RE-ARMing the immune response to bladder cancer with radiotherapy

Following demonstration of significant activity of atezoluzimab in refractory metastatic urothelial cancer (1); randomised trials showed improved survival with PD1/PD-L1 agents compared to second line chemotherapy (2). As a result, treatment with PD1/PD-L1 immune checkpoint inhibitors has become a standard NICE and ESMO-approved treatment for metastatic urothelial cancer. Despite these successes, with some patients being long term survivors on therapy, disappointingly the majority of patients experience early progression on treatment. For these patients there is a paucity of options. Targeted agents have yet to gain real clinical traction in bladder cancer - some biomarker-led approaches e.g. the FGFR inhibitor erdafitinib show promise (3), but, as only ~15% of patients have the sensitive mutations, these are unlikely to benefit the majority of patients and remain at some distance from routine clinical use. Antibody-conjugated chemotherapy may also be an option (4), but it is uncertain whether this will be readily available in the clinic in the near future. There is, therefore, a clear clinical need to try to make immune checkpoint inhibitors (ICI) work better and for more people.

An intriguing observation in the ImVigor 210 trial of the PD-L1 inhibitor atezolizumab in patients with metastatic urothelial cancer was that 17% of patients experienced a late clinical response after initial progression on treatment – this was on top of the 15% of patients showing an early response shortly after initiation of atezolizumab (5). It has been demonstrated that radiotherapy increases expression of PD-L1 in both murine and human models of urothelial cancer (6), leading to various radiotherapy/ICI combinations being evaluated in the radical setting. As recently reviewed in Clinical Oncology (7), these observations raise the intriguing possibility that addition of radiotherapy could tip the immunological balance to further enhance responses and increase the number of patients who, after failing to show an initial response to ICI, have a delayed response.

The RE-ARM trial (ISRCTN12606219) addresses this hypothesis in a randomised phase II design with a trial schema as shown in figure 1. One hundred and two patients with stable disease at best after 3-6 cycles of atezolizumab, given as part of routine care, will be randomised between palliative radiotherapy (20Gy in five fractions) plus atezolizumab, or continuation of atezolizumab alone. The primary endpoint of RE-ARM is the objective radiological response rate (complete or partial response) at 9 weeks after the start of study treatment according to RECIST v1.1 criteria, excluding the planned radiotherapy site. The trial aims to detect an absolute increase in response rate of at least 15% for the combination arm at 9 weeks, compared with the control arm (assuming 15% response in control, 1:1 randomisation, 80% power, 1-sided 0.2 significance level).

Randomised reports of abscopal responses to radiotherapy plus ICI are currently lacking in metastatic urothelial cancer, whilst reports in other tumour types show diverse results. A recent combined analysis of two phase 1/2 randomised studies of pembrolizumab, with or without radiotherapy, in metastatic non-small cell lung cancer showed a best out-of-field

(abscopal) response rate (ARR) of 41.7% (30/72) when radiotherapy was added, versus a response rate of 19.7% (15/76) with pembrolizumab alone (odds ratio [OR] 2·96, 95% CI 1·42–6·20; p=0·0039) (8). Median overall survival was extended from 8·7 months (6·4–11·0) with pembrolizumab alone to 19·2 months (14·6–23·8) with pembrolizumab plus radiotherapy (0·67, 0·54–0·84; p=0·0004) (8). In contrast, a recently reported randomised phase II study of nivolumab plus or minus stereotactic radiotherapy (SBRT) (8x3Gy) in metastatic head and neck cancer showed no improvement in the rates of out of field abscopal responses, progression free or overall survival with SBRT (9). The UK PERM trial randomised patients with metastatic melanoma to pembrolizumab with or without radiotherapy (8Gy x 3 to up to three tumour sites)(10), but was halted due to poor recruitment. The above varying results have led some to advocate for more aggressive strategies including ablation of all radiologically-visible disease, high doses per fraction and/or addition of other ICI beyond the PD1/PD-L1 axis such as anti-TIGIT agents.

The limited reports to date of ICI plus radiotherapy in urothelial cancer suggest, firstly, that radiotherapy might be best given during ICI, rather than beforehand (11) – an approach that is also supported by pre-clinical data (12). In a small phase I study, concomitant irradiation of 3 x 8Gy to a single site, prior to cycle 3 of pembrolizumab, resulted in RECIST v1.1 response in non-irradiated lesions in four of nine patients (44%). Secondly, the high rates of bowel and urinary toxicity seen in the PLUMMB trial of pembrolizumab plus hypofractionated radiotherapy (13), and a second phase I trial incorporating pelvic radiotherapy (14), indicate that an ICI/radiotherapy interaction may be present, but that caution is warranted with high radiotherapy doses to the pelvis. RE-ARM incorporates both of these factors in an adaptive randomised design and is an exciting opportunity for the UK to systematically address the role of radiotherapy plus ICI in the control of metastatic urothelial cancer.

Specific aspects of trial design which differ from the randomised studies above include the pre-selection for non-responders to ICI, which means the RE-ARM trial population is likely to be enriched for patients with immune cold or immune-excluded tumour phenotypes. The radiotherapy dose schedule of 20Gy in five fractions has been in part pragmatically selected based on ease of delivery across different UK radiotherapy centres; however, it is also fairly similar to the 30Gy in 6 fractions that has been shown to optimally induce type I interferon and abscopal responses in a pre-clinical context (15). A further strategy to optimise response includes guidance to centres to preferentially irradiate larger lesions in locations considered more immunogenic, such as visceral and nodal metastases, as opposed to bone metastases. The outcomes following irradiation of liver metastases in RE-ARM will be particularly intriguing in view of recent pre-clinical findings that a single 8Gy radiotherapy treatment to the liver can reprogram the tumour microenvironment (TME), thus enhancing systemic responses to ICI (16). This is particularly relevant since we know that liver metastases predict for inferior responses to ICI across different tumour sites (16, 17).

Patients who fail to show an initial response to ICI will exhibit considerable biological heterogeneity. Recent unbiased integrative analyses of baseline tumours in IMvigor 210 and Checkmate 275 have combined bulk RNA seq and single cell sequencing. Here, the ratio between an adaptive immune response signature and a pro-tumourigenic inflammation

signature best predicted response to ICI (18); such signatures were predominantly derived from diverse myeloid populations (18). This builds on previous insights into ICI response in urothelial cancer; these include the relevance of tumour mutational burden as a positive predictor of response (19), as well as the association between enrichment with cancer-associated fibroblasts, increased TGF beta signalling and ICI resistance (20). Additionally, antibiotic use within 30 days of starting ICI in IMvigor 210 and 211 was associated with inferior responses, which intriguingly was not seen in patients receiving chemotherapy in IMvigor 211 (21). The balance of bacterial versus fungal strains is known to be relevant to radioresponsiveness (22), and both these finding demonstrate the likely relevance of the microbiome to clinical responses in RE-ARM.

The biological heterogeneity described above is likely to mean there will be some patients who just need an immunological "nudge" to enable a response to combined ICI/radiotherapy whereas, sadly, other patients will show rapid progression despite combination treatment. Going forward, the field needs to prospectively identify patients with such divergent responses and better understand the biological hallmarks of differential response. For this reason, comprehensive integrative translational profiling is embedded in the design of RE-ARM. We are enormously grateful to the participating NHS hospitals for their support for the collection of baseline tumour biopsies, longitudinal bloods and planned microbiome samples. Where sites have the relevant interventional radiology support available, we are also planning to incorporate paired biopsies pre and post-RT. Here, single cell sequencing should provide high resolution understanding of intra-tumoural TME changes in a small cohort of patients.

Patients who present with metastatic bladder cancer have a one year survival of only 33% (23). These dismal survival statistics relate in part to a historical lack of funding for bladder cancer, relative to other tumour sites (24). RE-ARM is an exciting opportunity to systematically evaluate whether an affordable and readily-available experimental treatment (radiotherapy) can augment responses to immune checkpoint blockade. We are grateful to the many UK centres taking part in RE-ARM and for their help with recruiting patients to this important study. Other UK sites interested in participating are invited to contact the trial coordination team [REARM-icrctsu@icr.ac.uk].

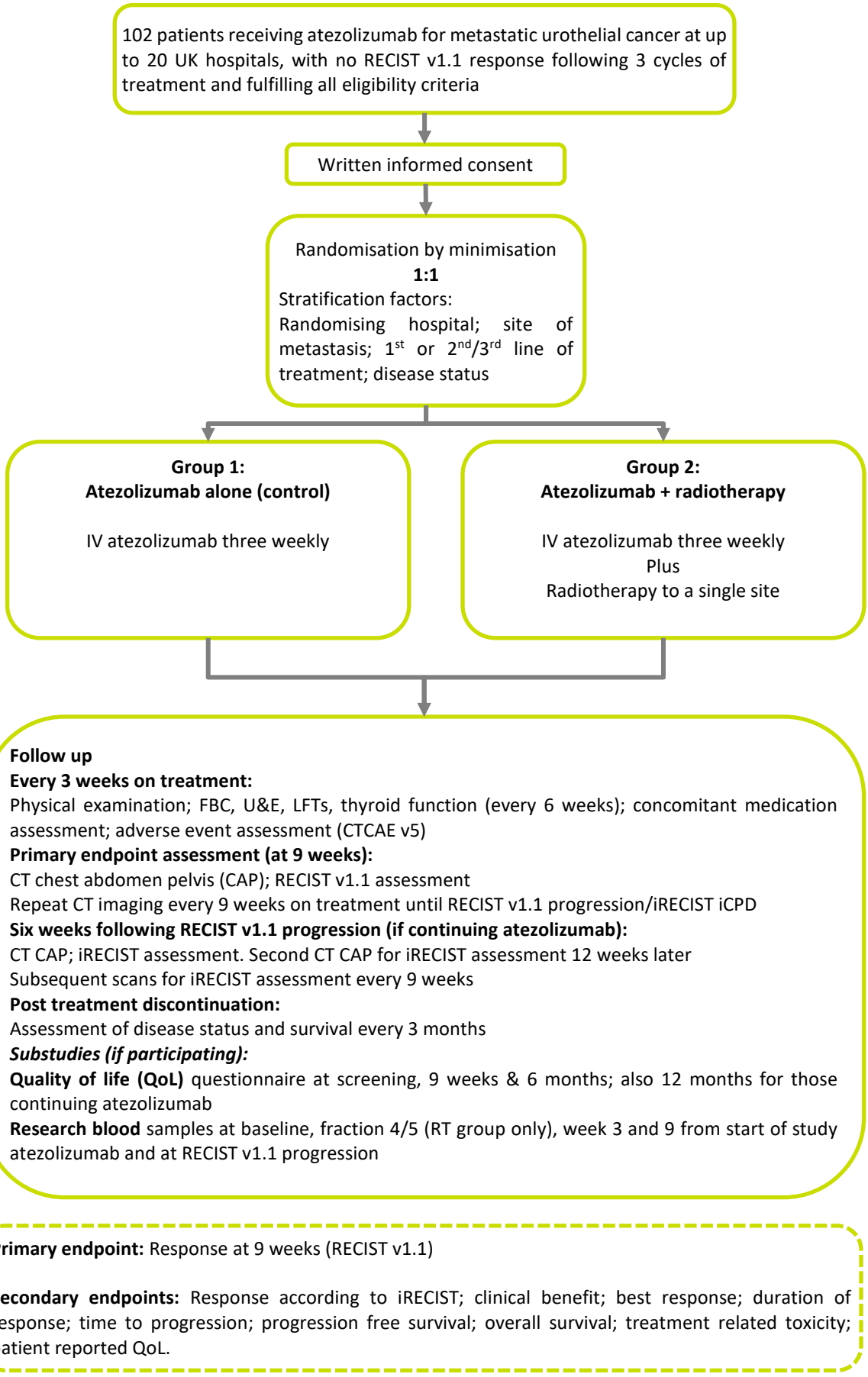
Acknowledgements

RE-ARM is an investigator initiated study supported by Roche Products Ltd and endorsed by Cancer Research UK (CRUKE/19/009). RE-ARM is sponsored by The Institute of Cancer Research and coordinated by the Clinical Trials and Statistics Unit at the Institute of Cancer Research (ICR-CTSU) which receives core funding from Cancer Research UK (C1491/A25351). We acknowledge NHS funding to the NIHR Biomedical Research Centre at The Royal Marsden and the ICR.

References

1. Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014;515(7528):558-62, doi:10.1038/nature13904.
2. Bellmunt J, Bajorin DF. Pembrolizumab for Advanced Urothelial Carcinoma. N Engl J Med. 2017;376(23):2304, doi:10.1056/NEJMc1704612.
3. Loriot Y, Necchi A, Siefker-Radtke AO. Erdafitinib in Urothelial Carcinoma. Reply. N Engl J Med. 2019;381(16):1594-5, doi:10.1056/NEJMc1911187.
4. Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Duran I, Lee JL, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. N Engl J Med. 2021;384(12):1125-35, doi:10.1056/NEJMoa2035807.
5. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016;387(10031):1909-20, doi:10.1016/S0140-6736(16)00561-4.
6. Wu CT, Chen WC, Chang YH, Lin WY, Chen MF. The role of PD-L1 in the radiation response and clinical outcome for bladder cancer. Sci Rep. 2016;6:19740, doi:10.1038/srep19740.
7. Wilkins A, Ost P, Sundahl N. Is There a Benefit of Combining Immunotherapy and Radiotherapy in Bladder Cancer? Clin Oncol (R Coll Radiol). 2021;33(6):407-14, doi:10.1016/j.clon.2021.02.014.
8. Theelen W, Chen D, Verma V, Hobbs BP, Peulen HMU, Aerts J, et al. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Respir Med. 2021;9(5):467-75, doi:10.1016/S2213-2600(20)30391-X.
9. McBride S, Sherman E, Tsai CJ, Baxi S, Aghalar J, Eng J, et al. Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma. J Clin Oncol. 2021;39(1):30-7, doi:10.1200/JCO.20.00290.
10. Yip K, Melcher A, Harrington K, Illidge T, Nobes J, Webster A, et al. Pembrolizumab in Combination with Radiotherapy for Metastatic Melanoma - Introducing the PERM Trial. Clin Oncol (R Coll Radiol). 2018;30(4):201-3, doi:10.1016/j.clon.2018.01.001.
11. Sundahl N, Vandekerkhove G, Decaestecker K, Meireson A, De Visschere P, Fonteyne V, et al. Randomized Phase 1 Trial of Pembrolizumab with Sequential Versus Concomitant Stereotactic Body Radiotherapy in Metastatic Urothelial Carcinoma. Eur Urol. 2019;75(5):707-11, doi:10.1016/j.eururo.2019.01.009.
12. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res. 2014;74(19):5458-68, doi:10.1158/0008-5472.CAN-14-1258.
13. Tree AC, Jones K, Hafeez S, Sharabiani MTA, Harrington KJ, Lalondrelle S, et al. Dose-limiting Urinary Toxicity With Pembrolizumab Combined With Weekly Hypofractionated Radiation Therapy in Bladder Cancer. Int J Radiat Oncol Biol Phys. 2018;101(5):1168-71, doi:10.1016/j.ijrobp.2018.04.070.
14. Marcq G, Souhami L, Cury FL, Salimi A, Aprikian A, Tanguay S, et al. Phase 1 Trial of Atezolizumab Plus Trimodal Therapy in Patients With Localized Muscle-Invasive Bladder Cancer. Int J Radiat Oncol Biol Phys. 2021;110(3):738-41, doi:10.1016/j.ijrobp.2020.12.033.
15. Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ, et al. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun. 2017;8:15618, doi:10.1038/ncomms15618.

16. Yu J, Green MD, Li S, Sun Y, Journey SN, Choi JE, et al. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. Nat Med. 2021;27(1):152-64, doi:10.1038/s41591-020-1131-x.
17. Tumeh PC, Hellmann MD, Hamid O, Tsai KK, Loo KL, Gubens MA, et al. Liver Metastasis and Treatment Outcome with Anti-PD-1 Monoclonal Antibody in Patients with Melanoma and NSCLC. Cancer Immunol Res. 2017;5(5):417-24, doi:10.1158/2326-6066.CIR-16-0325.
18. Wang L, Sfakianos JP, Beaumont KG, Akturk G, Horowitz A, Sebra RP, et al. Myeloid Cell-associated Resistance to PD-1/PD-L1 Blockade in Urothelial Cancer Revealed Through Bulk and Single-cell RNA Sequencing. Clin Cancer Res. 2021;27(15):4287-300, doi:10.1158/1078-0432.CCR-20-4574.
19. Galsky MD, Saci A, Szabo PM, Han GC, Grossfeld G, Collette S, et al. Nivolumab in Patients with Advanced Platinum-resistant Urothelial Carcinoma: Efficacy, Safety, and Biomarker Analyses with Extended Follow-up from CheckMate 275. Clin Cancer Res. 2020;26(19):5120-8, doi:10.1158/1078-0432.CCR-19-4162.
20. Mariathasan S, Turley SJ, Nickles D, Castiglioni A, Yuen K, Wang Y, et al. TGFbeta attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. Nature. 2018;554(7693):544-8, doi:10.1038/nature25501.
21. Hopkins AM, Kichenadasse G, Karapetis CS, Rowland A, Sorich MJ. Concomitant Antibiotic Use and Survival in Urothelial Carcinoma Treated with Atezolizumab. Eur Urol. 2020;78(4):540-3, doi:10.1016/j.eururo.2020.06.061.
22. Shiao SL, Kershaw KM, Limon JJ, You S, Yoon J, Ko EY, et al. Commensal bacteria and fungi differentially regulate tumor responses to radiation therapy. Cancer Cell. 2021;39(9):1202-13 e6, doi:10.1016/j.ccell.2021.07.002.
23. Cancer Research UK Bladder Cancer Statistics 2018 (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/survival#heading-Three).
24. Van Hemelrijck M, Patel P, Mouw KW. Editorial: Bladder Cancer - A Cinderella Cancer: Advances and Remaining Research Questions. Front Oncol. 2020;10:1749, doi:10.3389/fonc.2020.01749.


102 patients receiving atezolizumab for metastatic urothelial cancer at up to 20 UK hospitals, with no RECIST v1.1 response following 3 cycles of treatment and fulfilling all eligibility criteria
Written informed consent
Randomisation by minimisation
1:1
Stratification factors:
Randomising hospital; site of metastasis; 1st or 2nd/3rd line of treatment; disease status
Group 1:
Atezolizumab alone (control)
IV atezolizumab three weekly
Group 2:
Atezolizumab + radiotherapy
IV atezolizumab three weekly
Plus
Radiotherapy to a single site
Follow up
Every 3 weeks on treatment:
Physical examination; FBC, U&E, LFTs, thyroid function (every 6 weeks); concomitant medication assessment; adverse event assessment (CTCAE v5)
Primary endpoint assessment (at 9 weeks):
CT chest abdomen pelvis (CAP); RECIST v1.1 assessment
Repeat CT imaging every 9 weeks on treatment until RECIST v1.1 progression/iRECIST iCPD
Six weeks following RECIST v1.1 progression (if continuing atezolizumab):
CT CAP; iRECIST assessment. Second CT CAP for iRECIST assessment 12 weeks later
Subsequent scans for iRECIST assessment every 9 weeks
Post treatment discontinuation:
Assessment of disease status and survival every 3 months
Substudies (if participating):
Quality of life (QoL) questionnaire at screening, 9 weeks & 6 months; also 12 months for those continuing atezolizumab
Research blood samples at baseline, fraction 4/5 (RT group only), week 3 and 9 from start of study atezolizumab and at RECIST v1.1 progression
Primary endpoint: Response at 9 weeks (RECIST v1.1)
Secondary endpoints: Response according to iRECIST; clinical benefit; best response; duration of response; time to progression; progression free survival; overall survival; treatment related toxicity; patient reported QoL.