



A phase I/II study of stereotactic radiotherapy and pembrolizumab for oligometastatic renal tumours (RAPPORT): Clinical trial protocol

David Pryor^{a,b}, Mathias Bressel^c, Nathan Lawrentschuk^{c,d}, Ben Tran^{c,e}, Jennifer Mooi^{c,d}, Jeremy Lewin^{c,d}, Arun Azad^{c,d}, Duncan Colyer^c, Nitika Neha^c, Mark Shaw^{c,d}, Sarat Chander^{c,d}, Paul Neeson^{c,d}, Daniel Moon^{c,d}, Katharine Cuff^{a,b}, Simon Wood^{a,b}, Declan G. Murphy^{c,d}, Shahneen Sandhu^{c,d}, Sherene Loi^{c,d}, Shankar Siva^{c,d,*}

^a Princess Alexandra Hospital, Brisbane, Australia

^b University of Queensland, Brisbane, Australia

^c Peter MacCallum Cancer Centre, Melbourne, Australia

^d University of Melbourne, Parkville, Australia

^e Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

ARTICLE INFO

Keywords:

Immunotherapy
Oligometastases
Renal cell carcinoma
RCC
SABR
SBRT

ABSTRACT

Background: The management of oligometastatic clear cell renal cell carcinoma (ccRCC) varies widely, ranging from observation to resection or systemic therapies. Prolonged survival has been observed following resection or stereotactic ablative body radiotherapy (SABR). Immunotherapy combinations have shown survival benefits, however, toxicity is higher than that for monotherapy and complete response rates remain less than 10%. The combination of effective local therapies in conjunction with immunotherapy may provide more durable control and pre-clinical models have suggested a synergistic immune-priming effect of SABR.

Objectives and Methods: RAPPORT is a prospective, single arm, phase I/II study assessing the safety, efficacy and biological effects of single fraction SABR followed by pembrolizumab for oligometastatic ccRCC. The study will include 30 patients with histological confirmed ccRCC and 1–5 oligometastases, one or more of which must be suitable for SABR. Patients can have received prior systemic therapy but not prior immunotherapy. A single 20Gy of SABR is followed 5 days later by 8 cycles of 200 mg pembrolizumab, every 3 weeks. Adverse events are recorded using CTCAE V4.03 and tumour response evaluated by Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1). Tumour tissue and peripheral blood samples will be collected pre-, during and post-treatment to assess longitudinal changes in immune subsets.

Outcomes and significance: The RAPPORT study will provide important safety and early efficacy data on the combination of SABR and pembrolizumab in oligometastatic ccRCC and will provide an insight into the underlying biological effects of combination therapy.

Trial registration: clinicaltrials.gov ID NCT02855203.

1. Introduction

Renal cell carcinoma (RCC) is the ninth most common cancer in Australia and the ninth most common cancer in men worldwide [1,2]. The incidence of RCC is rising, particularly in patients aged 70–90 years [3]. Overall, 17% of patients present with metastatic disease and another 50% of patients initially treated with curative intent will develop metastatic disease [4,5].

Patients who present with limited sites of spread (oligometastatic

disease), have highly variable disease courses. Management strategies have included initial periods of observation, resection or ablation of visible disease or early systemic therapy. Prolonged survival has been observed in patients with solitary or oligometastatic RCC whose disease is amenable to resection [6,7]. Both the National Comprehensive Cancer Network (NCCN) and the European Urology Association (EUA) guidelines recommend consideration of metastasectomy for patients with oligometastatic disease [8].

Surgery is not always feasible due to the location of the disease, the

* Corresponding author. Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Vic., 3000, Australia.

E-mail address: shankar.siva@petermac.org (S. Siva).

<https://doi.org/10.1016/j.conctc.2021.100703>

Received 15 March 2020; Received in revised form 27 September 2020; Accepted 1 January 2021

Available online 6 January 2021

2451-8654/© 2021 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

morbidity of the surgery and/or the patient's other medical comorbidities. The advent of stereotactic ablative body radiation therapy (SABR), allows for delivery of high biological doses of radiation using highly conformal, image guided techniques. SABR is being increasingly investigated as an effective local ablative therapy in the setting of RCC [9–11]. A meta-analysis of outcomes of 679 patients receiving SABR in the context of oligometastatic RCC found an estimated 1-year local control of 89.1% (95% confidence interval [CI]: 83.6–93.7%) [12]. The 1-year overall survival rates were 86.8% (95% CI: 62–99.8%). The incidence of any grade 3–4 toxicity was 0.7% (95% CI: 0–2.1%).

The mainstay of systemic therapy for this favourable metastatic clear cell RCC (ccRCC) population has comprised tyrosine kinase inhibitor (TKI) therapy. Increasingly a period of surveillance has been employed for patients with low volume disease that is not rapidly progressing. A review of data from five retrospective studies, one prospective cohort and a subgroup of a randomized phase III trial lend support to the strategy of deferral of TKI therapy and the use of local therapies where appropriate instead for carefully selected patients with oligometastatic RCC [13].

Immunotherapy returned to the forefront when single agent anti-PD1 therapy demonstrated superior overall survival when compared to everolimus in the second line setting [14]. More recently immunotherapy combinations in the first line setting have shown survival benefits in advanced disease, however, toxicity rates are higher than that for monotherapy and reported complete response rates remain less than 10% [15,16]. CheckMate-214 demonstrated superior overall survival with the combination of nivolumab plus ipilimumab compared to sunitinib in International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate or poor risk untreated advanced RCC [15]. Within the nivolumab plus ipilimumab cohort the objective response rate was 42%, complete response rate 9% and grade 3 or 4 adverse events occurred in 46% of patients. KEYNOTE-426 demonstrated superior overall survival with the combination of pembrolizumab plus axitinib compared to first line sunitinib in favourable, intermediate and poor risk RCC [16]. Within the pembrolizumab plus axitinib cohort the objective response rate was 59.3%, complete response rate 5.8% and grade 3 or higher adverse events occurred in 75.8% of patients. Specifically for pembrolizumab monotherapy, in 110 patients enrolled in cohort A of KEYNOTE-427, confirmed overall response rate was 33.6% (n = 36; 95% CI, 24.8–43.4) with 1 complete response (0.9%) and 35 (32.7%) partial responses [17]. In the context of oligometastatic disease, the combination of an effective local therapy in conjunction with immunotherapy may provide deeper responses and more durable control. In addition, pre-clinical models have suggested a potential synergistic immune-priming effect of SABR [18–20].

Single fraction 20Gy ablative RT has been shown to synergize with the T-cell checkpoint inhibitor anti-PD-1 in murine models, allowing for induction of an anti-tumour immune response by relief of tumour-mediated immunosuppression [18]. In another study, single fraction 30Gy RT to tumour nodules in a murine model resulted in an intense CD8⁺ T cell tumour infiltrate, and a loss of myeloid derived suppressor cells (MDSCs) [19]. In murine models of melanoma and renal cell carcinoma, single fraction 15Gy SABR in combination with PD-1 blockade has been demonstrated to synergize for additive tumour response in both the irradiated and distant tumour sites [20].

Whilst the overlapping toxicities of SABR and pembrolizumab are not yet fully understood, there does not appear to be overlapping mechanisms. Based on the observed rates of toxicity with SABR and anti-PD1 monotherapy when given alone, we hypothesised that the safety profile of this combination will be tolerable, and that the combination would prove to be clinically effective.

2. Patients and methods

2.1. Study design

RAPPORT is an investigator-initiated, prospective, multi-center, single arm, open-label, phase I/II study assessing the safety profile, efficacy and biological effects of single fraction SABR followed by pembrolizumab, an antibody targeted against anti-programmed cell death 1 (PD-1), in the setting of oligometastatic ccRCC.

2.2. Trial oversight and funding

The study was designed by the authors, sponsored by the Peter MacCallum Cancer Centre and funded by the Peter MacCallum Foundation through a philanthropic grant by the Bob Parker Family. Pembrolizumab was supplied by Merck Sharpe Dohme (MSD). The study was approved by the PMCC human research ethics committee and was conducted according to Good Clinical Practice guidelines. All patients are required to provide written informed consent. An independent data safety monitoring committee will review safety outcomes after 12 patients are enrolled.

2.3. Objectives and endpoints

The primary objective for this study is to determine the safety profile of SABR in combination with pembrolizumab. Safety (acute and long term) will be evaluated using CTCAE version 4.03 in all patients who have received at least one SABR treatment and one dose of pembrolizumab. After the end of treatment, each participant will be followed for 30 days for adverse event monitoring. Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0–1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. Serious adverse events will be collected for 90 days after the end of treatment.

Secondary objectives are to examine evidence of clinical efficacy of the combination in terms of overall survival (OS), time to local progression (TLP), distant progression free survival (DPFS), overall response rate (ORR), disease control rate (DCR) and change in pain rating. ORR will be measured, using RECIST 1.1 criteria at 3, 6, 12 and 24 months. Disease progression, as per RECIST 1.1, should be confirmed with repeat imaging 4–6 weeks later by the same imaging modality. Disease control is defined as complete response or partial response at any time after treatment commencement or stable disease for at least 6 months. The RECIST definition of complete response has been modified to include disappearance of the target tumour radiographically or complete metabolic response. Pain will be evaluated pre- and post-treatment using the Numerical Rating Scale pre-SABR treatment, prior to each cycle of pembrolizumab, then 3 monthly until 24 months after the end of SABR.

The exploratory objectives are to investigate the biological effects of the combination. These will include, but are not limited to; evaluation of PD-L1 expression in primary tumour and metastatic lesions using immunohistochemistry. Evaluation of longitudinal cellular and molecular changes in archival tumour tissue, and/or fresh tumour biopsies. This will include tumour infiltrating lymphocytes (TILs) and other markers. Evaluation of longitudinal changes in immunological subsets within peripheral blood.

2.4. Study population

Patients with a histological or cytological diagnosis of ccRCC, with the presence of oligometastases (1–5 metastases). One or more lesions must be deemed suitable for treatment with SABR. For patients with metastases involving the spine, lesions will be highly selected so they do not pose a significant risk for spinal canal impingement or spinal cord compression.

2.5. Key inclusion criteria

- Age of 18 years or older
- Has provided written informed consent for the trial.
- Histologically or cytologically confirmed metastatic ccRCC.
- Have oligometastatic (1–5 metastases), measurable disease based on RECIST 1.1.
- Have at least one metastasis for which SABR is deliverable.
- Treatment naïve or have previously received up to two lines of systemic treatment (excluding immunotherapy).
- ECOG performance status ≤ 2 .
- Demonstrate adequate organ function as defined in Table 1
- Life expectancy >12 months.

2.6. Key exclusion criteria

- Has received prior immunotherapy.
- Has received previous high dose radiotherapy (biological equivalent of >30 Gy in 10 fractions) to an area to be treated.
- Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks of registration or prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks of registration.
- Has evidence of untreated or active intracranial metastases
- Malignant pleural effusion.
- Has evidence of spinal cord compression or requires surgical fixation of bone lesion for stability (this must be performed before enrolment into the trial).
- Has a known additional malignancy that is progressing or requires active treatment.
- Has active autoimmune disease that has required active treatment in the past two years
- Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
- Is pregnant or breastfeeding.
- Has a known history of Human Immunodeficiency Virus (HIV), active Hepatitis B, active Hepatitis C or active tuberculosis.
- Has received a live vaccine within 30 days of registration.

Table 1
Adequate organ function laboratory values.

System	Laboratory Value
Haematological	
Absolute neutrophil count (ANC)	$\geq 1.5 \times 10^9/L$
Platelets	$\geq 100 \times 10^9/L$
Haemoglobin	≥ 90 g/L or ≥ 5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine OR Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) OR ≥ 60 mL/min for participant with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN OR Direct bilirubin \leq ULN for participants with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN OR ≤ 5 X ULN for participants with liver metastases
Albumin	
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

2.7. Trial treatments

The treatment regimen involves the delivery of a single fraction of highly conformal SABR to one or more sites of oligometastatic disease prior to receiving 8 cycles of pembrolizumab.

SABR treatment will be delivered on a linear accelerator using multiple coplanar or non-coplanar megavoltage fields or arcs. The gross tumour volume (GTV) will be delineated using CT \pm MRI. No additional margin will be added for microscopic spread with the exception of spine location where a clinical target volume (CTV) will be contoured according to the published international consensus guideline by Cox et al. [21]. For target volumes in the abdomino-thoracic region, tumour motion should be taken into account and an internal target volume (ITV) created by combining all positions of the GTV across the respiratory cycle utilising a 4-dimensional (4D) CT scan. A planning target volume (PTV) expansion of 5 mm on the ITV in the axial and craniocaudal direction is recommended as a minimum. For non-spine locations that do not require a 4D CT for motion management the PTV will be a 3–5 mm expansion on GTV. For spine locations the PTV is a 2 mm expansion on CTV.

A single dose of 20 Gy will be prescribed, however, a dose of 18Gy may be used as an alternative for more centrally located lung lesions or spinal lesions with a SINS score of >7 . The prescription isodose will be planned to cover 99% of the PTV, however, in the presence of an adjacent dose limiting organ at risk (OAR), $\geq 95\%$ coverage of the PTV will be accepted. For spine treatments at least 90% of the PTV should be covered by $\geq 90\%$ of the prescription dose. Normal tissue constraints are outlined in Table 2.

If after evaluation of a tumour location and treatment plan dosimetry, SABR is not technically or safely possible to deliver to all lesions, a conventional hypofractionated course of radiotherapy of 30–36 Gy at 3Gy per fraction should be delivered to non-SABR eligible lesions. In this scenario, delivery of SABR to other sites of disease should be scheduled

Table 2
Normal tissue contouring and dose constraints.

Organ	Contouring	Parameter ^a	Dose-Volume Constraints ^b
Kidney	Entire kidney	V10	33%
Spinal planning risk volume (PRV)	Spinal Cord + 3 mm expansion or Thecal Sac (1 cm above and below target)	Maximum dose	0.03 cc \leq 12Gy
Brain Stem	Including midbrain, pons and medulla	Maximum Dose	0.03 cc $<$ 12.5Gy
Skin (5 mm subcutis)	Body surface – 5 mm	Maximum Dose	0.03 cc \leq 24Gy
Small Bowel	All small bowel contoured 5 cm above and below PTV	Maximum Dose/Volume	30 cc \leq 12.5Gy
		Maximum Dose	0.03 cc \leq 30 Gy
Stomach	Entire Stomach	Maximum Volume	5cc \leq 22.5Gy
Liver	Entire liver	Maximum Dose/Volume	700 cc \leq 15Gy
Lung	Combined Left and right Lung - GTV	Maximum Dose/Volume	1000 cc \leq 7.4Gy
Oesophagus	Cricoid to gastro-oesophageal junction	Maximum Dose	0.03 cc \leq 15.4 Gy
Rectum	Recto-sigmoid to anal canal (solid structure)	Maximum Dose/Volume	20 cc \leq 14.3 Gy
Bladder wall	Entire structure	Maximum Dose/Volume	15 cc \leq 11.4 Gy
Heart/ Pericardium	Entire Structure	Maximum Dose/Volume	15 cc \leq 16Gy
Brachial Plexus	Including nerve roots	Maximum Dose	0.03 cc \leq 15.4 Gy

^a Maximum dose to 0.035 cc.

^b When planning more than one lesion a summary plan must be created. The dose constraints apply to the summary plan.

towards the end of, or immediately after, the course of conventional radiotherapy.

Pembrolizumab 200 mg is administered as a 30 min IV infusion every 3 weeks for 8 cycles beginning 5 days (+/- 3 days) after the last SABR. Dose delays and modifications are allowed for drug-related AEs. Treatment is to be discontinued for any life-threatening event, any severe or Grade 3 drug-related AE that recurs or any persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0–1 within 12 weeks of the last dose.

2.8. Follow-up procedures

Clinical and laboratory assessments: At each visit a physical examination, vital signs, weight, ECOG performance status and review of adverse events is undertaken. Full blood count, biochemical profile, thyroid function and coagulation profile is performed at each visit during the treatment phase.

Tumour evaluation: Screening CT and whole body bone scan should be completed within 35 days prior to study registration. Clinical and radiological tumour assessments will be performed by CT scan (or MRI as required) at 3 monthly intervals until 24 months post SABR treatment or if evidence of clinical progression.

Biological Evaluations: Whole blood samples for immune endpoints are collected prior to SABR, first dose of pembrolizumab, at cycle 2, 4 and 8 of pembrolizumab, at disease progression (if this occurs) and at 9 and 12 months post SABR treatment. Blood plasma samples for determination of circulating plasma tumour DNA and/or cytokines will be taken before the administration of every pembrolizumab treatment, and at 9, 12 and 24 months after end of SABR treatment at the time of imaging assessments. Tumour blocks from prior resections or biopsies of metastatic sites will be submitted. A request for newly obtained specimen (obtained up to 5 weeks prior to initiation of treatment) will be made, however, participation for this biopsy is optional. If feasible, an optional biopsy of a treated metastatic site will be performed at 9 months post completion of SABR and, in the event of disease progression, a sample from the metastatic site is also requested.

2.9. Statistical analysis plan

This is a Phase Ib/II study to evaluate the safety profile and efficacy that would then be evaluated in a larger and more appropriately powered future study. The sample size of 30 patients is pragmatic. The primary objective of the study is to provide a description of the safety profile of the combined SABR and pembrolizumab therapies. Table 3 illustrates different scenarios for grade 3 or 4 AEs rate ranging from 0% to 40% with the respective 95% exact confidence intervals, assuming 30 patients. For example, if the actual toxicity rate is 20%, the 95% confidence interval will be 8%–39%. Demographics and baseline characteristics of patients will be summarized using descriptive statistics. The analyses of the all endpoints will occur at 12 months after the last patient is recruited. No imputation for missing data is intended. Safety will be assessed using CTCAE v4.03 and the maximum toxicity grade of each adverse event will be derived and presented in table format. The proportion of patients who suffer from grade 3 or higher toxicities (each toxicity and overall) will be provided along with its exact 95% CI for all patients who have received at least one dose of pembrolizumab and completed at least one SABR treatment.

The Kaplan-Meier method will be used to describe TTLP, DPFS and OS curves. Estimates at 1 and 2 years will be provided with 95% confidence interval. TTLP will be assessed at lesion level and Kaplan-Meier estimates will be adjusted for patient effect. ORR (at 3, 6, 12 and 24 months after commencement of SABR treatment), DCR and best overall response will be described as percentages with exact 95% confidence intervals.

Pain will be described as change over time using linear mixed models. The linear mixed model will include time (as a factor) as fixed

Table 3

Confidence intervals for adverse event rates for sample size of 30 patients.

Number of patients with grade 3 ⁺ AE	Grade 3 ⁺ AE rate	95% confidence interval
1	3%	0%–17%
2	7%	1%–22%
3	10%	2%–27%
4	13%	4%–31%
5	17%	6%–35%
6	20%	8%–39%
7	23%	10%–42%
8	27%	12%–46%
9	30%	15%–49%
10	33%	17%–53%
11	37%	20%–56%
12	40%	23%–59%

AE; Adverse event.

effect and patients as random effect. Mean and 95% confidence intervals will be calculated for each time point and the data will be displayed graphically. If strong floor effect is observed or if the assumptions of the model do not hold, simple descriptive statistics will be provided instead for each time point.

A Safety Monitoring Committee (SCM) was formed prior to trial activation, to review the information from the safety analyses performed after the first 12 patients completed SABR and 12 weeks of pembrolizumab treatment.

3. Discussion

Management options for metastatic ccRCC have evolved rapidly over the last few years. Resection or ablation of oligometastatic disease has remained a mainstay of management while the new generation of immunotherapy agents and combination therapies have seen a subset of patients achieve durable remission. When this study was initially designed the phase 3 data for the new generation of immunotherapy agents had not yet matured. Prospective data was lacking on the effectiveness and safety of SABR in combination with anti-PD1 agents in ccRCC. The study commenced accrual in November 2016 with data analysis expected in 2021.

The RAPPORT study will provide important data on the safety profile and potential efficacy of the combination of SABR and anti-PD1 therapy that can inform the design of future randomized studies. It also provides an opportunity to explore biological correlates to enable a better understanding of the oligometastatic RCC phenotype and the mechanisms behind any immunological interactions of SABR and immunotherapy.

Author declaration

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

Acknowledgements

Funding support from Peter MacCallum Foundation philanthropic donation, drug supply by Merck Sharpe Dohme (MSD).

References

- [1] Australian Institute of Health and Welfare, Cancer in Australia 2019. Cancer Series no.119. Cat. No. CAN 123, AIHW, Canberra, 2019.
- [2] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *Ca - Cancer J. Clin.* 68 (6) (2018 Nov) 394–424.

- [3] W.H. Chow, S.S. Devesa, J.L. Warren, J.F. Fraumeni Jr., Rising incidence of renal cell cancer in the United States, *J. Am. Med. Assoc.*: *J. Am. Med. Assoc.* 281 (17) (1999) 1628–1631.
- [4] C.J. Kane, K. Mallin, J. Ritchey, M.R. Cooperberg, P.R. Carroll, Renal cell cancer stage migration: analysis of the National Cancer Data Base, *Cancer* 113 (1) (2008) 78.
- [5] J.D. Maldazys, J.B. deKernion, Prognostic factors in metastatic renal carcinoma, *J. Urol.* 136 (1986) 376–379.
- [6] L. Tosco, H. Van Poppel, B. Freja, G. Gregoraci, S. Joniau, Survival and impact of clinical prognostic factors in surgically treated metastatic renal cell carcinoma, *Eur. Urol.* 63 (4) (2013) 646–652.
- [7] S.C. Murthy, K. Kim, T.W. Rice, et al., Can we predict long-term survival after pulmonary metastasectomy for renal cell carcinoma? *Ann. Thorac. Surg.* 79 (3) (2005) 996–1003.
- [8] B. Ljungberg, L. Albiges, K. Bensalah, et al., EAU Guidelines on Renal Cell Carcinoma: 2018 Update, *European urology*, 2018.
- [9] G. Kothari, F. Foroudi, S. Gill, N.M. Corcoran, S. Siva, Outcomes of stereotactic radiotherapy for cranial and extracranial metastatic renal cell carcinoma: a systematic review, *Acta Oncol.* (2014) 1–10.
- [10] S. Siva, G. Kothari, A. Muacevic, et al., Radiotherapy for renal cell carcinoma: renaissance of an overlooked approach, *Nat. Rev. Urol.* 14 (9) (2017 Sep) 549.
- [11] S. Siva, D. Pham, T. Kron, et al., Stereotactic ablative body radiotherapy for inoperable primary kidney cancer: a prospective trial, *BJU Int.* 120 (5) (2017 Nov) 623–630.
- [12] N.G. Zaorsky, E.J. Lehrer, G. Kothari, et al., Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies, *Eur Urol Oncol* 2 (5) (2019 Sep) 515–523.
- [13] L.M. Pickering, M.O. Mahgoub, D. Mukherji, Is observation a valid strategy in metastatic renal cell carcinoma? *Curr. Opin. Urol.* 25 (5) (2015) 390–394.
- [14] R.J. Motzer, B. Escudier, D.F. McDermott, et al., Nivolumab versus everolimus in advanced renal-cell carcinoma, *N. Engl. J. Med.* 373 (19) (2015 Nov 5) 1803–1813.
- [15] R.J. Motzer, N.M. Tannir, D.F. McDermott, et al., Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma, *N. Engl. J. Med.* 378 (14) (2018 Apr 5) 1277–1290.
- [16] B.I. Rini, E.R. Plimack, V. Stus, et al., Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, *N. Engl. J. Med.* 380 (12) (2019 Mar 21) 1116–1127.
- [17] D.F. McDermott, J.L. Lee, C. Szczylik, et al., Pembrolizumab monotherapy as first-line therapy in advanced clear cell renal cell carcinoma (accRCC): results from cohort A of KEYNOTE-427, *J. Clin. Oncol.* 36 (15) (May 20, 2018), 4500-4500, suppl.
- [18] L. Deng, H. Liang, B. Burnette, et al., Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice, *J. Clin. Invest.* 124 (2) (2014 Feb) 687–695.
- [19] A. Filatenkov, J. Baker, A.M. Mueller, et al., Ablative tumor radiation can change the tumor immune cell microenvironment to induce durable complete remissions, *Clin. Canc. Res.* 21 (16) (2015 Aug 15) 3727–3739.
- [20] S.S. Park, H. Dong, X. Liu, et al., PD-1 restrains radiotherapy-induced abscopal effect, *Cancer Immunol Res* 3 (6) (2015 Jun) 610–619.
- [21] B.W. Cox, D.E. Spratt, M. Lovelock, et al., International spine radiosurgery consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery, *Int. J. Radiat. Oncol. Biol. Phys.* 83 (5) (2012) e597–605.