Introduction

Fifty years ago Mole described the indirect impact of radiation on sites distant from the irradiated volume as the "abscopal effect" [1]. Demaria and Formenti subsequently demonstrated that this is an immune mediated phenomenon with T cells involvement [2], and readers are referred to the excellent review on the effect of radiotherapy on the tumour micro-environment and the immune system [3,4] . Interest among clinicians, on this subject, was stimulated by the increasing reports concerning the induction of the abscopal effect by radiotherapy, in patients who were treated with immune checkpoint inhibitors, for different cancers. Kang et al reported no fewer than 50 registered clinical studies currently open, investigating the potential synergistic effect between radiotherapy and various immune checkpoint modulators for different tumour types [5]. PERM is a randomised phase 2 trial currently open in the UK. This trial aims to test the hypothesis that irradiating one or more of the metastatic disease sites, in addition to the concurrent administration of pembrolizumab, will improve the response rate for patients with metastatic melanoma (NCT02562625).

Why combination?

Response rates to single agent immune check point inhibitors, for patients with metastatic melanoma, range from 10% - 20% for ipiliumab to 30-45% for PD-1 inhibitors pembrolizumab and nivolumab[6]. Combination treatment, with CTLA-4 and PD-1 inhibitors, improves the response rate to 58%, at the expense of increased treatment related toxicities[7]. This still leaves approximately a third of non-responders, who may benefit from different combinations of immune checkpoint modulators and conventional therapies and the design of these combinations may be guided by the immune micro-environment of the tumour[8]. Gajewski et al hypothesized that patients with a non-immunogenic tumour are unlikely to respond to immunotherapy alone [9]. Factors, intrinsic to the tumour itself, such as its mutational burden [10], neo-antigen heterogeneity [11], microenvironment [12], and those related to its host such as the HLA-type, germline polymorphisms in immune cell receptors and the gut microbiota can impact on the immunogenicity of the tumour [12]. Smyth et al. classified tumour micro-environments on the basis of the presence or absence of tumour infiltrating lymphocytes (TILs), and their PD-L1 expression [8]. Strategies to promote immunogenic cell death, and activate the immune system to prime the T cells may help to convert immunologically "cold" tumours. For example tumours lacking in tumour infiltrating lymphocytes, may be converted into tumours with a more "inflamed phenotype", thus improving their response to checkpoints modulation [9]. This can be achieved by combining immune check point modulators with oncolytic viruses[13] chemotherapy [14] or radiotherapy[4].

Radiation can result in the release of tumour antigens and molecules collectively known as the "damage associated molecular pattern" (DAMP) such as HMGB-1, DNA, RNAs Calreticulin[15]. These DAMPs promote the maturation of dendritic cells and their 'cross priming', in which the extracellular tumour antigens are presented by dendritic cells to CD8+ cytotoxic T cells, via the MHC class I loading pathway. This process is known to play an important role in inducing tumour immunogenicity [16], and possibly mediate radiation induced cytotoxicity[17]. Radiation can also activate the "STING" pathway, which up-regulates the expression of type 1 interferon [18] and MHC-Class 1 molecules and the generation of novel peptides [19]. T cells recruitment into the tumour microenvironment may also be improved, with the generation of appropriate chemokines and the

increase in blood flow to the tumour micro-environment, following the irradiation of the tumour micro-environment[20]. The synergistic effect between radiation and the blockade of the PD-1 pathway has been demonstrated in multiple pre-clinical studies [17,21,22]

Safety of radiation and PD-1 inhibitor combination

Reports to date, related to the safety of combining radiotherapy with immune checkpoint inhibitors, are reassuring. Anderson et al. [23] reported the outcome of 131 melanoma patients with brain metastases, who underwent SRS or hypofractionated cranial radiotherapy whilst receiving pembrolizumab or ipilimumab concurrently. No acute grade 3-4 toxicities was observed, and the complete and partial response rate was 62%, among patients receiving pembrolizumab and radiotherapy concurrently [23]. Bang et al reviewed the outcome of 133 patients who received radiation, and at least one cycle of an immune check point inhibitors for their melanoma, lung, or renal cancer [24]. 56 patients underwent radiotherapy within 14 days of their immunotherapy, and their radiotherapy schedules ranged from 8Gy/1# to 37.5Gy/15#. Treatment was directed to brain metastases in more than half of the patients, but extra-cranial sites were also irradiated. Grade 3 toxicities were reported in 1% of the patients who received PD-1 inhibitor alone with radiotherapy. In contrast, Liniker et al. [25] reported grade 3 or 4 related adverse event in 4 out of a cohort of 35 patients (11%) – three of them were cutaneous in nature.

The PERM trial

In the PERM trial, patients with metastatic melanoma are randomised to receive either pembrolizumab alone, or in combination with radiotherapy (Figure 1). In the combination arm, they will receive 24Gy in 3 fractions, to the target lesion between cycle 1 and cycle 2 of pembrolizumab. PERM is not a SABR trial per se, as radiotherapy can be delivered by electrons, IMRT or SABR; whichever is most appropriate for the target chosen for irradiation. For example, cutaneous or superficial nodal deposits will be most conveniently covered by electrons. However, for mediastinal metastatic nodes, SABR techniques are likely to be necessary. The use of SABR in the PERM trial will be reimbursed by NHS England for approved centres. Patients must have at least two disease sites so that one lesion can be irradiated, whilst the second can serve as the index lesion for subsequent response assessment. Intra-cranial lesions and those in the abdomen cannot be irradiated, to avoid the risk of radiation induced brain necrosis and colitis. The primary endpoint for this study is the response rate as assessed by RECIST criteria 12 weeks from the start of pembrolizumab treatment. Biopsies already taken, and some further samples in selected centres, will be collected subject to patients' consent for translational research. We aim to recruit 234 patients in total into this study.

Conclusion

PERM is unique among currently open radiotherapy-immune check point modulator trials, as it has a control arm in which patients can be randomised to receiving checkpoint inhibitor only. We believe this will provide the strongest clinical evidence to evaluate whether radiotherapy can augment the

effect of immune modulation. Its result may provide another treatment strategy for patients with metastatic melanoma unsuitable for combination immunotherapy and useful toxicity data to help trial design for other tumour sites, which may benefit from a similar treatment approach of radiotherapy and immune checkpoint modulators combination.

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Figure 1

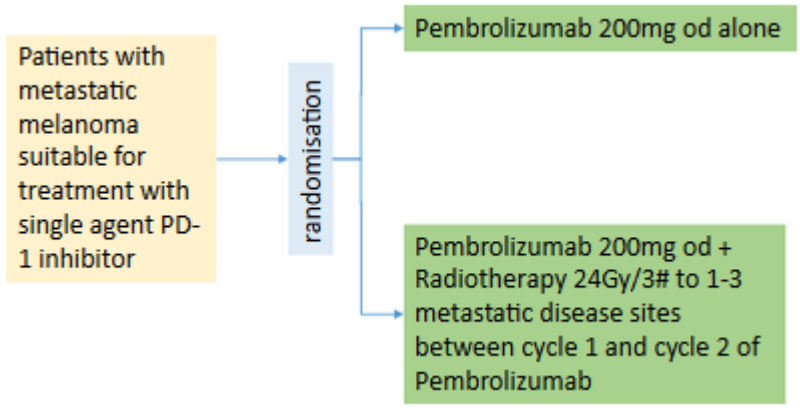

Fig 1. Schema for the PERM trial