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Immunotherapy of Ipilimumab and Nivolumab in Patients with Advanced Neuroendocrine Tumors: A Subgroup Analysis of the CA209-538 Clinical Trial for Rare Cancers

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ABSTRACT

Purpose: Combination immunotherapy with anti–CTLA-4 and anti–PD-1 blockade has demonstrated significant clinical activity across several tumor types. Neuroendocrine tumors (NET) are a heterogeneous group of rare tumors with limited treatment options. CA209-538 is a clinical trial of combination immunotherapy with ipilimumab and nivolumab in rare cancers, including advanced NETs.

Patients and Methods: CA209-538 is a prospective multicenter clinical trial in patients with advanced rare cancers. Patients received treatment with nivolumab at a dose of 3 mg/kg and ipilimumab at 1 mg/kg every three weeks for four doses, followed by nivolumab 3 mg/kg every two weeks and continued for up to 96 weeks, until disease progression or the development of unacceptable toxicity. Response was assessed every 12 weeks by RECIST 1.1. The primary endpoint was clinical benefit rate (CBR; complete remission + partial remission + stable disease).

Results: Twenty-nine patients with advanced NETs received treatment. Three (10%) patients had low-, 13 (45%) had intermediate-, and 13 (45%) had high-grade tumors; lung was the most common primary site (39%). The objective response rate was 24% with a CBR of 72%; 43% of patients with pancreatic neuroendocrine neoplasms (NEN), and 33% of patients with atypical bronchial carcinoid achieved an objective response. The median progression-free survival was 4.8 months [95% confidence interval (CI): 2.7–10.5] and overall survival was 14.8 months (95% CI: 4.1–21.3). Immune-related toxicity was reported in 66% of patients with 34% experiencing grade 3/4 events.

Conclusions: Combination immunotherapy with ipilimumab and nivolumab demonstrated significant clinical activity in subgroups of patients with advanced NETs including patients with atypical bronchial carcinoid and high-grade pancreatic NENs.

Introduction

Neuroendocrine neoplasms (NEN) constitute a heterogeneous group of rare tumors. Given the wide distribution of neuroendocrine cells throughout the body, neuroendocrine tumors (NET) can arise in almost any organ or tissue, with the most common sites being the gastrointestinal tract and the lung (1). NETs are considered rare malignancies but their incidence has risen over the last decade.

Current treatments for patients with advanced NETs differ depending on the histologic grade and the site of tumor origin. Low- and intermediate-grade tumors are commonly treated with somatostatin analogues (2, 3) and receive targeted therapy with the mTOR inhibitor everolimus at the time of disease progression (4, 5). Recently, peptide receptor radionuclide therapy (PRRT) has also demonstrated significant clinical activity in patients with low-grade midgut NETs (6). In contrast to low and intermediate NETs, patients with advanced high-grade NENs generally receive platinum-based doublet chemotherapy as first-line treatment (7); however, their overall prognosis is poor (8).

Immunotherapy using checkpoint inhibitors that block the programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) axis and reinvigorate anti-tumor specific T-cell responses have emerged as a highly effective therapy in a significant proportion of patients across a range of malignancies (9). There is currently only very limited evidence for immunotherapy with anti–PD-1/PD-L1 agents in patients with NETs; early trials suggest a low-level activity in patients treated with single-agent therapy (10, 11). Immunotherapy using combined anti–PD-1 and anti–CTLA-4 blockade has demonstrated increased efficacy compared with single-agent anti–PD-1 treatment in patients with advanced melanoma, renal cell carcinoma, microsatellite-instable colorectal cancer, and subsets of non–small cell lung cancer (12, 13).

Combination treatment using the anti–PD-1 antibody nivolumab and the anti–CTLA-4 antibody ipilimumab has been investigated in patients with advanced NETs in two clinical trials enrolling patients with rare cancers, CA209-538 and DART SWOG 1609. We report here the outcome of the neuroendocrine cohort of the CA209-538 clinical

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ClinicalTrial registration: ClinicalTrials.gov registry: NCT02923934.

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Translational Relevance

Immunotherapy with anti–PD-1/PD-L1 blockade has demonstrated significant clinical activity across several cancer types. Neuroendocrine tumors are a heterogeneous group of rare cancers with limited treatment options for patients with advanced disease. Immunotherapy with single-agent anti–PD-1 therapy has shown low response rates in patients with advanced neuroendocrine tumors. CA209-538 investigated combined anti–CTLA-4 and PD-1 blockade using ipilimumab and nivolumab demonstrating a high response rate in patients with high-grade neuroendocrine neoplasms and atypical bronchial carcinoid. The findings of CA209-538 in conjunction with the results of the DART SWOG 1609 trial justify further investigation of this treatment regimen in patients with advanced high-grade neuroendocrine neoplasms and atypical bronchial carcinoid. Ongoing translational research will focus on identifying biological correlates of response.

trial. Translational research to identify predictive biomarkers for response are currently ongoing.

Patients and Methods

Study design

CA209-538 is a multicentre, open label, phase II study conducted at five sites in Australia (Austin Health, Peter McCallum Cancer Centre, and Monash Health, Melbourne; Blacktown Hospital, Sydney; and Albury Wodonga Health, local sponsor was the Olivia Newton-John Cancer Research Institute). Eligible patients were aged 18 years or older and had a histologically confirmed metastatic rare cancer. Patients with advanced neuroendocrine neoplasms were enrolled with the exclusion of patients with small cell lung carcinoma. Patients had at least one measurable lesion according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Other inclusion criteria were a life expectancy of three months or more and an adequate organ function. Patients could either be treatment naïve or had received prior systemic therapy with a minimum washout period of 28 days before initiation of study treatment. Disease progression following prior therapy was not an inclusion requirement. Key exclusion criteria were active brain metastases and a history of autoimmune conditions. Archival tumor tissue, or a fresh tumor biopsy during screening, were required for predictive biomarker analysis. Tumors were graded and classified according to the following schemes: World Health Organization (WHO) 2019 for gastrointestinal and pancreatic neoplasms, WHO 2015 for lung and thymic neoplasms, WHO 2014 for cervical tumors, and WHO 2015 for prostate neuroendocrine carcinoma.

The clinical trial protocol was reviewed and approved by the Institutional Review Board at Austin Health (Melbourne, Australia) and was undertaken in accordance with the Declaration of Helsinki and the guidelines of Good Clinical Practice. Written informed consent was obtained from all participants prior to enrollment in the study.

Treatment

Nivolumab and ipilimumab were administered intravenously at a dose of 3 mg/kg over a period of 30 minutes and 1 mg/kg over 90 minutes, respectively, every three weeks for four doses (induction phase), followed by nivolumab monotherapy at a dose of 3 mg/kg every two weeks (maintenance phase) until disease progression, unacceptable toxicity, or a maximum of two years after enrollment. Dose reductions were not permitted; however, study treatment could be interrupted to enable recovery from adverse reactions for up to 6 weeks. If treatment was discontinued, patients were followed up until disease progression or initiation of a different treatment. Tumor assessments were performed by radiologic assessment (CT of brain, chest, abdomen, pelvis) at baseline and then every 12 weeks during treatment or follow-up. A confirmatory scan was performed 6 weeks after the first restaging scan at week 18. Tumor response was assessed according to RECIST version 1.1. Patients with evidence of progressive disease at their first restaging scan at week 12 were permitted to continue on study treatment at the discretion of the investigator for another six weeks until radiologic confirmation of progression at week 18. Safety analyses were performed on all patients who received at least one dose of study treatment. Laboratory monitoring and safety assessments were performed at baseline and every two to three weeks prior to treatment according to the study protocol. Adverse events were graded in accordance with the NCI Common Terminology Criteria for Adverse Events version 4.0 and collected during treatment and for 100 days after the last dose received.

Outcomes

The primary endpoint was the proportion of patients with disease control at week 12 (complete response, partial response, or stable disease) according to RECIST criteria. The secondary objective was identification of a tumor agonistic predictive biomarker or immune signature.

Statistical analysis

Given the heterogeneous nature of the patient population, statistics were descriptive and no sample size calculation was undertaken. The survival curves (overall survival and progression-free survival) were generated using Graphpad Prism v8.3.0 software, using the Kaplan–Meier product limit method. Descriptive statistics (median, confidence intervals) were also performed using this software.

Results

Patient characteristics

Between November 2017 and September 2019, 29 patients with advanced NETs were enrolled into the CA209-538 clinical trial (Supplementary Table S1). The demographics of the study population and disease characteristics are outlined in **Table 1**. The majority of patients had a NET of lung origin (39%) with atypical bronchial carcinoid being the most common tumor type. Ten patients (36%) had tumors with a gastroenteropancreatic origin including 7 patients (25%) with a pancreatic primary. Three (10%) patients had low-grade, 13 (45%) had intermediate-grade, and 13 (45%) had high-grade tumors. All patients had sporadic NETs apart from one patient with a thymic neuroendocrine carcinoma that occurred on the background of a multiple endocrine neoplasia, type 2A syndrome.

The majority of patients (90%) had received prior systemic therapy with 59% having received at least two lines of treatment. In keeping with the large number of patients with high-grade tumors, 86% of patients had received prior chemotherapy with the most commonly used regimen being a platinum/etoposide doublet. Twenty-one percent of patients had previously received PRRT and all patients were

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Table 1. Patient demographics and disease characteristics.

Gender	
Male	17 (59%)
Female	12 (41%)
Age (years)	57 (20–82)
ECOG performance status (at entry)	
0	10 (34%)
1	19 (66%)
Setting	
First line	3 (10%)
Second line	9 (31%)
≥2 lines (range 2–5)	17 (59%)
Prior treatments	
Chemotherapy	25 (86%)
Platinum/Etoposide	15 (52%)
Temozolomide/Capecitabine	14 (48%)
Peptide receptor radionuclide therapy (PRRT)	6 (21%)
Everolimus	2 (7%)
Sunitinib	2 (7%)
Pembrolizumab	1 (3%)
Tumor types	
Lung	11 (38%)
Typical bronchial carcinoid	1
Atypical bronchial carcinoid	9
Large cell pulmonary neuroendocrine carcinoma	1
Gastroenteropancreatic	10 (34%)
Pancreatic NET	5
Pancreatic NEC	2
Gastroesophageal junction NEC	1
Gastric NET	1
Colonic NEC	1
Thymus	4
Unknown primary	2
Prostate	1
Cervix	1
Grade	
Low	3 (10%)
Intermediate	13 (45%)
High	13 (45%)

Abbreviations: NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

immunotherapy naïve, apart from one who received single-agent anti–PD-1 therapy with pembrolizumab prior to enrollment.

Efficacy

Overall, 20 of 29 (69%) patients were alive at the time of data analysis and 8 (27%) patients died from disease progression. One patient was lost to follow-up.

Nineteen (65%) of all patients completed the induction treatment with four doses of nivolumab and ipilimumab and 5 (17%) patients progressed clinically during the induction phase and received only one or two treatment doses. Five (17%) patients discontinued treatment during the induction period due to grade 3/4 immune-related adverse events (irAE). Fifteen patients entered into the maintenance phase with fortnightly nivolumab infusions and 2 patients came off study for progressive disease at their first radiologic assessment at week 12.

The objective response rate of the entire cohort was 24% (7 of 29 patients; **Fig. 1A**). Fourteen patients had stable disease as their best radiologic response leading to a clinical benefit rate of 72%. Nine of the 14 patients with stable disease had tumor regressions that did not meet the criteria of a partial response. Five patients (17%) progressed clinically prior to the first restaging scan and were taken off study and 3 (10%) patients had progressive disease at their first restaging scan. The median progression-free and overall survival were 4.82 months [95% confidence interval (CI): 2.71–10.53] and 14.78 months (95% CI: 4.07–21.25), respectively (**Fig. 2**).

Objective responses were achieved in 31% and 23% of patients with high-grade and intermediate-grade tumors, respectively. Five out of 7 responders had an intermediate- or high-grade NET and 2 had neuroendocrine carcinoma. In contrast, no responses were seen in the 4 patients with low-grade tumors (Supplementary Table S2). Three of 9 (33%) patients with atypical bronchial carcinoid achieved an objective response including 2 complete remissions; responses are ongoing in these 3 patients (20+, 25+, 26+ months; **Fig. 1B**). In addition, 3 of 7 (43%) patients with pancreatic NENs obtained a response; all 3 responders had high-grade tumors, including 2 patients with grade 3 pancreatic neuroendocrine tumors (pNET) and 1 patient with pancreatic neuroendocrine small cell carcinoma. One of the responding pNET patients had failed prior single-agent anti–PD-1 therapy.

Safety

Nineteen of 29 (66%) patients experienced irAEs of any grade (**Table 2**). A grade 3 or higher immune-related toxicity occurred in 10 (34%) patients with hepatitis being the most commonly reported (14%). Other severe irAEs included enterocolitis, myocarditis, and diabetes mellitus. Two patients had a grade 3/4 serum lipase elevation, without associated symptoms or radiologic changes to suggest pancreatitis. There were no treatment-related deaths.

Discussion

NETs are a heterogeneous group of rare malignancies that have been challenging to study leading to gaps in knowledge to guide best treatment. Clinical trials with somatostatin analogues (2, 3), mTOR (4, 5, 14), and VEGF inhibitors (15) and PRRT (6) have demonstrated progression-free survival benefits for patients with low- and intermediate-grade small bowel and pancreatic NETs. Prospective trials, however, are lacking for patients with high-grade neuroendocrine neoplasms and are limited for low- and intermediate-grade NETs of non-gastroenteropancreatic origin. Our study cohort reflects this by an enrichment of the study population for high-grade tumors and NETs of pulmonary origin.

Patients with advanced high-grade neuroendocrine carcinoma have a poor prognosis (8) and generally receive platinum-based doublet chemotherapy leading to median survival of approximately 12 months (7). The duration of response to chemotherapy is generally short lived and second-line treatment options are lacking. In our patient cohort, we observed a 31% response rate for patients with high-grade neuroendocrine neoplasms with the majority of responders achieving durable responses. Responses were seen in patients with neuroendocrine carcinomas of the gastroesophageal junction and pancreas and in patients with high-grade pancreatic NETs. It has recently been recognized that patients with high-grade pancreatic NENs constitute a heterogeneous group of patients regarding their prognosis, whereby well-differentiated and poorly differentiated high-grade neoplasms can be discriminated on the basis of morphology with treatment outcomes that differ (16). Our dataset is too small to make conclusions of any difference in responsiveness to dual checkpoint inhibition for high-grade pancreatic NEN subgroups and an additional cohort of the DART SWOG 1609 trial that enrolls exclusively this patient population may shed further light on this.

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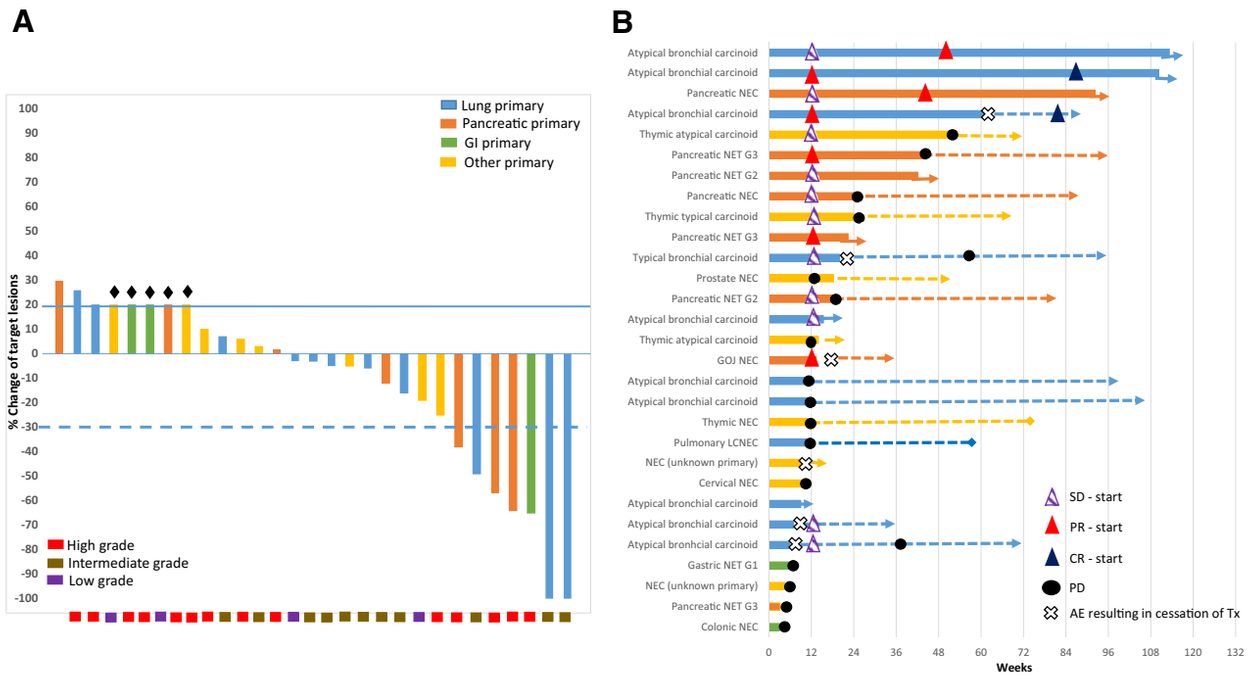

Figure 1.

A, Waterfall plot of the best objective response measured as the maximum change from baseline in the sum of the longest diameter of each target lesion. The panel at the bottom defines the tumor grade; patients marked (◆) progressed clinically prior to their first restaging CT scan. **B,** Swimmer plot demonstrating time to response and duration of study treatment. Patients were monitored for survival after cessation of treatment (▬▬▶), end of follow-up due to death represented by (▬▬◆). Abbreviations: GOJ, gastroesophageal junction; LCNEC, large cell neuroendocrine carcinoma; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

We also observed promising activity of the combination treatment in patients with atypical bronchial carcinoid. Patients with atypical bronchial carcinoid have a poor prognosis with a median survival of 16 months (17). Current treatment options for this patient population are limited to the mTOR inhibitor everolimus alone (5) or combination treatment with somatostatin analogues leading to progression-free survival benefits (14, 18). Objective responses with everolimus-based treatments are very low (5). In contrast, 3 of 9 patients with atypical bronchial carcinoid treated with combination immunotherapy in our trial obtained an objective response including 2 patients with complete remissions. All responses are currently ongoing.

We observed high-grade immune-related toxicity in 34% of our patients which is in keeping with clinical trials using the same treatment regimen in patients with other malignancies including advanced melanoma and metastatic renal cell carcinoma (13). In

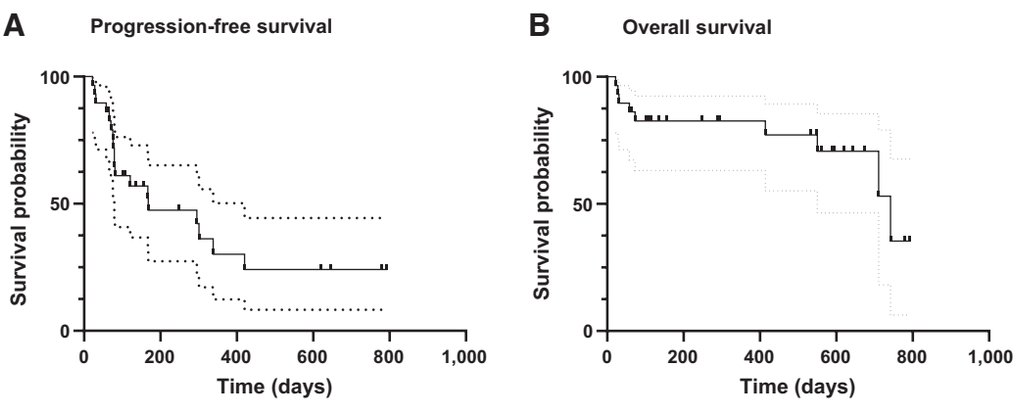

Figure 2.

Kaplan–Meier curve of (**A**) progression-free survival and (**B**) overall survival.

Table 2. Frequency of irAEs.

	Grade 1/2	Grade 3/4
Dermatologic (Rash, Pruritus)	8 (28%)	0 (0%)
Arthralgia/Arthritis	5 (17%)	0 (0%)
Endocrine		
Thyroiditis/Hypothyroidism	4 (14%)	
Hypophysitis	1 (3%)	
Diabetes mellitus		1 (3%)
Hepatitis	1 (3%)	4 (14%)
Enterocolitis/Diarrhea	3 (10%)	2 (7%)
Pancreatitis/Lipase increased	2 (7%)	2 (7%)
Pneumonitis	1 (3%)	0 (0%)
Myocarditis	0 (0%)	1 (3%)

addition, no unexpected patterns of immune-related toxicity were observed with autoimmune hepatitis being the most frequent high-grade irAE.

Our results confirm and complement the findings of the DART SWOG 1609 trial (19). In keeping with the findings of DART, we observed a higher response rate to combination immunotherapy with ipilimumab and nivolumab in patients with high-grade NENs. However, unlike DART, our study cohort also included patients with pancreatic NETs in which we observed a high response rate. This suggests that patients with high-grade pancreatic NENs can obtain substantial benefit from dual checkpoint blockade. An additional finding in our study has been that a significant percentage of atypical bronchial carcinoid tumors are responsive to combination immunotherapy.

The DART trial used a different treatment schedule with ongoing six weekly administrations of ipilimumab as opposed to an induction therapy of four administrations of combined treatment followed by single-agent nivolumab maintenance treatment used in our trial. Despite the different dosing schedules, the rate of high-grade immune toxicity was comparable in both trials with one third of patients developing severe irAEs.

Clinical evidence to guide treatment decisions in rare cancers is inevitably limited and tumor agnostic biomarkers are required to best select patients for treatment. PD-L1 expression on tumor cells and tumor mutational burden have shown to enrich for responses to anti–PD-1/PD-L1 therapy in several malignancies (20) and ongoing translational research will assess whether these, as well as other exploratory markers, are predictive for treatment response to anti–CTLA-4/PD-1 blockade in patients with advanced NETs.

Overall the clinical efficacy with combined CTLA-4/PD-1 blockade observed in our study and the DART trial compares favorably to the modest activity that has been seen in trials using single-agent anti–PD-1 or PD-L1 blockade in similar patient populations (10, 11). Therefore, combination immunotherapy should be further investigated in patients with high-grade NENs independent of primary tumor site and in patients with atypical bronchial carcinoid.

Disclosure of Potential Conflicts of Interest

O. Klein reports grants and non-financial support from Bristol-Myers Squibb and grants from the Federal Department of Health of Australia during the conduct of the study. D. Kee reports personal fees from Bristol-Myers Squibb (travel support and speaker fees) and personal fees from Novartis (advisory board fees) during the conduct of the study. B. Markman reports personal fees from Novartis and Amgen outside of the submitted work. C.R. Underhill reports grants from Border Medical Oncology Research Unit (funding for this study) during the conduct of the study. M.S. Carlino reports personal fees from MSD, Bristol-Myers Squibb, Novartis (consultant advisor and honoraria), Roche, Ideaya, Merck Serono, Sanofi, Nektar, and Eisai (consultant advisor) outside of the submitted work. C. L. Scott reports non-financial support from AstraZeneca and Roche Australia (non-reimbursed advisory boards and travel support); non-financial support from Takeda and MSD (non-reimbursed advisory board); and other support from Clovis Oncology and Beigene (in kind research support), Eisai Co (funded research support and non-reimbursed advisory board support), and Sierra Oncology (funded research support). A. Nagrial reports personal fees from Bristol-Myers Squibb, Merck Sharp Dohme, Roche, and AstraZeneca outside of the submitted work. A. Behren reports grants from Bristol-Myers Squibb and the Federal Department of Health during the conduct of this study. J. Palmer reports grants and non-financial support from Bristol-Myers Squibb (investigator sponsored clinical trial funding and drug supply) during the conduct of the study. J.S. Cebon reports grants from Bristol-Myers Squibb and the Australian Government Medical Research Future Fund (to institution for study costs including laboratory and project management expenses) and the Australian Government Medical Research Future Fund, and reports grants and personal fees from Bristol-Myers Squibb, Merck Sharp Dohme, Amgen (honoraria, trial support, advisory board fees all paid to institution), and Novartis (clinical trial costs, advisory board fees paid to institution) outside of the submitted work. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

O. Klein: Conceptualization, data curation, formal analysis, investigation, writing-original draft, writing-review and editing. **D. Kee:** Resources, formal analysis, investigation, writing-original draft, writing-review and editing. **B. Markman:** Resources, investigation, writing-original draft, writing-review and editing. **M. Michael:** Resources, investigation, writing-original draft, writing-review and editing. **C. Underhill:** Resources, investigation, writing-original draft, writing-review and editing. **M.S. Carlino:** Resources, investigation, writing-original draft, writing-review and editing. **L. Jackett:** Formal analysis, writing-review and editing. **C. Lum:** Resources, investigation, writing-review and editing. **C. Scott:** Resources, investigation, writing-review and editing. **A. Nagrial:** Resources, investigation, writing-review and editing. **A. Behren:** Formal analysis, investigation, writing-review and editing. **J.Y. So:** Resources, investigation, writing-review and editing. **J. Palmer:** Resources, data curation, writing-original draft, writing-review and editing. **J. Cebon:** Conceptualization, resources, supervision, investigation, writing-original draft, writing-review and editing.

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