International Journal of Radiation Oncology biology • physics

www.redjournal.org

Scientific Letter

Dose-limiting Urinary Toxicity With Pembrolizumab Combined With Weekly Hypofractionated Radiation Therapy in Bladder Cancer

Alison Claire Tree, FRCR, MD(Res),*,† Kelly Jones, MSc,* Shaista Hafeez, FRCR, PhD,*,† Mansour Taghavi Azar Sharabiani, PhD,* Kevin Joseph Harrington, FRCP, PhD,*,† Susan Lalondrelle, FRCR, MD(Res),*,† Merina Ahmed, FRCR, MD(Res),*,† and Robert Anthony Huddart, FRCR, PhD*,†

**Royal Marsden NHS Foundation Trust, London, UK; †Institute of Cancer Research, London, UK*

Received Jan 16, 2018, and in revised form Apr 10, 2018. Accepted for publication Apr 24, 2018.

Summary

In the PLUMMB trial first dose cohort combining Pembrolizumab (100mg three weekly) and radiotherapy (36 Gy in 6 fractions, given weekly) in patients requiring radiotherapy for bladder cancer, dose limiting toxicity was seen. Two of the first five patients experienced Grade 3 urinary toxicity

There is currently significant interest in the potential benefits of combining radiation and immune checkpoint blockade (ICB) to stimulate both regional and distant abscopal immune responses. In melanoma and lung cancer, patients who have received radiation therapy during ICB appear to have prolonged survival. The PLUMMB trial (Pembrolizumab in Muscle-invasive/Metastatic Bladder cancer) (NCT02560636) is a phase I study to test the tolerability of a combination of weekly radiation therapy with pembrolizumab in patients with metastatic or locally advanced urothelial cancer of the bladder. In the first dose-cohort, patients received pembrolizumab 100 mg 3-weekly, starting 2 weeks before commencing weekly adaptive bladder radiation therapy to a dose of 36 Gy in 6 fractions. The first dose-cohort was stopped after 5 patients, having met the predefined definition of dose-limiting toxicity. Three patients experienced grade 3 urinary toxicities, 2 of

Reprint requests to: Dr Alison Claire Tree, FRCR, MD(Res), Consultant Clinical Oncologist, The Royal Marsden, Downs Rd, Sutton, Surrey, SM2 5PT, UK. Tel: 020 8642 6011; E-mail: Alison.tree@icr.ac.uk

Conflict of interest: AT, RH, KH, MA and SL report grant funding from MSD. AT reports a grant from Elekta, personal fees from Bayer, Ferring, Janssen and Astellas outside of the submitted work. KH reports grants from MSD and AstraZeneca, and personal fees from MSD, AstraZeneca, BMS, Merck and Pfizer. SL reports personal fees from Roche outside of the submitted work. KJ has no conflicts to disclose. SH reports educational travel fees from MSD. MA reports a grant from BMS outside of the submitted work. RH reports a grant from MSD and CRUK, outside of the submitted work, and personal fees or support from BMS, MSD, Roche and Janssen.

Funding: The PLUMMB trial has been supported by Royal Marsden/Institute of Cancer Research NIHR Biomedical Research Centre and an unrestricted educational grant from MSD.

Acknowledgements—This paper represents independent research part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Int J Radiation Oncol Biol Phys, Vol. 101, No. 5, pp. 1168–1171, 2018

https://doi.org/10.1016/j.ijrobp.2018.04.070

likely due to trial treatment. The trial will be amended to reduce radiotherapy dose. We suggest caution when using large dose per fraction in the pelvis in combination with immunotherapy.

which were attributable to therapy. One patient experienced a grade 4 rectal perforation. In view of these findings, the trial has been paused and the protocol will be amended to reduce radiation therapy dose per fraction. The authors advise caution to those combining radiation therapy and ICB, particularly when radiation therapy is given at high dose per fraction for pelvic tumours. The PLUMMB trial met the protocol-defined definition of dose-limiting toxicity and will be amended to reduce radiation therapy dose.

Introduction

There is currently significant interest in the potential benefits of combining radiation and immune checkpoint blockade (ICB) to stimulate both regional and distant abscopal immune responses (1). In melanoma (2) and lung cancer (3), patients who have received radiation therapy during ICB appear to have prolonged survival. A number of ongoing clinical trials are addressing the role of radiation-ICB combinations, particularly in clinical settings in which ICB has been shown to prolong survival as monotherapy.

The PLUMMB (Pembrolizumab in Muscle-invasive/Metastatic Bladder cancer) study (NCT02560636) is a phase 1 dose-escalation study in which pembrolizumab is added to weekly hypofractionated bladder radiation therapy in patients with localised disease who are too frail for daily radiation therapy (4) or who have significant local symptoms in the context of metastatic disease. This radiation therapy regimen is used as standard for this group in PLUMMB. The study employs a standard phase 1 3 + 3 design, with dose-escalation of pembrolizumab from 100 mg to 200 mg (total dose) in the absence of dose-limiting toxicity (DLT) during the acute phase after radiation therapy. Pembrolizumab was started before radiation therapy in line with preclinical evidence suggesting synergy occurs when ICB is given before or during radiation therapy (1, 5).

Methods and Materials

Between September 2016 and July 2017, 5 patients were treated in cohort 1. Eligible patients had histologically confirmed, muscle-invasive bladder cancer which was either metastatic (4 patients) or localised in a patient too frail for daily treatment (1 patient). Eligible patients had performance status 0-1, had measurable disease by RECIST v 1.1 or cystoscopy and were permitted to have received previous platinum-based chemotherapy in the metastatic setting. Pembrolizumab was delivered at a dose of 100 mg starting 2 weeks before radiation therapy commenced, and thereafter was given at a dose of 100 mg 3-weekly. Radiation therapy was delivered according to standard protocols, using the 'plan-of-the-day' approach, to a dose of 36 Gy in 6 weekly fractions (4). This approach uses 3 PTV expansions (small, medium and large) to account for variation in bladder size on the

Table 1 Toxicities recorded in the first 5 patients

Patient number	Disease stage	Maximum CTCAE* toxicity during DLT period†	DLT	Significant events other than DLT
001	T3N1M1	G2 anaemia‡ G2 fatigue‡ G2 pain	No	G3 renal haematoma (post-stent) G3 urinary tract infection Progressive disease
002	T2N0M1	G3 urinary tract/bladder infection G3 haematuria	No (see text)	Progressive disease
003	T2N1M1a	G3 cystitis (non-infective)‡	Yes	G4 bowel perforation G3 peripheral oedema (legs)
004	T2bN0M0	G2 urinary urgency G2 urinary incontinence	No	n/a
005	T3bN0M1	G3 urinary pain‡ G3 fatigue‡	Yes	G3 atrio-ventricular block§

* Common terminology criteria for adverse events.
† Dose-limiting toxicity (DLT) window extends from first pembrolizumab infusion to 11 weeks post-completion of radiation therapy.
‡ Denotes toxicity judged to be related to trial treatment.
§ Relationship to treatment uncertain.

day of treatment, with the smallest appropriate PTV being selected by the treating radiographers at the time of each fraction (6). Acute toxicity was assessed weekly during radiation therapy and, thereafter, 3-weekly using the common terminology criteria for adverse events (CTCAE) version 4. Pembrolizumab was scheduled to be continued until progression, or for 12 months in the setting of localised disease. The protocol stated that maximal tolerated dose (MTD) would be declared if 2 or more patients in the first 6-patient cohort experienced dose-limiting toxicity (DLT), defined as any grade 4 toxicity, any grade 3 non-haematological toxicity likely related to treatment within 11 weeks of completing radiation therapy, or radiation therapy interruption for >5 days.

Results

The first cohort of the trial was stopped early after recording DLT events in 2 of the first 5 patients (Table 1). All patients completed 6 fractions of radiation therapy. No patients experienced significant immune-related side effects.

Patients 003 and 005 had protocol-defined DLT events judged to be related to treatment. In both cases, symptoms of bladder irritation (cystitis or pain) were severe. Additionally, patient 002 had recurrent problems with haematuria (the initial indication for palliative radiation therapy) and urinary sepsis, and patient 1 had urinary obstruction. The authors cannot rule out some contribution from trial treatment. Patients 001 and 004 also experienced urinary symptoms, but at a lower grade. The safety review committee was convened, per protocol, and the trial has been suspended at the current doses.

Discussion

A number of investigators have reported retrospective studies showing that combinations of pembrolizumab and (mostly) palliative radiation therapy are tolerable (2, 3, 7). Interestingly, however, careful review highlights a non-significant trend to increased in-field toxicities in these studies.

With such small numbers in the PLUMMB trial, it may be that we have made a type I error in suspending recruitment. The dose of radiation therapy used in this trial is standard in many UK centres, and has been used as standard for decades, with good results (4, 5). Our previous experience has shown that a proportion of patients (around 9%) will experience emergent grade 3 toxicity with the radiation therapy dose-fractionation used in PLUMMB (4). At 12 months after radiation therapy only 4.5% have ongoing grade 3 toxicity in the urinary or bowel domains. Cummulative incidence of local progression at 12 months is 7% (4).

The prominent urinary toxicity encountered in the first 5 patients of this study is far greater than we would have anticipated with this schedule and met the pre-determined criterion for declaring maximum tolerated dose (MTD) in this setting. The authors believe that the relative paucity of data regarding hypofractionated radiation therapy combined with ICB in pelvic malignancy means that it would be prudent to amend the study at this point.

Pembrolizumab itself does not appear to have a dose-response curve and no maximally tolerated dose was noted in the initial trials of this agent (8). Therefore, in retrospect, dose-escalation of radiation therapy (rather than of pembrolizumab) may have been a better design. At the time, we were reluctant to reduce the dose of radiation therapy, an effective and well tolerated regimen, for an uncertain benefit of adding pembrolizumab. Such a dose-reduced design would also mandate recruiting only metastatic patients since, for patients with locally-advanced disease, radiation therapy to 36 Gy in 6 fractions controls disease for the patient's lifespan (4), effectively rendering dose reduction unethical.

In light of these findings, we will amend the eligibility to focus on patients with symptomatic metastatic disease and reduce the dose of radiation therapy to 24 Gy in 4 fractions (6 Gy per fraction) and, if well tolerated, escalate to 30 Gy in 5 fractions, followed by an expansion phase. If 24 Gy in 4 fractions is not well tolerated, we will de-escalate the dose per fraction.

Conclusions

We advise caution to those combining radiation therapy and ICB, particularly when radiation therapy is given with a high dose hypofractionated schedule for pelvic tumours. The PLUMMB trial met the protocol-defined definition of dose-limiting toxicity and will be amended to reduce radiation therapy dose.

References

1. Sharabi AB, Lim M, DeWeese TL, et al. Radiation and checkpoint blockade immunotherapy: Radiosensitisation and potential mechanisms of synergy. *Lancet Oncol* 2015;16:e498-e509.
2. Koller KM, Mackley HB, Liu J, et al. Improved survival and complete response rates in patients with advanced melanoma treated with concurrent ipilimumab and radiotherapy versus ipilimumab alone. *Cancer Biol Ther* 2017;18:36-42.
3. Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: A secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol* 2017;18:895-903.
4. Hafeez S, McDonald F, Lalondrelle S, et al. Clinical outcomes of image guided adaptive hypofractionated weekly radiation therapy for bladder cancer in patients unsuitable for radical treatment. *Int J Radiat Oncol Biol Phys* 2017;98:115-122.
5. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res* 2014;74:5458-5468.

6. McDonald F, Lalondrelle S, Taylor H, et al. Clinical implementation of adaptive hypofractionated bladder radiotherapy for improvement in normal tissue irradiation. *Clin Oncol (R Coll Radiol)* 2013;25:549-556.
7. Aboudaram A, Modesto A, Chaltiel L, et al. Concurrent radiotherapy for patients with metastatic melanoma and receiving anti-programmed-death 1 therapy. *Melanoma Res* 2017;27:485-491.
8. Patnaik A, Kang SP, Rasco D, et al. Phase I study of pembrolizumab (MK-3475; Anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. *Clin Cancer Res* 2015;21:4286-4293.