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Safety monitoring of two and four-weekly adjuvant durvalumab for patients with stage III NSCLC: implications for the COVID-19 pandemic and beyond

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ABSTRACT

Durvalumab is the first approved adjuvant immunotherapy agent for patients with stage III NSCLC treated with concurrent chemoradiotherapy and is associated with improved overall survival. In order to minimise the number of hospital visits for patients receiving durvalumab during the COVID-19 pandemic we implemented 4-weekly (20 mg/kg) durvalumab in place of 2-weekly infusions at The Royal Marsden Hospital. We assessed the potential impact of the safety of a 4-weekly schedule in patients receiving adjuvant durvalumab. We carried out a retrospective study of 40 patients treated with 2-weekly and 4-weekly infusions of durvalumab prior to and during the COVID-19 pandemic. Clinical documentation was analysed from 216 consultations across 40 patients receiving 2-weekly durvalumab and 66 consultations of 14 patients who switched from 2-weekly to 4-weekly durvalumab during the COVID-19 pandemic. In patients receiving 2-weekly durvalumab, the rate of grade 3 and 4 toxicities was 15 % compared to 7% in patients receiving 4-weekly durvalumab. Pre-existing autoimmune disease was considered a risk factor for the development of grade 3 or 4 toxicities. We did not observe any difference in the rate of grade 1 and 2 toxicities between the two groups. Our findings support the use of 4-weekly durvalumab during the COVID-19 pandemic and beyond, obviating the need for 2-weekly face-to-face consultations and blood tests, relevant given the current pandemic and the need to re-structure cancer services to minimise patient hospital visits and exposure to SARS-CoV-2.

1. Background

Monoclonal antibodies (mAb) targeting the PD-1/PD-L1 axis are widely used in a number of solid cancers with manageable toxicities. Durvalumab, an anti-PD-L1 agent, is the first approved immunotherapy for patients with stage III NSCLC following concurrent chemoradiotherapy (CRT) and improves overall survival [1]. Durvalumab is administered as a two-weekly infusion for one year.

The dosing schedules of immune checkpoint monoclonal antibodies have been re-evaluated, with modification to a higher dose given less frequently not compromising clinical efficacy or safety [2].

Pharmacokinetic data from the PACIFIC trial (NCT02000947) [1] explored the steady state of the durvalumab at doses including the licensed dose of 10 mg/kg every 2 weeks and 20 mg/kg every 4 weeks during the dose-escalation and exploration phases. These regimens are supported by pharmacokinetic modelling based on two previous durvalumab early phase studies, ATLANTIC (NCT02087423) [3] and Study1108 (NCT169356) [4]. It was observed that the doses achieved a steady state along with saturation of both longitudinal markers of soluble and membrane-bound serum PD-L1 at similar rates. Other trials support to observation of similar safety and tolerability of 4-weekly and 2-weekly durvalumab [5,6]. Data from trials such as MYSTIC (NCT02453282) [7] and CASPIAN (NCT03043872) [8] studies that use 20 mg/kg in 4-weekly regimens are eagerly awaited.

Although trial pharmacokinetic data demonstrates the biological rationale for 4-weekly durvalumab dosing there are additional factors to

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consider in a "real life" patient population. For example, a reduced number of consultations may result in toxicities not being reported promptly which could compromise the medical management of low-grade toxicities, potentially leading to higher rates of grade 3/4 toxicity.

The World Health Organization (WHO) declared the coronavirus (COVID-19) outbreak a global pandemic on 11th March 2020 [9]. In order to minimise the number of hospital visits for patients receiving durvalumab, two urgent measures were instigated at our institution; (i) remote monitoring of patients via telephone consultations and (ii) commencement of 4-weekly (20 mg/kg) durvalumab in place of 2-weekly as approved by NICE (National Institute for Health and Care Excellence) in response to the COVID-19 pandemic [10]. The telephone consultations were structured in a similar fashion to face-to-face consultations and any medical concerns prompted a face-to-face review. Moreover, all patients undergoing durvalumab treatment were had access to a 24 hour Macmillan hotline managed by oncology trained nurses and doctors.

We assessed the potential impact of the safety measures instigated in response to the COVID-19 pandemic (i.e. a 4-weekly durvalumab with no 2-weekly consultations) postulating that 4-weekly safety monitoring and durvalumab administration would have similar rates of grade 3/4 toxicity as compared with 2-weekly durvalumab.

2. Methods

Data were obtained from the retrospective review of electronic patient records of 40 patients commencing standard 4-weekly durvalumab after concurrent CRT for stage III NSCLC at The Royal Marsden Hospital. All patients received treatment between November 2018 and March 2020, prior to the COVID-19 pandemic. We subsequently obtained data from all patients within this cohort who switched from 2-weekly to 4-weekly durvalumab during the COVID-19 pandemic. Documented adverse events were graded according to the CTCAE, version 5.0. Any adverse event (grade 1–4), including blood test abnormalities were recorded for each hospital visit. Local institutional approval for the study was obtained.

3. Results

A total of 40 patients, all with Stage III NSCLC (non-squamous 31/40, squamous 9/40), treated with concurrent CRT were included in this study. The clinical characteristics of these patients are summarised in Table 1. The median age of the patients included in the study was 68.5 years (range 37−83 years).

We analysed clinical documentation from 216 consultations across 40 patients receiving 2-weekly durvalumab. In addition, we analysed clinical documentation from 66 consultations from 14 out of 40 of these patients who switched from 2-weekly to 4-weekly durvalumab infusions during the COVID-19 pandemic.

The median number of consecutive consultations from which clinical documentation was analysed was 6 covering a period of 12 weeks and 5 consultations covering a period of 20 weeks for patients receiving 2-weekly and 4-weekly durvalumab respectively. This timeframe represents a snapshot in two time periods (before and during the COVID-19 pandemic) of the whole durvalumab treatment duration for any given patient. The median number of 2 or 4-weekly cycles received per patient at the time of the clinical documentation being reviewed was 15 (range 1–26) for patients receiving 2-weekly durvalumab and 3 (range 1–6) for patients receiving 4-weekly durvalumab during the COVID-19 pandemic.

In patients receiving 2-weekly durvalumab, a grade 3 or 4 toxicity was documented in a total of 6/40 patients (15 %; Table 2) (3/6 pneumonitis, 2/6 skin toxicity, 1/6 colitis) and durvalumab was discontinued in 5 out of 6 of these patients due to toxicity. In patients receiving 4-weekly durvalumab during the COVID-19 pandemic, a grade 3 or 4 toxicity was documented in 1/14 (7%) of patients (Table 2; myositis) with subsequent discontinuation of durvalumab.

Table 1
Clinical characteristics of patients included in the study.

Patients (N = 40)	
Age - median (range in years)	68.5 (37−83)
Sex - no (%)	
Male	22 (55)
Female	18 (45)
Disease stage	
IIIA	16 (40)
IIIB	12 (30)
IIIC	7 (17.5)
Other	IIA 2 (5), IIB 3(7.5)
WHO performance status - no (%)	
0	21 (52.5)
1	19 (47.5)
EGFR mutation status - no (%)	
Negative	35 (87.5)
Positive	1 (2.5)
Unknown	4 (10)
PD-L1 expression level - no (%)	
<25 %	16 (40)
>25 %	17 (42.5)
Unknown	7 (17.5)
Histology - no (%)	
Squamous	9 (22.5)
Non-squamous	31 (77.5)

WHO: world health organisation, EGFR: epidermal growth factor receptor, PD-L1: programmed death-ligand 1.

On review of the 7 patients (6 receiving 2-weekly durvalumab and 1 receiving 4-weekly durvalumab) who experienced grade 3 or 4 toxicities, they were noted to have pre-existing co-morbidities, with over half of these patients having pre-existing autoimmune conditions. The three patients that developed pneumonitis had pre-existing respiratory conditions (2 chronic obstructive pulmonary disease (COPD) and 1 radiation induced pneumonitis) and the two patients that developed autoimmune skin toxicities had a pre-existing diagnosis of psoriasis. Moreover, the patient that developed grade 3 myositis during 4-weekly durvalumab had a background of psoriatic arthritis requiring sulfasalazine treatment. Of note, none of the patients that experienced grade 1 or 2 toxicities had any pre-existing autoimmune conditions.

Of the 40 patients receiving 2-weekly durvalumab, a total of 28/40 (70 %) patients reported grade 1 and 2 durvalumab-related adverse events (Table 2) in 37/216 (17 %) of consultations. Of the 14/40 patients who went on to receive 4-weekly durvalumab during the COVID-19 pandemic, a total of 12/14 (85.7 %) patients reported grade 1 and 2 adverse events in (Table 2) 28/66 (42 %) of consultations.

In those patients receiving 2-weekly durvalumab 30/216 (13.9 %) consultations resulted in the prescription of a new drug or an alteration in the dose of a pre-existing medication including thyroxine (8), carbimazole (1), aciclovir (2), nystatin (5), itraconazole (2), steroids (5), antihistamines (3), analgesia (2), topical emollients (3) simple linctus (1). In those receiving 4-weekly durvalumab 16/66 (24 %) of consultations resulted in the prescription of a new drug or an alteration in the dose of a pre-existing medication including thyroxine (6), steroids (6), analgesia (7), oral antibiotics (4) and topical emollients (3).

4. Discussion

In this retrospective study of 40 patients with stage III NSCLC, treated with durvalumab, we analysed clinical documentation from 216 clinical consultations in patients receiving 2-weekly durvalumab and 66

Table 2
Adverse events related to durvalumab in the 2-weekly and 4-weekly patient cohorts.

Event Type	2-weekly durvalumab (n = 40 patients)		4-weekly durvalumab (n = 14 patients)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any event	88 (34 patients)	6 (6 patients)	48 (13 patients)	1 (1 patient)
Cough	9 (10 %)	0	1 (2%)	0
Pneumonitis	4 (4.5 %)	3 (3%)	3 (6%)	0
Fatigue	10 (11 %)	0	2 (4%)	0
Dyspnoea	8 (9%)	0	3 (6%)	0
Diarrhoea	1 (1%)	1 (1%)	0	0
Pyrexia	0	0	2 (4%)	0
Nausea	0	0	2 (4%)	0
Pneumonia	1 (1%)	0	1 (2%)	0
Arthralgia	3 (3%)	0	1 (2%)	0
Upper respiratory tract infection	1 (1%)	0	1 (2%)	0
Pruritus	3 (3%)	0	0	0
Rash	8 (9%)	2 (2%)	4 (8%)	0
Constipation	1 (1%)	0	1 (2%)	0
Backpain	3 (3%)	0	0	0
Musculoskeletal pain	4 (4.5 %)	0	1 (2%)	0
Anaemia	0	0	1 (2%)	0
Myositis	0	0	1 (2%)	1 (2%)
Peripheral sensory neuropathy	1 (1%)	0	1 (2%)	0
Limb oedema	1 (1%)	0	0	0
Dry skin	2 (2%)	0	3 (6%)	0
Dizziness	0	0	4 (8%)	0
Blurred vision	0	0	1 (2%)	0
Agitation (mood disturbance)	2 (2%)	0	0	0
Weight loss	1 (1%)	0	0	0
Abdominal pain	2 (2%)	0	0	0
Oropharyngeal pain	2 (2%)	0	1 (2%)	0
Oral thrush	4 (4.5 %)	0	0	0
Dry mouth	1 (1%)	0	0	0
Hypothyroidism	10 (11 %)	0	8 (17 %)	0
Hyperthyroidism	6 (7%)	0	1 (2%)	0
Hyperglycaemia	0	0	2 (4%)	0
Lymphopaenia	0	0	2 (4%)	0
ALT rise	0	0	1 (2%)	0

ALT: alanine aminotransferase.
40 patients were included in the 2-weekly cohort and 14 of these patients switched to 4-weekly treatment during the COVID-19 pandemic. Percentages refer to the % of each adverse event in relation to the total number of adverse events.

consultations from 14 patients who switched from 2-weekly to 4-weekly durvalumab. We observed that a significant grade 3 or 4 event occurred in 15 % of patients undergoing 2-weekly durvalumab and 7% in patients that switched from 2-weekly to 4-weekly durvalumab. Pre-existing comorbidities including autoimmune disease were considered risk factors for the development of grade 3/4 toxicities.

In contrast to the PACIFIC trial data in which 142/460 (30.9 %) adverse events were reported as grade 3/4, we report 6/88 (6.8 %) adverse events as grade 3/4 events in patients receiving 2-weekly durvalumab and 1/48 (2%) grade 3 or 4 adverse events in patients who switched from 2-weekly to 4-weekly durvalumab. The difference observed between the PACIFIC data and our data may be due differing adverse event reporting criteria and the limited number of clinic visits analysed in our cohort of patients, representing a snapshot in time of the whole durvalumab treatment journey. Given the above we conclude that 4-weekly durvalumab with 4-weekly monitoring is considered safe in our patient population, not resulting in toxicity levels above that predicted by the PACIFIC data.

Our findings provide preliminary support for the use of 4-weekly durvalumab beyond the COVID-19 pandemic, obviating the need for 2-weekly consultations and blood tests, relevant given the current pandemic and the need to re-structure cancer services to minimise patient hospital visits and exposure to SARS-CoV-2. Where possible, the use of 4-weekly durvalumab may be complemented with emergency telephone contact details that patients can access should they develop any new symptoms in between their 4-weekly clinic appointments. We also recommend tailoring an individual monitoring plan to the individual patient characteristics. Based on our data, patients with pre-existing autoimmune conditions may require closer monitoring during 4-weekly durvalumab treatment, for example 2-weekly mid cycle consultations.

Whilst the findings in our study provide initial support for the switch to 4-weekly durvalumab with telephone consultations for the safety monitoring of these patients, there are several limitations of the data presented. This study is limited by its small sample size and is based on findings obtained from a our institution only. Moreover, the findings are based on the retrospective analysis of medical records which relies on accurate documentation of the clinical consultation and interpretation of the events that took place based on the documentation reviewed. Furthermore, we have not explored the safety profile of patients that commenced de-novo 4-weekly durvalumab due to the limited number of these patients treated at our institution. Therefore, there may be a bias in the findings observed as the patients receiving 4-weekly durvalumab in our study were those that were tolerating 2-weekly durvalumab treatment prior to switching to 4-weekly treatment. Finally, it is important to note that patients may exhibit different behaviour during a pandemic and may be more or less likely to seek medical help due their underlying anxieties.

5. Conclusion

Given our findings, we have now transitioned to 4-weekly durvalumab infusions as permitted during the COVID-19 pandemic with 4-weekly telephone consultations and blood tests for the majority of patients. This obviates the need for a consultation and blood test at two weeks, thereby minimising the number of hospital visits for patients whilst still maintaining efficacy and minimising exposure to SARS-CoV-2. Not only is this likely to have a significant improvement in the cancer patient experience but important financial implications for health care providers that may form part of the financial recovery plan for the effect of the COVID-19 pandemic. Whilst we have focused on durvalumab in this study, it is plausible that the findings observed maybe relevant to other immune checkpoint inhibitors used in the context of metastatic NSCLC.

Contribution authors

Study concepts: KJ, AbM, AM, MoB.
Study design: KJ, AbM, AM, MoB.
Data acquisition: KJ, AbM, MO, CMW, NY, SP, MD, JB, AM, MoB.
Quality control of data and algorithms: Not applicable.
Data analysis and interpretation: KJ, AbM, MO, CMW, NY, SP, MD, JB, AM, MoB.
Statistical analysis: KJ, AbM, AM, MoB.
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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. M O'Brien sits on advisory boards for MSD, Abbvie, BMS, BI and Pierre Fabre. S Popat has received honoraria from BMS, Roche, Takeda, AstraZeneca, Pfizer, MSD, EMD Serono, Guardant Health, AbbVie, Boehringer Ingelheim, Medscape, Tesaro, Paradox, Incyte, OncLive and receives direct funding from Elsevier. S

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