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MSD

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

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1. ABSTRACT

Background:

In patients (pts) with muscle invasive bladder (MIBC) suitable for definitive chemoradiotherapy (CRT), we hypothesise that the addition of pembrolizumab may be safe and improve efficacy.

A pre-planned safety analysis was performed after the first 10 of planned 30 pts were enrolled and completed treatment.

Data here is from these 10 patients presenting toxicity and efficacy up to 12 weeks post treatment.

Patient population:

- Maximally TURBT resected non-metastatic MIBC and ECOG 0-1
- Desire bladder preservation or are ineligible for cystectomy

Treatment and endpoints:

- 64Gy in 32 daily radiotherapy (RTx) fractions to the whole bladder alone over 6.5 wks
- 6 concurrent doses of weekly cisplatin at 35mg/m^2 IV
- Pembrolizumab was commenced with radiation 200mg IV q3 wks*7
- Surveillance cystoscopy, urine cytology and CT chest-abdomen-pelvis were performed 12 & 24 weeks post CRT
- Primary endpoint is feasibility, defined by a satisfactory low rate of unacceptable toxicity of a) G3-4 non-urinary adverse events (AE) or b) failure of completion of planned CRT according to defined parameters
- Secondary endpoints include complete cystoscopic response without metastatic disease at 12 & 24 weeks, loco-regional PFS, metastatic DFS, and overall survival
- A 2-stage design was planned, with accrual to be halted if >5 of the first 10 pts experienced unacceptable toxicity up to 12 weeks post treatment

Results:

- All 10 pts completed the course of CRT and pembrolizumab without alteration in radiation dose or schedule
- 1 patient had a dose of cisplatin withheld
- 4/10 pts experienced G3-4 non-urinary adverse events within 12 wks
- 1 immune related AE interrupted pembrolizumab delivery (G2 nephritis)
- By week 31, 9/10 pts achieved a complete cystoscopic response to treatment post CRT and were free of distant metastatic disease

Conclusions:

- Interim results indicate that pembrolizumab and CRT shows satisfactory safety, and promising efficacy in MIBC
- There were no unexpected safety signals
- Follow up of these 10 and additional pts will better define the efficacy and safety of the combination
- Enrolment is ongoing with 20 pts recruited of a planned total of 30

2. STUDY STATUS

- 6 sites open for recruitment across Australia
- Have enrolled 20 of planned 30 patients as of February 2020

Study Chair: A/Prof Andrew Weickhardt

3. BACKGROUND

Objective response rates to PD-1/PD-L1 inhibitors in met TCC 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 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%

4. 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

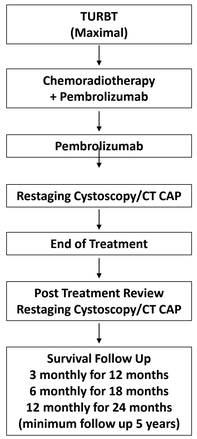
5. STATISTICAL CONSIDERATIONS

Primary endpoint of the study is feasibility
Tested for by a satisfactorily low rate of unacceptable toxicity
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

A Simon two-stage design was planned with analysis after first 10 pts
- Regimen to be deemed unsafe if >5 unacceptable toxicities in the 1st 10 pts
- Powered so 90% chance of concluding unsafe if the true underlying unacceptable toxicity rate is 50%

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

6. TRIAL OVERVIEW



7. SAFETY

The first 10 patients were treated between July 2017 and July 2019.

Unacceptable toxicities (UT), defined by the protocol are shown below:

Table 1: Description of unacceptable toxicities

Subject ID	Type of UT	CTCAE Term	Weeks from first Rx
A2	G3 AE	Anemia	22
A3	G3 AE	Haematuria	21
P1	G3 AE	Kidney Infection	3
R2	G3 AE	Hypertension	4

Note urinary frequency/urgency/non infective cystitis was not included in the definition of unacceptable toxicity.

There were no G3-4 immune related toxicities within 12 weeks of Rx.

There were no significant dose interruptions of cisplatin (≥ 2 doses withheld or <66% cisplatin delivered) or delays in radiation (beyond 7 weeks)

There were no significant dose delays in pembrolizumab (over 6 week delay).

7. SAFETY *(continued)*

Table 2: Adverse events in observed at grade 2 or above, or grade 1 in more than one patient

	Grade (n=10)			
Adverse Event	1	2	3	Total
Urinary Frequency/Urgency	6	1	1	8 (80%)
Hematuria	2	0	1	3 (30%)
Anemia	1	0	1	2 (20%)
Pyelonephritis/Urinary Sepsis	0	0	2	2 (20%)
Hypertension	0	0	1	1 (10%)
Constipation	1	2	0	3 (30%)
Fatigue	4	1	0	5 (50%)
White Blood Cell Decreased	0	1	0	1 (10%)
Lymphocyte Count Decreased	0	1	0	1 (10%)
Fever	0	1	0	1 (10%)
Hematoma	0	1	0	1 (10%)
Edema Limbs	0	1	0	1 (10%)
Nephritis (autoimmune)	0	1	0	1 (10%)
Diarrhea	4	0	0	4 (40%)
Urinary Tract Pain	3	0	0	3 (30%)
Rash Maculo-Papular	3	0	0	3 (30%)
Weight Loss	2	0	0	2 (20%)
Any Adverse Event[†]	3	2	5	10 (100%)

[†]Number of patients whose worst AE was G1,2,3 and total. Note there were no grade 4-5 toxicities

Table 3: Dosing intensity and patient disposition

ID	Weeks Rx	% cisplatin	Doses Pembro	Reason Rx terminated	Status
C1	18	100	7	-	Alive
A1	18	100	7	-	Alive
A2	15	100	6[A]	Progression	Dead
A3	19[B]	100	7	-	Alive
S1	18	100	7	-	Alive
S2	18	96[C]	7	-	Alive
A4	18	100	7	-	Alive
P1	18	83[D]	7	-	Alive
R1	18	100	7	-	Alive
R2	15[E]	100	6	G2 nephritis	Alive

A. Last dose not given due to disease progression.
B. Treatment delayed 1 week as patient on holiday.
C. Last dose of cisplatin reduced due to thrombocytopenia.
D. Cisplatin omitted in week 4 due to obstructed nephrostomy.
E. Last dose pembrolizumab not given due to G2 nephritis.

8. TUMOR RESPONSE

Table 4: Tumor response first 10 patients at week 19 and 31 week visit

Best Response	Week 19	Week 31
Complete Response	9/10 (90%)*	9/10 (90%)
Partial Response	0	0
Stable disease	0	0
Progression	1/10 (10%)	1/10 (10%)

Tumor response assessment with urine cytology, rigid cystoscopy and CT CAP at week 19 and 31. *Three patients had cystoscopy performed at week 23.

Efficacy is a secondary endpoint of study and is assessed by proportion of patients achieving a complete response (CR) as best response at either 1st or 2nd cystoscopic examination after completing therapy.

Additional efficacy measures such as overall survival, metastatic disease-free survival and locoregional progression-free survival is being collected.

9. DISCUSSION

This trial reports interim data on safety and efficacy from the first 10 patients of a planned 30 patient phase II trial of immunotherapy and chemoradiation in bladder cancer.

There was an acceptable rate of toxicity in the first 10 patients at the interim analysis.

There were no G3-4 immune related toxicities within 12 weeks of completing treatment. One patient out of 10 developed grade 2 nephritis and missed a single dose of pembrolizumab.

Early efficacy data is promising but numbers are small and follow up short.

Recruitment continues to this trial with a planned 20 of 30 patients recruited as of February 2020.

Larger global industry sponsored randomized trials are currently underway.

Abstract # 485

For questions or comments email:
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research trials outcomes

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