

ORIGINAL ARTICLE

Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib

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Background: Concurrent programmed death-ligand-1 (PD-(L)1) plus osimertinib is associated with severe immune related adverse events (irAE) in epidermal growth factor receptor (*EGFR*)-mutant non-small-cell lung cancer (NSCLC). Now that PD-(L)1 inhibitors are routinely used as adjuvant and first-line treatments, sequential PD-(L)1 inhibition followed by osimertinib use may become more frequent and have unforeseen serious toxicity.

Methods: We identified patients with *EGFR*-mutant NSCLC who were treated with PD-(L)1 blockade and *EGFR*-tyrosine kinase inhibitors (TKIs), irrespective of drug or sequence of administration (total $n = 126$). Patient records were reviewed to identify severe (NCI-CTCAE v5.0 grades 3–4) toxicity.

Results: Fifteen percent [6 of 41, 95% confidence interval (CI) 7% to 29%] of all patients treated with sequential PD-(L)1 blockade followed later by osimertinib developed a severe irAE. Severe irAEs were most common among those who began osimertinib within 3 months of prior PD-(L)1 blockade (5 of 21, 24%, 95% CI 10% to 45%), as compared with >3–12 months (1 of 8, 13%, 95% CI 0% to 50%), >12 months (0 of 12, 0%, 95% CI 0% to 28%). By contrast, no severe irAEs were identified among patients treated with osimertinib followed by PD-(L)1 (0 of 29, 95% CI 0% to 14%) or PD-(L)1 followed by other *EGFR*-TKIs (afatinib or erlotinib, 0 of 27, 95% CI 0% to 15%). IrAEs occurred at a median onset of 20 days after osimertinib (range 14–167 days). All patients with irAEs required steroids and most required hospitalization.

Conclusion: PD-(L)1 blockade followed by osimertinib is associated with severe irAE and is most frequent among patients who recently received PD-(L)1 blockade. No irAEs were observed when osimertinib preceded PD-(L)1 blockade or when PD-(L)1 was followed by other *EGFR*-TKIs. This association appears to be specific to osimertinib, as no severe irAEs occurred with administration of other *EGFR*-TKIs.

Key words: *EGFR*, osimertinib, PD-1, irAE, TKI

Introduction

The treatment paradigm for advanced non-small-cell lung cancer is rapidly changing. Introduction of multiple new therapies concurrently into standard practice [1–4] can lead to clinical challenges related to optimal sequencing of therapies and unexpected overlapping toxicity [5]. Osimertinib, a third-generation

epidermal growth factor receptor tyrosine kinase inhibitor (*EGFR*-TKI), was recently approved as the front-line therapy for patients with metastatic *EGFR* mutant lung cancers [4]. At the same time, anti-programmed death-ligand-1 (PD-(L)1) antibodies have increasingly been incorporated into the routine care for nearly all patients with non-small-cell lung cancer (NSCLC). Pembrolizumab, an anti-PD-1 antibody, was recently approved

as the front-line therapy with or without chemotherapy in patients with metastatic NSCLC and durvalumab was approved following chemoradiotherapy for locally advanced, unresectable stage III NSCLC [1–3].

Despite ostensibly unrelated mechanisms of action, there is growing concern that the combination of PD-(L)1 and EGFR-TKIs may be associated with an increased risk of toxicity [6, 7]. A phase Ib clinical trial of concurrent durvalumab (anti-PD-L1) plus osimertinib (TATTON) was halted due to high rates of interstitial lung disease [6]. Additionally, a recent database analysis of patients who received nivolumab as well as any EGFR-TKIs during their treatment course was associated with increased risk of pneumonitis [7]. However, there are important remaining uncertainties, including differentiation of the relative risk of individual EGFR-TKIs, the importance of sequence and timing of anti-PD-(L)1 antibodies and EGFR-TKI, and characterizing the clinical course, severity, and management of adverse events that may occur.

Here, we examined all patients with *EGFR*-mutant lung cancers treated with PD-(L)1 and EGFR-TKIs at Memorial Sloan Kettering Cancer Center (MSKCC) to address critical questions regarding the relative risk of toxicity with sequential anti-PD-(L)1 antibodies and EGFR-TKIs.

Methods

All patients with *EGFR*-mutant lung cancer who were treated with PD-(L)1 inhibitors (pembrolizumab, nivolumab, atezolizumab, or durvalumab) and an EGFR-TKI between March 2011 and September 2018 were identified at MSKCC. Patients treated with concurrent therapy ($n=25$) were excluded as these were largely patients treated in yet unpublished clinical trials. Each individual sequential EGFR-TKI and PD-(L)1 event was treated separately in patients who received multiple EGFR-TKIs.

Patients' medical and pharmacy records were reviewed to extract demographic and clinical data, as well as the specific drugs received. Clinical notes, radiology reports, and hospitalization records were reviewed during PD-(L)1 and EGFR-TKI treatment to identify severe (grades 3–5) immune-related toxicities. Events were considered a bona fide immune-related adverse event (irAE) if documented as immune-mediated in real time by the primary oncologist involved in the care of the patient and supported by radiologic and/or pathologic evidence. Adverse events that were possibly immune-mediated but had alternative or mixed etiologies were termed 'indeterminate irAEs' and considered separately. The NCI Common Terminology Criteria for Adverse Events Version 5 (NCI-CTCAE) was used to grade toxicities.

The duration of treatment of PD-(L)1 blockade and EGFR-TKI was measured from the time of drug initiation to discontinuation of drug or censored at the date of last follow-up for patients remaining on drug at the time of data analysis. Data were updated until patient death or data lock on 15 September 2018. This study was approved by the Institutional Review Board at MSKCC.

Patient characteristics and toxicity were analyzed according to the sequence and timing of PD-(L)1 and EGFR-TKI, as well as based on the specific EGFR-TKI received.

Results

We identified 126 patients with advanced *EGFR*-mutant NSCLC treated with PD-(L)1 blockade and EGFR-TKI between March 2011 and September 2018 at MSKCC, inclusive of 180 distinct sequential drug exposures. Seventy-four (59%) patients received

nivolumab, 27 (21%) pembrolizumab, 17 (14%) atezolizumab, and 8 (6%) durvalumab. Among our cohort, during their disease course, 104 (83%) received erlotinib, 58 patients (46%) received osimertinib, 23 (18%) received afatinib, and 2 (2%) received gefitinib.

Severe irAEs with PD-(L)1 inhibitors and osimertinib

Forty-one patients were treated with sequential PD-(L)1 blockade followed by osimertinib and 29 patients were treated with sequential osimertinib followed by PD-(L)1 (inclusive of 9 patients who received osimertinib both before and after PD-(L)1 inhibition, who were counted in both groups due to distinct sequences of exposure and periods of irAE assessment). The clinical characteristics of these patients were typical of patients with metastatic *EGFR*-mutant NSCLC (Table 1).

Six of 41 [15%, 95% confidence interval (CI) 7% to 29%] patients treated with PD-(L)1 blockade followed by osimertinib experienced severe irAEs. By contrast, 0 of 29 (0%, 95% CI 0% to 14%) patients treated with osimertinib followed by PD-(L)1 blockade experienced an irAE. There were not evident clinical differences between those who received PD-(L)1 followed by osimertinib or the reverse sequence (Table 1). Among those who developed irAEs (Figure 1), half (3 of 6) received PD-(L)1 therapy in the first-line metastatic setting and EGFR-TKI immediately followed PD-(L)1 therapy (5 of 6). In all cases, there was no history of autoimmune disease or irAEs during the preceding PD-(L)1 blockade therapy to increase subsequent risk of toxicity. Pneumonitis with EGFR-TKIs has been previously observed to be more common in Asian populations [7]. Two of six patients with irAE identified as Asian and four identified as Caucasian.

Severe irAEs occurring in patients treated with sequential PD-(L)1 blockade followed by osimertinib included four cases of grade 3 pneumonitis, one cases of grade 3 colitis, and one case of grade 4 hepatitis (Figure 1). Five out of six patients required hospitalization. The four patients with pneumonitis responded to high-dose steroids with resolution of symptoms over weeks to months. The patient with colitis (patient #4) required long-term steroids as well as two doses of infliximab, although continuing osimertinib treatment throughout most of this course; the colitis eventually resolved despite continued osimertinib. The patient with hepatitis (patient #6) required cellcept in addition to high-dose steroids to treat ongoing grade 4 liver function abnormalities.

This patient was restarted on full-dose osimertinib 18 days after resolution of hepatitis and had recurrent grade 3 hepatitis 12 days later, at which time osimertinib was stopped and transaminitis resolved. Two other patients restarted full-dose osimertinib 70 and 79 days after resolution of the initial irAE and neither have had recurrent toxicity. Additionally, the two patients who received other TKIs (erlotinib and afatinib) after osimertinib was discontinued have not experienced exacerbated or recurrent irAEs.

In addition to these bona fide irAEs, there were four additional patients with indeterminate irAEs. Each was hospitalized within weeks of starting osimertinib for shortness of breath and treated with an empiric combination of steroids and antibiotics and improved. It could not be determined whether these events represented true irAEs or a mix of etiologies. Although these events

Table 1. Clinical characteristics of patients who received sequential programmed death-ligand-1 (PD-(L)1) blockade followed by osimertinib and osimertinib followed by PD-(L)1 blockade

Characteristic	PD-(L)1 then osimertinib (N = 41)	Osimertinib then PD-(L)1 (N = 29)
Age, years	61 (30–79)	56 (36–85)
Sex		
Male	14 (34)	5 (17)
Female	27 (66)	24 (83)
Race		
White	25 (61)	23 (80)
Asian	9 (22)	5 (17)
Other	7 (17)	1 (3)
PD-(L)1		
Nivolumab	24 (59)	16 (55)
Pembrolizumab	9 (22)	10 (35)
Atezolizumab	8 (19)	3 (10)
Durvalumab	0 (0)	0 (0)
Time on PD-(L)1, days	69 (14–789)	42 (11–189)
Time between PD-(L)1 and osimertinib, days	61 (12–1446)	5 (1–256)
Time on osimertinib, days	167 (15–927)	119 (30–707)
Severe immune-related adverse event	6 (15)	0 (0)

The demographics, treatment sequence and interval, and toxicity for the patients who received PD-(L)1 and osimertinib is shown.

were of indeterminate origin and we have not included them in the primary count of irAEs in this cohort, it is possible that the true rate of irAEs with sequential PD-L1 followed by osimertinib is higher than reported here.

Temporal associations with severe irAEs

The onset of irAE typically occurred within the first few weeks after beginning osimertinib, except in one case (median 20 days, range 14–167). Toxicity occurred irrespective of duration of PD-(L)1 blockade, with two patients who received only one dose of PD-1/PD-L1 blockade followed by osimertinib with subsequent grade 3 pneumonitis.

In the majority of cases with irAEs, the time interval from last dose of PD-(L)1 and start of osimertinib was short (median 23 days, range 17–299) (Figure 2). irAEs were most common among those whose last dose of PD-(L)1 blockade was within 3 months of beginning osimertinib, 5 of 21 (24%, 95% CI 10% to 45%) within 3 months, 1 of 8 (13%, 95% CI 0% to 50%) within 3–12 months, 0 of 12 (0%, 95% CI 0% to 28%) >12 months) (Figure 2). Although severe irAEs may still occur with several months latency between PD-1 blockade and beginning osimertinib, none of the patients with greater than 1-year interval between last dose of PD-(L)1 therapy and start of osimertinib developed severe irAE on osimertinib.

Severe irAEs with PD-(L)1 inhibitors and first-/second-generation EGFR-TKIs

We also examined the potential association between PD-(L)1 inhibitors and the first- and second-generation EGFR-TKIs. Of the patients who received erlotinib after PD-(L)1 inhibitors

($n = 20$), none developed severe irAEs while on erlotinib (median time interval from between last dose of PD-(L)1 and start of erlotinib 19 days, range 4–186). Notably, one patient who had previously had stopped durvalumab and tremelimumab due to grade 3 colitis tolerated erlotinib treatment 3 months later without new or recurrent immune-related toxicity. No patients who received afatinib after PD-(L)1 inhibitors ($n = 7$) had serious irAEs (median time interval from between last dose of PD-(L)1 and start of afatinib 57 days, range 8–468). No patients received gefitinib after PD-(L)1 inhibitors at our institution.

Discussion

We found that the sequential use of PD-(L)1 blockade and osimertinib is associated with severe irAEs (pneumonitis and colitis). Importantly, this appears to be a drug-specific, rather than class-specific, interaction between osimertinib and PD-1 blockade that is responsible for the severe irAEs seen. The toxicity appears temporally associated with last dose of PD-(L)1 blockade and generally appears within weeks of starting osimertinib. Awareness of this potential interaction is needed to minimize inadvertent toxicity and to determine strategies to optimally select and sequence available therapies for patients with advanced lung cancers.

With the increasing breadth of treatment options for patients with newly diagnosed NSCLC, the optimal approach for the front-line therapy and how to integrate routine molecular testing requires thoughtful consideration. In cases where molecular results are not immediately available at initial visit with an oncologist, it may be tempting to begin PD-(L)1 blockade with or without chemotherapy [2, 3] while awaiting results, with the plan

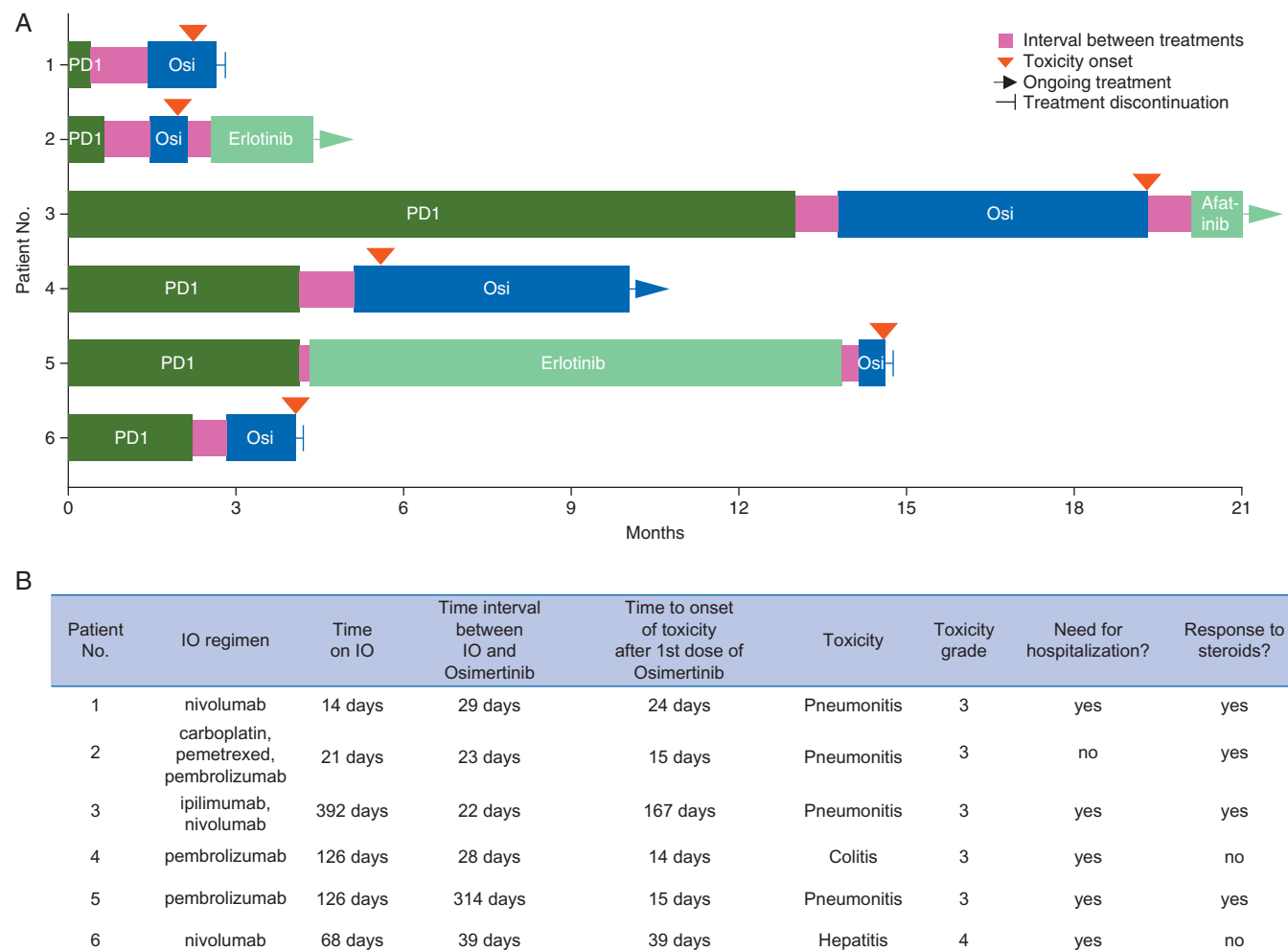


Figure 1. Sequential programmed death-ligand-1 (PD-(L)1) blockade and osimertinib schema of patients who developed severe immune-related adverse events. (A) Flow diagram of clinical course of six patients treated with PD-1 inhibitors followed by osimertinib who developed severe immune-related adverse events. Patient 1, 3, and 6 received other lines of therapy before PD-(L)1 blockade. (B) Patients who developed severe immune-related adverse events. osi, osimertinib; PD1, PD-(L)1 inhibitor; IO, immunotherapy.

to switch to osimertinib if an *EGFR* mutation is found for patients with metastatic disease. In locally advanced, unresectable stage III disease, all patients with NSCLC may receive durvalumab as standard practice [1], irrespective of *EGFR* status. These approaches may have important consequences on the safety of future use of osimertinib in patients with *EGFR*-mutant NSCLC. If osimertinib is subsequently prescribed, patients should be monitored closely for irAEs, especially if there has been <3-month interval since last PD-L1 blockade.

Our experience is consistent with prior reports of combining PD-(L)1 inhibitors and EGFR-TKIs. Reported in abstract form, TATTON (concurrent durvalumab plus osimertinib) revealed 38% (13/34) and 15% (5/34) of patients treated with the combination experienced any grade and grade 3–4 interstitial lung disease, respectively [6]. This rate of severe irAEs mirrors the rate we found. As is common in patients with lung cancer, there were additional indeterminant pulmonary events in our report that could not be definitively adjudicated as an irAE, such that the actual rate of severe irAEs may be higher than reported here. In any case, the incidence was much higher than prior experiences with osimertinib (4% [4]) or PD-(L)1 inhibitors (3% [8]) alone, and

as a result enrollment was halted in this and other similar studies. The toxicity described in our report demonstrates it is not only concurrent therapy with PD-(L)1 blockade and osimertinib that warrants caution. In addition, awareness that toxicity is not limited to pneumonitis and may impact other organs is needed.

A recent analysis of Food and Drug Administration Adverse Event Reporting System database found the use of nivolumab and EGFR-TKIs associated with pneumonitis (25%, 18/70) [7], primarily in Japanese patients. Our experience in contrast suggests that this association may be specifically related to sequential use of any PD-(L)1 inhibitors and osimertinib and is not evidently associated with patients of a specific race. Recent studies of erlotinib plus atezolizumab and erlotinib plus nivolumab did not demonstrate excess toxicity or pneumonitis with PD-(L)1 inhibitor + erlotinib combination [9, 10]. Consistent with these other studies, we found no grade 3 or 4 toxicity with sequential PD-(L)1 blockade followed by erlotinib.

The specific sequence and timing of therapy is an important determinant of risk of irAEs due to the prolonged receptor occupancy of anti-PD-(L)1 antibodies (lasting months [11]). By contrast, the half-life of osimertinib is relatively short ($T_{1/2}$ 55 hours

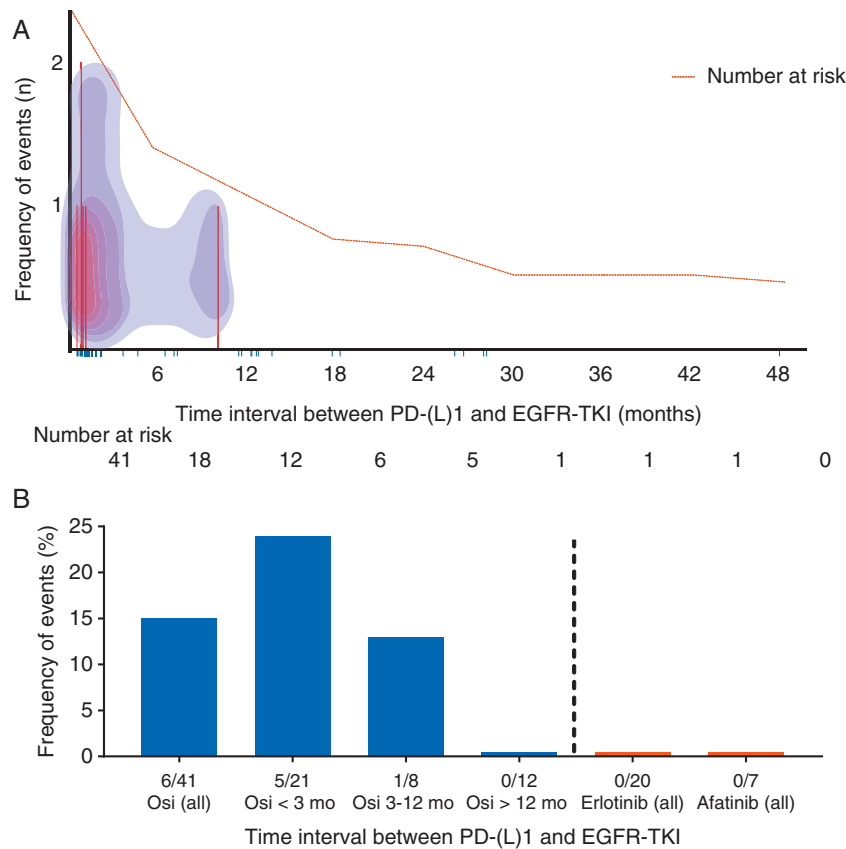


Figure 2. Temporal association heatmap and bar diagram of programmed death-ligand-1 (PD-(L)1) blockade and osimertinib. (A) Frequency of severe immune-related adverse events on osimertinib over time interval since last dose of PD-(L)1 inhibitor. Heatmap is displayed with red color shade (online) signifying highest density of events (white color signifies no events). Dashed blue lines (online) under x-axis signify patient end of treatment without experiencing severe immune-related adverse events and red dashed lines (online) above x-axis represent events. Number of patients at risk of severe immune-related adverse events are list below x-axis at 6-month intervals and represented by black dotted line on figure. (B) Frequency of severe immune-related adverse events by epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) since last dose of PD-(L)1 inhibitor.

[12]) such that initial osimertinib followed later by subsequent anti-PD-(L)1 would not be expected to have substantial overlapping exposure. Indeed, we have not observed evident toxicity in patients treated with osimertinib followed by anti-PD-(L)1 therapy and we did not observe toxicity after a 1-year interval between PD-(L)1 anti-PD-(L)1 therapy and osimertinib. Receptor occupancy of anti-PD-(L)1 antibodies may also vary among patients [11], which may account for why we did observe one late irAE (>6 months after last PD-(L)1).

The mechanisms to explain the synergistic toxicity of these ostensibly distinct therapies are not clear and warrant future investigation. Recently, EGFR-TKIs were shown to differentially enhance T-cell-mediated killing of tumor cells by increasing both basal and IFN gamma induced MHC class-I presentation [13]. Thus, it is possible that osimertinib has underappreciated immunomodulatory effects.

Our analysis has several limitations. The conclusions we can draw from our findings are limited as a retrospective, single-center study although the determination of irAEs relied upon prospective, real-time determination by the treating clinician. Although this is the largest cohort of sequential PD-(L)1 and

EGFR-TKIs to be reported, our sample size was modest. The clinical relevance of the findings has prompted us to report these findings now to facilitate expeditious community awareness, but larger studies will be needed to more definitively determine the incidence of irAEs, verify the relative risk of individual EGFR-TKIs, and determine the incidence of more minor irAEs. In particular, additional data will be needed to clarify the relative risk of afatinib and gefitinib following PD-(L)1 blockade and if there is differential incidence among ethnic populations. Finally, some toxicity of other patients may have been attributed to other causes such as infection or progression of disease, which may underestimate the reported immune-related toxicity and are inherent limitations of retrospective analyses. This may in part be related to the lack of awareness of the potential side effects of this combination, which we are eager to improve.

Our report highlights the need for thoughtful consideration when selecting initial treatment in patients with NSCLC. We suggest caution when considering the use of osimertinib in a patient recently treated with PD(L)-1 blockade. Providers should be aware of the high frequency of irAEs in this clinical setting, which is not limited to pneumonitis. These toxicities appear to emerge

quickly after osimertinib initiation and need to be immediately recognized in order to be treated appropriately. If sequencing from PD-(L)1 inhibition to EGFR-TKI therapy within a short time interval, patients should be monitored closely and the use of erlotinib may be a potential alternative. There could be a role for testing receptor occupancy of anti-PD-(L)1 antibodies to determine when it may be safe to initiate EGFR-TKI. Further investigation into the mechanism of toxicity and the relevant clinical circumstances will be necessary to better guide our patient care.

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