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Original Research

Delayed immune-related adverse events in assessment for dose-limiting toxicity in early phase immunotherapy trials

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Abstract ***Background:*** Immunotherapy (IO) agents can cause late-onset immune-related adverse events (irAEs). In phase I trials, observation for dose-limiting toxicities (DLTs) is typically limited to the first cycle. The incidence of delayed-onset DLTs and their potential impact on dose determination have not been fully elucidated.

Patients and methods: Consecutive patients enrolled in early phase IO trials at Princess Margaret Cancer Centre between August 2012 and September 2016 were retrospectively reviewed, applying trial-specific definitions for DLTs. A clinically significant AE (csAE) was defined as a treatment-related adverse event requiring corticosteroids, hormone replacement, IO delay or discontinuation.

Results: A total of 352 consecutive trial enrolments in 21 early phase clinical trials were included. Two-hundred seventy-eight patients (79%) received monotherapy and 74 (21%) received combination IO. Two hundred sixty (74%) patients experienced irAEs. There were two protocol-defined DLTs. Twenty (5.7%) patients had 24 csAEs qualifying as DLTs except for occurrence after the protocol-specified DLT period. One-hundred and six (10%) of irAEs were csAEs, including endocrine (26%), respiratory (14%), gastrointestinal (11%), general (10%), dermatological (8%), hepatic (8%), musculoskeletal (6%), pancreatic (6%),

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haematological, metabolic, neurological, cardiac (each 2%), infective and ocular (each 1%) events. The highest risk of first-onset csAE was during the first 4 weeks compared with the period from 4 weeks to end of treatment (odds ratio 3.13, 95% confidence interval 1.95–5.02). The median time to first onset csAE was significantly shorter with combination than monotherapy IO (32 vs. 146 days, $P < 0.001$).

Conclusions: In our series of early phase IO trials, the risk of csAE was highest during the initial 4 weeks on IO treatment, supporting the use of the conventional DLT period for dose escalation decision. However, there were 24 clinically significant late-onset DLTs in 5.7% of patients. Combination IO was associated with greater risk of and also earlier onset for csAE, which may need to be considered for early phase trial design.

1. Background

Immunotherapy (IO) agents are associated with a unique spectrum of toxicities, including the potential for late-onset immune-related adverse events (irAEs). Unlike traditional cytotoxic chemotherapy agents that cause toxicities in rapidly proliferating tissues such as the bone marrow and gastrointestinal tract, or molecularly targeted agents (MTAs) that produce toxicities in organs based upon expression of the target, IO agents can result in irAEs that affect any organ system [1,2]. Typically, these irAEs are managed with corticosteroids with or without additional immunosuppressive agents such as infliximab and mycophenolate.

The timing of irAEs are variable and may occur weeks to months post-IO [2]. This was initially described with an anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody ipilimumab, with dermatological toxicities observed at approximately 2–3 weeks, gastrointestinal and hepatic toxicities at 6–7 weeks, and endocrinologic events 9 weeks after treatment initiation [2]. The concurrent use of ipilimumab with the anti-programmed death 1 (PD-1) antibodies nivolumab [3–5] and pembrolizumab [6] resulted in higher rates of irAEs than seen with anti-PD1 monotherapy. New IO agents are increasingly being studied in combination that may heighten the risk of irAEs and influence the time course of these toxicities. Although patients are followed for late toxicities, there are few published reports of DLT-like events that occur after the DLT observation period from phase I IO trials [7, 8].

To identify the recommended phase II dose (RP2D) and schedule, early phase trials progressively increase drug dose levels after a pre-defined period of observation for dose-limiting toxicities (DLTs), that is, typically the first 3–4 weeks after initial dosing. This paradigm is based upon the evaluation of cytotoxic agents, where toxicities usually occur early and in a cyclical pattern. However, later onset toxicities occur with MTAs and IO agents that may be relevant to RP2D determination. For example, an analysis of phase I studies of MTAs found a similar proportion of grade (G) 3 or greater toxicities occurring during and after the first cycle of treatment [8]. Our aim was to examine for the occurrence of late-onset DLTs (otherwise DLT qualifying events occurring after the protocol-defined DLT period) and model the timing of clinically significant AE (csAEs) to explore optimal cut-offs for a DLT observation period in early phase IO trials.

2. Methods

2.1. Patients and treatment

We retrospectively reviewed consecutive patients at Princess Margaret Cancer Centre treated in early phase IO trials between August 2016 and September 2016. The trials examined immune checkpoint inhibitors, costimulatory molecules and agents affecting the tumour immune microenvironment, but we did not include patients treated on adoptive cell therapy or with oncolytic viruses. The data cut-off was 1 May 2017. This project was carried out as part of the Princess Margaret Cancer Centre Tumor Immunotherapy Program approved by a local institutional Research Ethics Committee (15–9269.6).

2.2. Adverse events

Toxicity assessment was performed by study investigators and sourced from electronic patient records. irAEs were toxicities considered by investigators to be related to study treatment with potential immunologic basis. Severity (Common Terminology Criteria for Adverse Events version 4.0 [CTCAE v4.0]), management, timing of onset and resolution of all-grade (G) irAEs were reviewed. We assessed for protocol-specific DLT events and their occurrence during or following protocol-specific DLT periods. csAE was defined as an irAE that required systemic therapy, led to drug delay or discontinuation.

2.3. Statistical analysis

A generalised estimating equation (GEE) model assessed the association between time on treatment and occurrence of first-onset csAE, adjusted for different treatment durations amongst patients. Using this model, the odds ratios (OR) for csAE occurrence at various time points (4, 6, 8 and 12 weeks) were determined. Logistic regression was used to assess for predictors of csAE; the variables tested were age (continuous variable), Eastern Cooperative Oncology Group (ECOG) performance status (PS; 0 or 1), number of prior systemic therapy (0, 1, 2 or 3+), prior IO (yes or no) and time on current IO (continuous variable). The analysis was repeated using a Cox regression model to consider the time to csAE. Significance was determined at the 0.05 level on univariate and multivariate analyses. In all above analyses where an irAE was recurrent, the earliest onset event was considered. Where an irAE occurred at different severities in the same patient within the one trial, the most severe event was considered. Patient demographics, treatment duration and outcome were recorded.

3. Results

3.1. Study population

There were 352 trial enrolments (two patients were each enrolled on two studies sequentially) where patients received at least one dose of IO across 21 early phase clinical trials (Table 1). Of these, 278 patients (79%) received monotherapy IO, while 74 (21%) were treated with IO-based combination. The class of IO treatment given predominantly consisted of immune checkpoint inhibitor, followed by agonistic antibody to co-stimulatory molecules. Specifically, 246 (70%) had anti-PD1, 84 (24%) anti-PD-L1 and 19 (5%) had anti-CTLA-4 either as monotherapy or in combination with another IO. Patients had a median age of 60 years (range 21–89 years), and 188 (53%) were female. All had ECOG PS of 0 (32%) or 1 (68%). The most common tumour types were melanoma (17%), head and neck (15%) and lung (14%) cancer. The median time on therapy was 13.3 weeks, with a range of 1–189 weeks. The majority (86%) of patients were IO naïve, and the median prior lines of therapy was 2. The median time on IO was 13.3 weeks, with 20 patients (6%) remaining on treatment at the time of data cut-off. The most common reason for cessation of therapy was progressive disease (81%). A total of 23 patients (7%) stopped because of treatment-related toxicity and/or other safety concerns, while 16 patients (5%) achieved a complete response and stopped treatment.

Table 1
Patient demographics.

Characteristic	Number of patients
Age, median (range) in years	60 (21–89)
Gender, n (%)	
Male	164 (47)
Female	188 (53)
ECOG performance status, n (%)	
0	112 (32)
1	240 (68)
Tumour type, *n* (%)	
Melanoma	61 (17)
Cutaneous	51 (14)
Mucosal	3 (1)
Ocular	7 (2)
Head and neck	54 (15)
Lung	50 (14)
Urological	39 (11)
Gynaecological	39 (11)
Gastrointestinal	30 (9)
Sarcoma	24 (7)
Colorectal	23 (7)
Breast	17 (5)
Endocrine	13 (4)
Central nervous system	1 (<1)
Prior lines of therapy, n (%)	
0	55 (16)
1	110 (31)
2	96 (27)
≥3	91 (26)
Prior immunotherapy, n (%)	
Yes	51 (14)
No	301 (86)
IO, n (%)	
Single-agent IO	278 (79)
Costimulatory molecules	31 (9)
Checkpoint inhibitor	247 (70)
Combination IO	74 (21)
Checkpoint inhibitor + checkpoint inhibitor	37 (10)
Checkpoint inhibitor + costimulatory molecule	30 (9)
Checkpoint inhibitor + tumour microenvironment modulator[a]	7 (2)
Time on treatment, median (range) in weeks	13.3 (1–189)
Patient outcome, n (%)	
Ongoing treatment	20 (6)
Cessation of therapy	
Progressive disease	286 (81)
Completed therapy/complete response	16 (5)
Toxicity	21 (6)
Other safety concerns	2 (1)
Withdrew consent/unknown	7 (2)
Total	352

IO, immunotherapy.
[a] Indoleamine 2,3-dioxygenase inhibitor, colony-stimulating factor 1 receptor inhibitor, performance status.

3.2. Occurrence of irAEs

A total of 260 (74%) patients had at least one irAE. In total, there were 1042 irAEs; 693 (67%) G1, 286 (27%) G2, 58 (6%) G3 and 5 (0.5%) G4 irAEs (Supplementary Table S1). G4 events included neutropenia (deemed possibly IO-related in the absence of recent chemotherapy exposure or other alternate explanations), hypophosphatemia, hyponatremia and two cases of lipase elevation without clinical pancreatitis. The G4 neutropenia occurred in an IO-naïve non–small cell

lung cancer patient who received monotherapy anti-PD1 antibody. The event occurred 63 days (9 weeks) post IO commencement. The patient stopped IO, and the neutropenia resolved without intervention. The G4 hypophosphatemia occurred in an IO-naïve pancreatic cancer patient 15 days 'post the first dose' of combination anti-PD1 with an investigational immune modulatory agent. The event qualified as a DLT. One case of G4 lipase elevation occurred in an IO-naïve renal cell carcinoma patient treated with combination anti-PD1 and anti-CTLA 4. The event occurred 109 days post-IO initiation and was treated with prednisone. Another case of G4 lipase elevation occurred 26 days post-monotherapy anti-PD1 antibody in an IO-naive high-grade serous ovarian cancer and was also managed with corticosteroids. The types of all-grade irAE in decreasing frequency were gastrointestinal (25%), general (including fatigue, infusion reaction and oedema, 18%), dermatological (15%), musculoskeletal (10%), respiratory (7%), endocrine (5%), hepatic (4%), ocular and pancreatic (each <2%), cardiac, infection, investigations, renal, reproductive and vascular (each <1%; Supplementary Table S1).

3.3. Occurrence and timing of csAEs

Of 1042 irAEs, 106 irAEs (10%) were classified as csAEs because of requirement for systemic therapy such as corticosteroids or hormonal replacement, with or without resultant delay or cessation of IO (Supplementary Table S1). Most csAEs were G2 (54%) or G3 (39%) events. Categories of csAE in decreasing frequency were endocrine (26%), respiratory (14%), GI (11%), general (10%), dermatological (8%), hepatic (8%), musculoskeletal (6%), pancreatic (6%), haematological, metabolic, neurological, cardiac (each 2%), infective and ocular (each 1%) events. On average, hepatic and GI csAEs occurred early (within the first 8 weeks on treatment). In contrast, respiratory, dermatological, musculoskeletal and endocrine events have onset between 11 and 14 weeks into treatment (Supplementary Figure S1). Nearly half of all csAE events (46%) occurred within the first 8 weeks of therapy, while the remainder of events occurred over a span of 146 weeks. The latest onset csAE was pericarditis at 146 weeks.

3.4. Risk of csAE over time

The risk of csAE occurrence over the time course of treatment was analysed, adjusted for the decreasing number of patients receiving ongoing IO therapy over time (Fig. 1). The OR for csAE occurrence within the first 4 weeks compared with after 4 weeks was 3.13 (95% confidence interval [CI] 1.95–5.02). To simulate different potential DLT assessment windows, cut-offs of 6, 8 and 12 weeks were applied, giving the ORs for csAE occurrence of 2.72 (95% CI 1.73–4.28), 2.56 (95% CI 1.63–4.01) and 2.80 (95% CI 1.76–4.44), respectively. The median time to first-onset csAE was significantly shorter amongst patients receiving combination compared with single-agent IO (32 vs. 146 days, $P < 0.0001$).

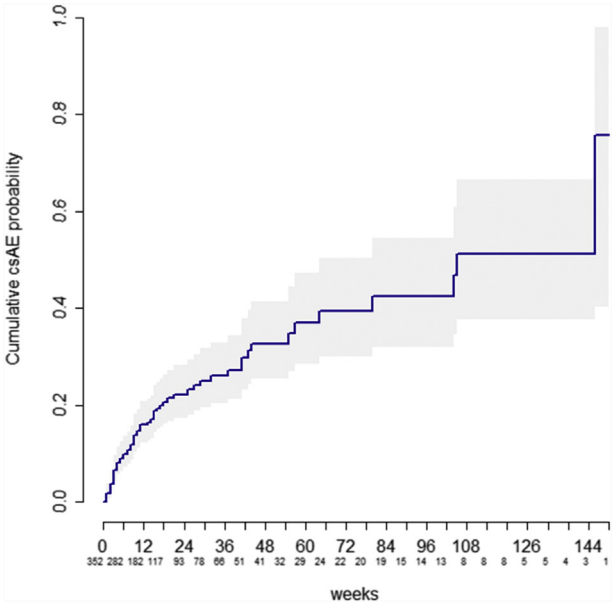

Fig. 1. Risk of clinically significant adverse event (csAE) over time on immunotherapy, Kaplan–Meier failure function curve for csAE occurrence with increasing time on treatment.

3.5. Occurrence and timing of DLTs

Two irAEs fulfilled protocol-defined DLT criteria (G4 hypophosphatemia and G3 hepatitis). Of the 106 csAEs, there were 24 csAEs (23%), which fulfilled DLT criteria but occurred outside the DLT period (Table 2). Twenty patients (5.7% of trial enrolments) experienced delayed-onset DLTs. These events included were five episodes of G3 dermatological toxicity (four cases of rash and one case of eosinophilic fasciitis), four cases of G3 colitis or diarrhoea, four cases of G3 pneumonitis, two cases of G3 hepatitis (aspartate transaminase and/or alanine aminotransferase rise), two cases of haematological toxicities (G3 anaemia and G4 neutropenia), two cases of G3 neurological toxicities (ataxia and cerebral vasculitis), two cases of G3 musculoskeletal events (arthritis and knee pain) and one case each of G3 oedema, G3 lipase elevation and G3 infection. The onset to these events ranged from 3 to 107 weeks post-IO initiation, after patients were treated with a median of four doses of IO therapy (range 1–36). In the majority of cases (16/24, 67%), the toxicity events occurred after the last dose of IO (range 4–77 days). The median time to csAE resolution ranged from 4 to 55 days and 18 (75%) of 24 cases required systemic corticosteroid therapy. In 12 of 20 cases (60%), the toxicity led to treatment discontinuation (four additional cases of IO were already on hold when toxicity occurred). Of these 24 otherwise DLT-qualifying events, five (21%) occurred in patients on combination IO, and 19 events (79%) in

Table 2
Late-onset dose-limiting toxicity (DLT) events.

AE class	Number of Cases	Grade and AE type	Number of IO doses prior AE onset	Time to onset, median (range) weeks	Corticosteroid use (number of Cases/total)	Other immuno-suppressant (number of Cases/total)	IO cessation/delay (number of Cases/total)	Time to resolution, median (range) days
Skin	5	G3 rash G3 eosinophilic fasciitis	3, 4, 4, 10, 36+	11 (6–85)	4/5	–	3/5 delay[a]	23 (8–55)
Gastrointestinal	4	G3 colitis G3 diarrhoea	2, 3, 5, 34	9 (4–104)	4/4	Infliximab 2/4	2/4 cessation 2/4 delay	6 (2–14)
Respiratory	4	G3 pneumonitis	1, 2, 5, 35	14 (3–104)	4/4	Infliximab 1/4	4/4 cessation	11 (5–11)
Hepatic	2	G3 hepatitis	18, 34	82 (57–107)	2/2	–	2/2 cessation	14 (12–15)
Haematological	2	G3 anaemia G4 neutropenia	4, 18	9, 41	1/2	Rituximab 1/2	2/2 cessation	22, 39
Neurological	2	G3 ataxia G3 cerebral vasculitis	3, 36+	47 (6–89)	1/2	–	1/2 cessation[b]	6 (4–7)
Musculoskeletal	2	G3 arthritis G3 knee pain	7; 13	25 (13–36)	1/2	–	1/2 cessation	21 (17–22)
General	1	G3 Oedema	3	14	1/1	–	0/1 cessation/delay[c]	22
Investigations	1	G3 Lipase elevation	2	10	0/1	–	0/1 cessation/delay	10
Infections	1	G3 shingles	3	7	0/1	0/1	0/1 cessation/delay	11

AE, adverse event; IO, immunotherapy; CR, complete response.
The table lists clinically significant adverse events (csAEs) meeting DLT criteria but occurred after DLT period.
[a] In the other two patients, IO treatment was already ceased (for CR and programmed death [PD], respectively) at G3 clinically significant AE onset.
[b] One patient ceased IO treatment because of toxicity, and the other withdrew consent for further treatment.
[c] Treatment had already ceased (due to PD) when G3 oedema occurred.

patients on monotherapy IO. These rates are comparable to the relative proportion of patients on each type of trial (21% monotherapy and 79% combination-based IO).

3.6. Predictors of csAE

On univariate analysis, response to IO and treatment with combination versus single-agent IO were predictors for experiencing a csAE event (Supplementary Table S2). On multivariate analysis, these remained as independent predictive factors of csAE. Patient age, ECOG PS, number of lines of prior systemic therapy, prior IO and time on current IO were not predictors of csAE event. Using a Cox regression model to consider the time to csAE, type of IO (combination vs. monotherapy) remained a significant predictor for csAE.

4. Discussion

DLTs during the protocol-defined observation periods are infrequent in phase I IO monotherapy trials [8]. Postel-Vinay *et al.* reviewed 13 phase I trials of anti-PD1 or anti-PD-L1 and anti-CTLA-4 monotherapy finding only one trial encountered DLTs [9]. In our series, there were only two DLT events out of 352 cases (0.6%). However, there were 24 events in 20 patients (5.7% of trial enrolments) that met protocol-specified criteria for DLTs but occurred after the protocol-specified DLT observation period. These represent clinically important events, 18 of 24 events (75%) required systemic corticosteroids, and four of these cases received additional immunosuppressive therapy such as infliximab.

Delayed-onset toxicities are not incorporated into traditional dose-escalation decision-making and are not routinely reported in phase I IO trials. In the review by Postel-Vinay *et al.* of phase I trials of anti-PD1 or anti-PD-L1 and anti-CTLA-4 antibodies, only one study (with tremelimumab) reported late-onset DLTs in four patients (two patients with autoimmune hepatitis, one with peripheral oedema and cellulitis and one with leukocytoclastic vasculitis, pruritis, skin exfoliation and rash). These four patients received study treatment at what was subsequently declared as the RP2D [7]. Delayed-onset toxicities from IO may not always represent dose-limiting events. In our series, of the 24 late-onset DLTs (csAEs that would have otherwise qualified as DLTs except for occurrence beyond the DLT window) recorded; only one occurred at a dose level that was subsequently determined to exceed the maximum tolerated dose (MTD). This suggests that late-onset DLTs may not affect RP2D determination but remain clinically significant for patient management, such as duration of surveillance for immune-related toxicities.

We examined the risk of csAEs over time, using different cut-offs (4, 6, 8 and 12 weeks) as surrogates for possible

DLT observation windows. Instead of analysing toxicities by grading system (e.g. G3 or G4), we considered csAEs, given their impact on clinical management. In our series of 352 trial enrolments, patients were most likely to experience their first csAE within the first 4 weeks on treatment compared with after 4 weeks (OR 3.13, 95% CI 1.95–5.02). When different cut-offs (6, 8 and 12 weeks) were applied, the risk of the first csAE event was always greater in the earlier period, with adjustment made for the decreasing number of patients remaining on treatment over time. These findings support continued utilisation of the traditional DLT period, which will capture the majority of severe toxicities that are relevant for dose escalation and RP2D determination. While our analysis also demonstrates the occurrence of delayed csAEs, these can be delayed for over 11–14 weeks, beyond a period for which is practical for DLT observation in a clinical trial. Nevertheless, it is important to collect and report delayed csAEs, as these may provide further refinement of dosing and scheduling through the drug development process.

The concept of DLT in immuno-oncology is further complicated by the lack of a clear relationship between dose and toxicity with most IO agents [8]. Exceptions are anti-CTLA-4 antibodies such as ipilimumab, where 10 mg/kg dosing is associated with greater incidence of adverse events such as colitis and hepatitis, compared with 3 mg/kg [10,11], and tremelimumab where toxicity was increased in doses above 1 mg/kg [12]. However, most other IO agents have not reported a linear relationship between dose and toxicity. As a result, the RP2D for most IO agents has not been determined based on the incidence of DLTs but relied on pharmacokinetic and pharmacodynamic parameters. For example, the MTD was not established in the dose-finding trials of nivolumab and pembrolizumab [13,14], with the toxicity profile similar across different dose levels tested. Furthermore, an updated analysis of nivolumab monotherapy in metastatic melanoma found no evidence of cumulative toxicity, with decreasing toxicity event rate with time on therapy (339, 201 and 134 events per 100 person-years at the 0–6, 6–12 and 12–24 months, respectively) [15].

IO agents are increasingly tested in combination. There is heightened risk of toxicities combining two IO agents, and the characteristic and timing of csAEs differ to that of IO monotherapy [1–3]. In contrast to the relative rarity of DLT events in phase I studies of IO monotherapy, a number of combination IO trials have encountered DLTs [12,16]. For the combination of ipilimumab and nivolumab, G3 or G4 irAEs are more frequent and occur earlier than with nivolumab alone [3]. Although not a randomised comparison, we also observed a higher frequency of csAE in patients treated on combination IO (24/74, 32%) compared with single-agent IO (51/278, 18%) in our cohort (OR 2.7, 95% CI 1.5–5.1, $P < 0.001$). Furthermore, csAEs occurred earlier in combination compared with single-agent IO. The median time to first-onset csAE in patients who received single-agent IO was 146 days (or 20–21 weeks) compared with 32 days (or 4–5 weeks). Our results are in line with the finding that 85% of new treatment-related select adverse events occurred within the first 16 weeks on nivolumab [1]. With combination IO, there appears to be earlier onset of adverse events with the peaks in G3 or G4 events at 50 and 90 days (i.e. at 8 and 13 weeks) [17]. Because of relatively small numbers of combination IO trials, this analysis is unable to conclude regarding DLT observation periods specifically for phase I studies of combination as opposed to monotherapy IO. However, it does highlight this may be a factor for consideration in IO trial design.

A relationship between irAE and therapeutic response to IO has been reported in some studies, such as with ipilimumab [18–20] and nivolumab [1], but not validated in other studies [17,21]. In a pooled analysis of nivolumab trials involving 576 metastatic melanoma patients, treatment-related select AEs correlated with higher objective response rate in a multivariable analysis adjusting for doses of nivolumab received, baseline lactate dehydrogenase (LDH), and tumour PD-L1 expression [1]. Similarly, our study in mixed tumours treated with a variety of IO agents also found patients who had objective response were more likely to experience a csAE. After adjustment of prognostic factors (age and ECOG PS) and time on treatment, response to IO remained the strongest predictor for csAE occurrence (OR 5.3, 95% CI 2.7–10.1, $P < 0.001$). Specific types of irAEs may be more clearly linked with response to treatment, such as vitiligo [22,23] although further validation is needed before any definitive conclusions can be made.

Our study has several limitations. We acknowledge the heterogeneity in IO agents and dose levels that are pooled in our retrospective analysis. An alternative approach to assessing DLT period for IO would be to perform individual patient analysis in a number of phase I trials for an in-depth analysis of dose–toxicity relationship. However, it may be challenging to draw conclusions because of small number of patients in each phase I study and limited DLTs events. We therefore conducted our analysis across a range of studies for adequate patient numbers in order to provide general observation regarding timing of csAE. Furthermore, different clinical trials had varying protocol requirements for the reporting of toxicity. For example, some studies mandated reporting of all laboratory abnormalities considered possibly related to study treatment. The frequency of monitoring of patient on study and during follow-up following study drug discontinuation was also not uniform. We recognise our patient population being highly selected, as they were all enrolled in early phase trials at a large academic medical centre. Our results cannot be generalised to other settings where there may be differences in patterns of immune-related toxicity, such as patients with poor PS

or medical comorbidities that would not be eligible for early phase clinical trials.

IO agents have the potential to cause delayed csAEs, including events otherwise qualifying as DLTs. Acknowledging this, using GEE modelling in our cohort found csAEs occurrence predominated in the first 4 weeks compared to after 4 weeks of treatment, adjusted for time on IO therapy. This supports relevance for the traditional DLT observation period, particularly in IO combination trials where toxicities are more prevalent and occur earlier. Further analyses of early-phase combination IO trials are needed to validate this finding. Late-onset DLTs should be reported in early IO trials as it is important for clinicians to be aware of these events, and they contribute to a more comprehensive assessment of the IO toxicity profile.

Conflict of interest statement

Disclosures on possible conflicts of interest are detailed separately for each author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.10.017.

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