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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Running Title: Combination immunotherapy in neuroendocrine tumors

Statement of 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 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 SWOG1609 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.

Abstract

Purpose

Combination immunotherapy with anti-CTLA-4 and anti-PD-1 blockade has demonstrated significant clinical activity across several tumour types. Neuroendocrine tumors (NETs) 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 multicentre clinical trial in patients with advanced rare cancers. Patients received treatment with nivolumab at a dose of 3mg/kg and ipilimumab at 1mg/kg every three weeks for four doses, followed by nivolumab 3mg/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 patients (10%) had low, 13 (45%) intermediate and 13 (45%) 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 (NENs) and 33% of patients with atypical bronchial carcinoid achieved an objective response. The median progression free survival was 4.8 months (95% CI: 2.7, 10.5) and overall

survival 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.

Trial registration: ClinicalTrials.gov registry: NCT02923934

Introduction

Neuroendocrine neoplasms constitute a heterogeneous group of rare tumors. Given the wide distribution of neuroendocrine cells throughout the body, NETs 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 histological grade and the site of tumour origin. Low and intermediate grade tumors are commonly treated with somatostatin analogues (2, 3) and receive targeted therapy with the mammalian target of rapamycin (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 PD-1 (programmed cell death protein 1)/PD-L1 (programmed death-ligand 1) axis and reinvigorate anti-tumour 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 neuroendocrine tumors; early trials suggesting a low level activity in patients treated with single agent therapy (10, 11). Immunotherapy using combined anti-PD-1 and anti-CTLA-4 (cytotoxic T-lymphocyte – associated protein 4) blockade has demonstrated increased efficacy compared to 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 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 2 study conducted at five Australia sites (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 Tumour (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 naive 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 tumour tissue, or a fresh tumour 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 the 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 enrolment into the study.

Treatment

Nivolumab and ipilimumab were administered intravenously at a dose of 3mg/kg over a period of 30 minutes and 1mg/kg over 90 minutes, respectively, every three weeks for four doses (induction phase), followed by nivolumab monotherapy at a dose of 3mg/kg every two weeks (maintenance phase) until disease progression, unacceptable toxicity or a maximum of two years after enrolment. Dose reductions were not permitted; however, study treatment could be interrupted to enable recovery from adverse reactions for up to six weeks. If treatment was discontinued patients were followed up until disease progression or initiation of a different treatment. Tumour assessments were performed by radiological assessment (computer tomography of brain, chest, abdomen, pelvis) at baseline and then every 12 weeks during treatment or follow up. A confirmatory scan was performed six 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 radiological 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 tumour 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 neuroendocrine tumors were enrolled into CA209-538 clinical trial (Supplementary Table 1). 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 tumour type. Ten patients (36%) had tumors with a gastroenteropancreatic origin including seven patients (25%) with a pancreatic primary. Three patients had low grade (10%), 13 (45%) intermediate and 13 (45%) 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. 21% of patients had previously received PRRT and all patients were immunotherapy-naïve, apart from one who received single agent anti-PD-1 therapy with pembrolizumab prior to enrolment.

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, five (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 (irAEs). Fifteen patients entered into the maintenance phase with fortnightly nivolumab infusions and two patients came off study for progressive disease at their first radiological assessment at week 12.

The objective response rate of the entire cohort was 24% (seven out of 29 patients) (Figure 1A). Fourteen patients had stable disease as their best radiological response

leading to a clinical benefit rate of 72%. Nine of the fourteen patients with stable disease had tumour 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 three (10%) patients had progressive disease at their first restaging scan. The median progression free and overall survival were 4.82 months (95% CI: 2.71,10.53) and 14.78 months (95% CI: 4.07,21.25) respectively (Figure 2). Objective responses were achieved in 31% and 23% of patients with high grade and intermediate grade tumors, respectively. Five out of seven responders had an intermediate or high grade NET and two a neuroendocrine carcinoma. In contrast no responses were seen in the four patients with low grade tumors (Supplementary Table 2). Three out of nine patients (33%) with atypical bronchial carcinoid achieved an objective response including two complete remissions. Responses are ongoing in all of these three patients (20+, 25+,26+ months) (Figure 1B). In addition, three out of seven patients (43%) with pancreatic NENs obtained a response; all three responders had high grade tumors, including two patients with grade 3 pancreatic neuroendocrine tumors (pNETs) and one patient with pancreatic neuroendocrine small cell carcinoma. One of the responding pNET patients had failed prior single agent anti-PD-1 therapy.

Safety

19 (66%) of 29 patients experienced immune–related adverse events (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 radiological changes to suggest pancreatitis. There were no treatment-related deaths.

Discussion

Neuroendocrine tumors 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 vascular endothelial growth factor 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 approximately12 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 recognised 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 based on morphology with treatment outcomes that differ (16). Our data set 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 enrols exclusively this patient population may shed further light on this.

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 is limited to the mTOR inhibitor everolimus alone (5) or in combination with somatostatin analogues leading to progression free survival benefits (14) (18). Objective responses with everolimus based treatments are very low (5). In contrast, three out of nine atypical bronchial carcinoid patients treated with combination immunotherapy in our trial obtained an objective response including two 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 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 neuroendocrine tumors 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 tumour agnostic biomarkers are required to best select patients for treatment. PD-L1 expression on tumour cells and tumour 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 if 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 favourably 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 tumour site and in patients with atypical bronchial carcinoid

Author's Contributions

Conception and design: O. Klein, J. Palmer, J. Cebon

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Figure Legends

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 tumour 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: NET, neuroendocrine tumour; NEC, neuroendocrine carcinoma; GOJ, gastro-oesophageal junction; LCNEC, large cell neuroendocrine carcinoma

Figure 2: Kaplan-Meier curve of overall survival and progression free survival

Gender	
Male	17 (59%)
Female	12 (41%)
Age (years)	57 (20-82)
ECOG Performance (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
Gastro-esophageal 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%)

Table 1: Patient demographics and disease characteristics
Abbreviations: NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma

	Grade 1/2	Grade 3/4
Dermatological (Rash, Pruritus)	8 (28%)	0 (0%)
Arthralgia/Arthritis	5 (17%)	0 (0%)
Endocrine Thyroiditis/Hypothyroidism Hypophysitis Diabetes mellitus	 4 (14%) 1 (3%)	 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%)

Table 2: Frequency of Immune related adverse events (irAEs)

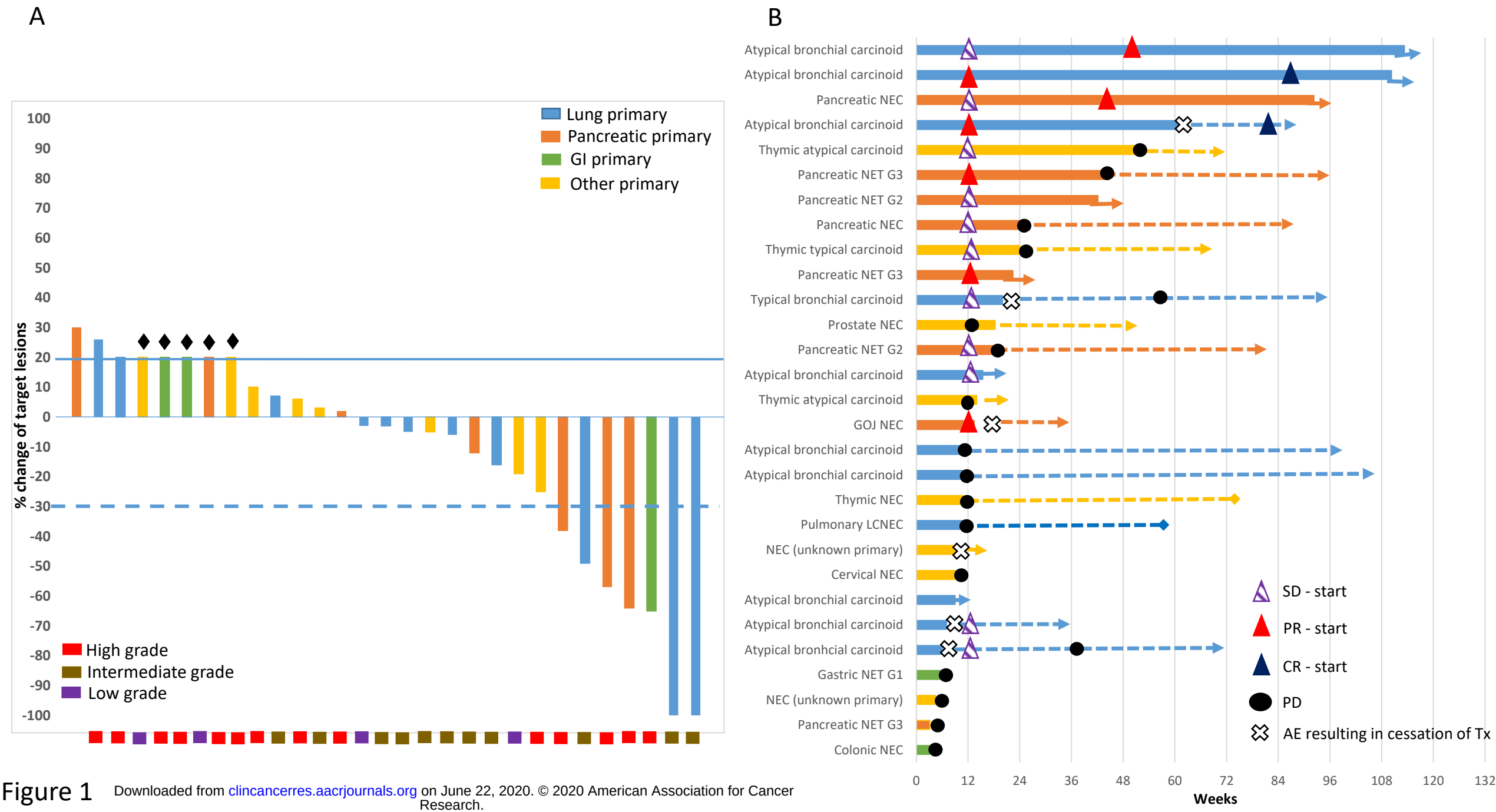
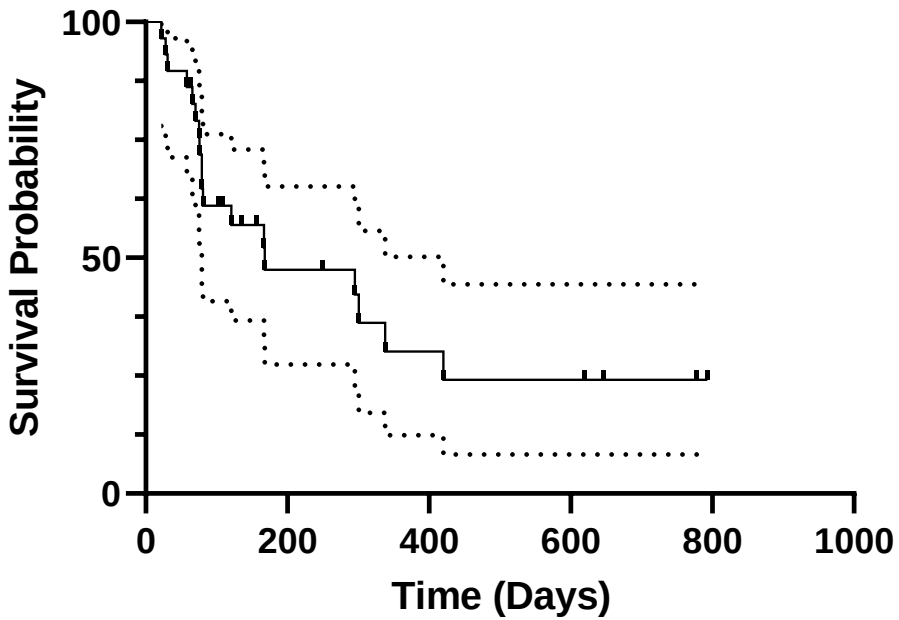


Figure 1

A Progression-free survival



B Overall survival

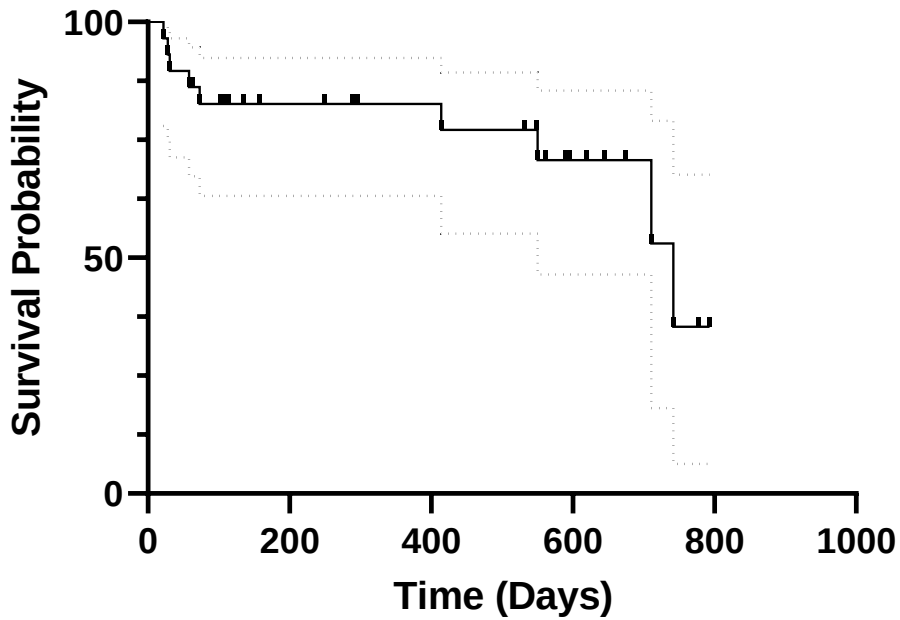


Figure 2

AACR American Association for Cancer Research

Clinical Cancer Research

Immunotherapy of Ipilimumab and Nivolumab in patients with advanced neuroendocrine tumours: a subgroup analysis of the CA209-538 clinical trial for rare cancers

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