
Distant Metastatic Disease Free Survival



No. at risk

All 28 20 6 1 0

Overall Survival

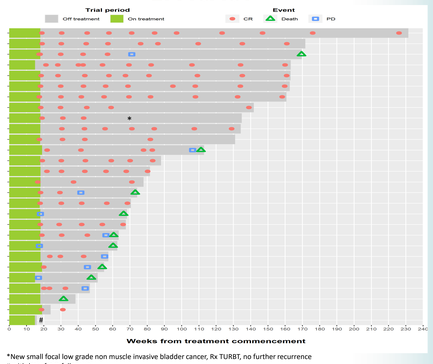


No. at risk (No. censored)

All 28 (0) 23 (3) 12 (9) 7 (13) 1 (18) 0 (19)

The median overall survival time is 39.0 months (95% CI: 17.1 - NE)
- **9 patients had died by the data cut-off date**
- **8/9 pts with metastatic disease at time of death; 1 pt from exac COPD**

EFFICACY



*New small focal low grade non muscle invasive bladder cancer, Rx TURBT, no further recurrence
withdrew from follow up

CONCLUSION

Pembrolizumab and Chemoradiation in MIBC appears safe
- **9/28 (32%) patients with a predefined toxicity event**
- **Only 2/9 unacceptable toxicities were definitely related to pembrolizumab**
- **Below the threshold to declare the combination unsafe (50%)**
- **Above predefined threshold of 30% to be 'definitely safe'**

In retrospect the predefined threshold was too stringent
- **Similar rate of G3/4 toxicity to other chemoradiation trials[8]**
- **Majority of G3/4 toxicities appear related to either MIBC, comorbidities, cisplatin**

There were a small number of irAEs needing steroids (3/28)
- **None interrupted delivery of chemoradiation**
- **These all occurred after >12 weeks of immunotherapy**

There is an encouraging 6 month CR rate (88%)
- **10/28 patients have experienced progression to date**

Similar toxicity and activity to other IO/ChemoRTx trials
- **Pembrolizumab + hypofractionated RTx + gemcitabine[9]**
  - ≥G3 AE rate 35%, 12 wk CR rate 83%,
- **Ipi/Nivo + hypofractionated RTx + Cape/MMC[10]**
  - ≥G3 AE rate 30%, 12 wk CR rate 100%

Larger global industry sponsored randomised trials are currently underway

1. ER Plimack et al, ASCO 2015
2. JE Rosenberg et al, The Lancet 2016
3. C Wu et al, Scientific Reports 2016
4. S Hiniker et al, NEJM 2012
5. J Vincent et al, Cancer Research 2010
6. G Giaccone et al, ESMO 2015
7. N Gogna et al, Radiotherapy and Oncology 2006
8. F Koga et al, International Journal of Urology 2012
9. Balar et al, ASCO 2021
10. De Ruiter et al, European Urology 2022

BaCT Centre for Biostatistics and Clinical Trials

research trials outcomes

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