Checkpoint inhibitor therapy for breast cancer, colon cancer, merkel cell carcinoma and sarcoma

Myron Klevansky¹ and Christos S Karapetis¹,²

¹. Flinders Medical Centre, Bedford Park, South Australia, Australia.
². Flinders University, Bedford Park, South Australia, Australia.

Abstract

Two of the most common cancers, breast and bowel cancer, seem 'immune' to immune therapy – but there are particular molecular subtypes of these cancers that are more responsive. Several types of cancer that occur rarely or uncommonly may also benefit from immune therapy. The rare cancers suffer from under-representation in phase 3 randomised controlled trials, as conducting such large scale studies in the setting of rare cancers is usually not feasible. This in turn affects regulatory approval and access to checkpoint inhibitors for these tumours. Nevertheless, reported activity of these drugs has led oncologists and patients to consider such therapy, particularly where no other active or effective therapy exists. This review article will review the evidence that supports immune therapy for such cancers.

Breast cancer

Breast cancer is the second most common cause of cancer death in Australian females with an estimated 3049 cancer deaths per year.¹ Novel treatment strategies are urgently required especially for subtypes that cannot be treated with targeted therapies. Breast cancer without evidence of hormone receptor expression or HER2 expression, so called triple-negative breast cancer (TNBC), is a cancer that is often relatively resistant to existing systemic breast cancer therapies. TNBC, when compared to other breast cancer subtypes, has shown more promise in terms of immunogenicity and therefore has been expected to respond more robustly to checkpoint inhibition therapy.² The presence of tumour infiltrating lymphocytes (TILS), interestingly, has been previously shown to be associated with not only improved survival but also improved response to chemotherapy.³

Phase 1 trials with the PD-1 antibody pembrolizumab and the PDL-1 antibody atezolizumab have demonstrated overall response rates (ORR) of approximately 20%. In the phase 1B KEYNOTE 012 study, 32 patients with PD1 positive (>1% staining in tumour or stroma) TNBC were administered pembrolizumab 10mg/kg, 2 weekly (111 screened, 65 PD-L1 positive).⁴ The median number of cycles administered was five (range 1 to 36) with an ORR of 18.5% and a median time to response of 17.9 weeks. The disease control rate was 25.9% (PR, CR or SD for > 24 weeks) with 37.5% of patients experiencing a decrease in tumour burden, including one CR and 4 PRs. The incidence of grade 3 to 5 events was 15.6%. All 32 patients included in this study had received previous chemotherapy, however, none of the patients with high LDH (>2 times normal upper limit) responded. The median duration of response had not been reached at publication.

The checkpoint inhibitor called atezolizumab has been evaluated in TNBC in a Phase1a study.⁵ Patients were administered atezolizumab at 15mg/kg, 20mg/kg or 1200mg every three weeks. Twenty-seven patients with TNBC were included in this study. Among the 21 of these patients who had PD-L1 evaluable disease (by immunohistochemistry 2+ or 3+) the ORR by RECIST was 24% with a 24 week PFS rate of 33%. 11% of patients had G3 or G4 events.

Clearly there is early promising evidence for the potential future therapeutic use of checkpoint inhibitors in the management of TNBC but further research is needed.
Colorectal cancer

It is estimated that Australia will see 16,682 new cases of colorectal cancer in 2017. It is the second most common cause of cancer death with 4071 deaths in 2014.5 The five year survival of metastatic disease is estimated at 13.9% despite the availability of several treatment options.7

Tumours harbouring DNA mismatch repair mechanism defects are hypermutated (i.e. bear a relatively heavy mutational burden) when compared to tumours that do not have such deficits. This generates more neo-antigens that can be recognised by the immune system as non-self, immunogenic antigens.8 The percentage of stage 4 colorectal cancers that have been variably reported as microsatellite instability high (MSI-H) or dMMR (mismatch repair deficient) is between 3.5 and 6.5%.9,10

In a phase 2 study, Pembrolizumab was administered at 10mg/kg every 14 days to three cohorts of patients; stage IV colorectal dMMR (11 patients), MMR proficient (21 patients) and non-colorectal, solid, stage IV dMMR malignancies (9 patients).6 All groups were heavily pre-treated. The 20 week survival and response rates were reported as per RECIST 1.1 and immune related response criteria. In the dMMR group the immune related objective response rate was 40% (4/10 assessed patients) and the immune related progression free survival was 78% (7/9 assessed patients). In the pMMR cohort there were no immune related objective responses and the immune related progression free survival at 20 weeks was 11% (2/18 assessed patients). The median follow up was 20 weeks for the pMMR cohort and 36 weeks for the dMMR cohort. Those patients who were assessed at 20 weeks were included in the analysis for 20 week PFS. According to the analysis by RECIST, four of the 10 patients who were able to be assessed for RECIST, four (40%) had an objective response with a rate of disease control (CR, PR and SD at 20 weeks) of 90%. None of the 18 assessed patients in the pMMR group had a RECIST objective response and the disease control rate was 11% (2/18 patients).

Median OS and PFS in the dMMR group were not reached while in the pMMR group median PFS was 2.2 months (95% CI 1.4 to 2.8) with a median OS of five months. The median time to response for the dMMR group was 28 weeks. In regards to CEA substantial decreases were seen in seven of 10 dMMR patients and none of the pMMR cohort. Adverse events of interest included rash or pruritus (24%), thyroiditis, hypothyroidism or hypophysitis (10%) and asymptomatic pancreatitis (15%). Upon analysis of the whole-exome sequences, a mean of 1782 somatic mutations per tumour in the dMMR cohort were seen versus 73 in the pMMR group. Furthermore, 30 cases were evaluated for PDL1 and CD8 by immunohistochemistry at the invasive front of the tumour and within the tumour. There was a greater density of CD8 positive lymphocytes in the dMMR group and PD-L1 expression at the tumour invasive front was only seen in the dMMR cohort. Importantly, patients with germline dMMR (Lynch syndrome) were less likely to respond when compared to sporadic dMMR patients at 27% (3/11) versus 100% (6/6) p=0.009.

The results from an expanded cohort of 53 patients were presented at the ASCO 2016 Annual Scientific Meeting.11 The response rate in the dMMR group of 28 patients was 50% with a disease control rate of 89% with respective rates for the pMMR cohort of 0 and 16%. Median PFS and OS for the dMMR cohort was not reached versus 2.4 and 6 months for pMMR (HR 0.135 p<0.001 and HR 0.247 p=0.001). The 24 month OS for the dMMR cohort was 66%.

Results from the CheckMate 142 study were recently published in Lancet Oncology. CheckMate 142 also suggests benefit for checkpoint inhibition in dMMR colorectal cancer.13 The study is ongoing and is a multicentre, open-label, phase 2 trial, enrolling patients with histologically confirmed metastatic or recurrent dMMR (by IHC or PCR) colorectal adenocarcinoma. Patients were required to have at least one prior line of treatment including a fluoropyrimidine and irinotecan or oxaliplatin. Most were heavily pre-treated. Patients were administered nivolumab 3mg/kg every two weeks until disease progression. Seventy-four patients were enrolled and at a median of 12 months of follow-up 23 patients (31.1%) had achieved an objective response which 59% of patients achieving disease control at 12 weeks. The median time to response was 2.8 months with a median duration of response had not been reached at the time of reporting. Grade 3 and 4 events were recorded in 15 (20%) of patients of whom five discontinued secondary to colitis, deranged ALT, acute kidney injury, duodenal ulcer and stomatitis. Twenty-three patients died while on study with no deaths related to treatment. Responses were recorded irrespective of PD-L1 staining suggesting that PD-L1 is not a biomarker for...
Pembrolizumab and subsequently nivolumab (240mg every two weeks) have been granted accelerated approval by the FDA in patients with MSI-H or dMMR colorectal cancer that has progressed following conventional chemotherapy.\textsuperscript{13,14} Regulatory approval and further phase 3 data will be required prior to immune therapy entering standard use in Australia.

**Merkel cell carcinoma**

Merkel cell carcinoma is a rare and poor prognosis malignancy. Once disseminated, Merkel cell carcinoma seldom has durable responses with conventional chemotherapy. It has an incidence in Australia of 1.6 per 100 000 per year.\textsuperscript{15}

The Javelin Merkel 200 study was an open label, single group phase 2 international multicentre study. 88 patients with histologically confirmed merkel cell carcinoma were enrolled. All had received at least one prior line of chemotherapy. Patient study enrolment was not based on PD-L1 expression or Merkel cell polyomavirus status. Patients received avelumab intravenously at 10mg/kg every two weeks.\textsuperscript{16} The primary end point was objective response assessed by RECIST 1.1. Seventy-four patients had samples assessable for PD-L1 expression (Dako) and 77 for Merkel cell polyomavirus IHC. Of those assessable, 59% were PD-L1 positive (>1%) and 60% were Merkel cell polyomavirus positive. Of the 88 patients 28 patients had an objective response (ORR 31.8% CI 21.9 – 43.1), eight (9%) of which were complete responses and 20 of which were partial responses. Responses were durable with a PFS at six months of 40% and an overall survival at six months of 69%. Median overall survival was 11.3 months

In a post hoc analysis objective responses were achieved in 34.5% (20 of 58) who were PD-L1 positive and 18.8% (three of 16) who were PD-L1 negative. Objective responses occurred in 26.1% (12 of 46) of patients who were polyomavirus positive and 35.5% (11 of 35) who were negative. Five grade 3 treatment events were reported in four patients (5%) including lymphopaenia, ALT derangement and isolated laboratory abnormalities. There were no grade 4 or 5 events reported.

Javelin Merkel 200 demonstrated durable responses in chemo-refractory patients with Merkel cell carcinoma irrespective of PD-L1 or Merkel cell polyomavirus status and avelumab has been approved by the FDA in this setting.

Pembrolizumab has also shown activity in metastatic Merkel cell carcinoma with a phase 2 study of 26 treatment naïve patients.\textsuperscript{18} Pembrolizumab was administered at 2mg/kg every three weeks. Objective responses were seen in 56%, 14 of 25 evaluable patients, which included four CRs and 10 PRs. The six month PFS was 67%. PD-L1 expression did not correlate with objective response and responses were observed in polyomavirus positive and negative patients. 15% of patients experience a grade 3 or 4 adverse event.

Checkpoint inhibitors represent a valuable option in the second line setting, with durable responses and manageable toxicity. Avelumab has received accelerated FDA approval for Merkel Cell Carcinoma, including patients who have not received prior chemotherapy.\textsuperscript{18}

**Sarcoma**

The activity of checkpoint inhibition immune therapy for sarcoma is being evaluated, but results are preliminary and studies are ongoing. In the SARCO28 trial, 80 patients were evaluable for response following immune therapy with pembrolizumab. All had pre-treated sarcoma. In 13 patients with Ewing’s sarcoma, there were no responses. Only one patient of 22 with osteosarcoma achieved a response. One patient of five with chondrosarcoma achieved a response and the overall response rate for soft tissue sarcomas was 18%.\textsuperscript{19} Alliance A091401 was a multicentre phase 2 study of nivolumab +/- ipilimumab for patients with metastatic sarcoma. There was minimal activity when nivolumab was used alone (RR 5%, 2 responses in 38 patients) but more activity was seen with the combination of nivolumab plus Ipilimumab (RR 16%, six responses in 38 patients).\textsuperscript{20} The experience of single centres is also suggesting limited activity of checkpoint inhibitors in this setting. An Australian single centre experience of immune therapy for adolescents and young adults reported some activity
in Ewing’s sarcoma. In 13 patients with Ewing’s sarcoma, there were two responses including one complete metabolic response in a patient with lung and bone metastases. Another retrospective review, this time from the New York University Cancer Institute, three responses were reported in 14 patients that received at least six cycles of single agent nivolumab.

These small prospective phase 2 studies and retrospective single centre experiences suggest a potential role for immune therapy in selected cases, but response rates are low. A better understanding of patient and tumour selection factors and a true measure of the benefit in terms of survival prolongation is needed.

References

13. FDA [Internet]. FDA approves first cancer treatment for any solid tumor with a specific genetic feature; c2017 [cited 2017 Sep 17]. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm
14. FDA [Internet]. FDA grants nivolumab accelerated approval for MSI-H or dMMR colorectal cancer; c2017 [cited 2017 Sep 17]. Available at: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm569366.htm
18. FDA [Internet]. FDA approved first treatment for rare form of skin cancer; c2017 [cited 2017 Sep 17]. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm548278.htm

