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Immune-related adverse events in the treatment of non-Hodgkin lymphoma with immune checkpoint inhibitors

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Immune checkpoint inhibitors (ICIs) show efficacy in the treatment of non-Hodgkin lymphomas (NHL). However, these agents are associated with a unique group of side effects called immune-related adverse events (irAEs). We conducted an observational retrospective/prospective study on patients with relapsed/refractory NHL treated with ICI to determine the incidence of irAEs assessing the type, severity, and timing of onset, outcome and relationship with study drugs of these events. Thirty-two patients underwent ICI as single agent (N=20) or in combination (N=12). Ten patients (31.3%) developed at least one irAE for a total of 17 irAEs. Median time to presentation of irAEs was 69 days (range 0–407) with a median resolution time of 16 days (range 0–98). Progression free survival at 24 months for patients who developed an irAE was 40% and 31.8% for who did not. Overall survival for the two groups did not differ (at 24 months 40.0% and 62.5% for patients without and with irAE, respectively), but the median for who developed an irAE was not reached. The incidence of irAEs was associated with better long-term survival in NHL treated with ICIs but patients' disease conditions need to be carefully evaluated to decide the optimal management.

Abbreviations

AE	Adverse event
ASCT	Autologous stem cell transplantation
BV	Brentuximab vedotin
CR	Complete response
DFS	Disease free survival
ICI	Immune checkpoint inhibitor
irAE	Immune-related adverse event
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Anti-programmed cell death 1
PD-L1	Anti-programmed cell death ligand 1
PR	Partial response
PFS	Progression free survival
PMBCL	Primary mediastinal B-cell lymphoma
R/R	Relapsed/refractory
SAE	Serious adverse event

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Immune checkpoint inhibitors (ICIs), a new class of cancer therapeutic agents, seem to play an important role in the management of non-Hodgkin lymphomas (NHL) even though data are limited to clinical trials results^{1–4}. ICIs have been approved for use in different malignancies including metastatic melanoma, advanced non-small cell lung cancer, metastatic renal cell carcinoma, refractory Hodgkin's lymphoma, refractory primary mediastinal B-cell lymphoma (PMBCL, only by U.S. Food and Drug Administration), metastatic bladder cancer, and advanced head and neck cancer. For relapsed/refractory (R/R) NHL patients, who represent an unmet medical need, new encouraging results emerged for PMBCL, T-cell lymphomas and some B-cell lymphomas, even for rare extranodal ones^{1,4–6}. However, specific toxicities related to ICIs are immune-related, differently from the side effects observed in previous oncologic treatment⁷. These immune-related adverse events (irAEs) are due to an excessive solicitation of the immune system—due to the mechanistic of each molecular target (i.e., cytotoxic T-Lymphocyte Antigen 4 [CTLA-4], and anti-programmed cell death 1 [PD-1] and anti-programmed cell death ligand 1 [PD-L1] network), may attack any organ and body district. In addition, irAEs can manifest at different timepoints both during treatment and even after the end of immunotherapy. IrAEs represent bystander effects from activated T-cells and it is plausible that patients responding to ICIs may present autoimmune toxicities (e.g. due to a more treatment-responsive immune system, or cross-reactivity between tumor and host tissue, or loss of central and peripheral tolerance towards self-antigens). Mild initial symptoms may suddenly become significantly worse and severe; therefore, it is extremely important to diagnose irAEs correctly, to determine their severity, and intervene correctly as soon as possible after their onset⁷. There is no prospective data on these toxicities, and guidelines or recommendations for lymphomas are currently based on symptomatic management from the ongoing clinical trials. Furthermore, guidelines are principally referred to solid neoplasia⁷. Hematologic irAEs induced by PD-1 or PD-L1 inhibitors are rare and potentially life-threatening. The most common clinical presentations are neutropenia, autoimmune hemolytic anemia, immune thrombocytopenia, and aplastic anemia⁸. Extra-hematologic irAEs are often low-grade and manageable, but they have the potential to be life-threatening and extremely severe if not promptly treated or managed incorrectly⁹. Among the irAEs, interstitial pneumonia, colitis, thyroiditis, hepatitis, skin rash, vitiligo, hypophysitis, autoimmune diabetes mellitus, renal dysfunction, myasthenia gravis, neuropathy, myositis, and uveitis are the most representative⁷.

Clinical issues emerged and include whether ICIs should be administered to patients with autoimmune disease and whether patients that develop irAEs should continue or not the immunotherapy. Furthermore, the onset of these irAEs events varies⁷. Key questions regarding the relationship between irAEs onset and ICIs efficacy remain. The most pertinent of these involve whether irAEs site, severity, timing of onset and management shape ICIs efficacy¹⁰.

In addition, the combination of immunotherapies in the near future means that hematologists will interface with a higher incidence and severity of irAEs.

Most of the data comes from solid neoplasia; there is little information on lymphomas, especially on NHL for which ICIs have not yet been approved worldwide.

Herein, we discuss our experience with ICIs in R/R NHL beginning to address these questions.

Methods

An observational retrospective/prospective study was conducted on patients with R/R NHL treated with ICIs at our Institution. The study was approved by our local Ethical Committee (Comitato Etico Area Vasta Emilia Centrale di Bologna, IRCCS Azienda Ospedaliero-Universitaria di Bologna, approval id code 730/2019/Oss/AOUBo) and registered in the Italian Registry of Observational Studies. Patients provided signed informed consent, as applicable, in accordance with the Declaration of Helsinki. All methods were performed in accordance with the relevant and applicable guidelines and regulations.

Primary objective of the study was to determine the incidence of irAEs in patients affected by NHL undergoing ICIs treatment also assessing the type, severity, and timing of onset, management, outcome and relationship with study drugs of these events.

Secondary objectives were activity and disease control of ICIs along with their relationship with irAEs onset.

Patients remained in follow-up till the resolution of irAEs.

Objective response rate (ORR) was defined as the sum of complete response (CR) and partial response (PR) rates at the end of ICIs treatment and before any type of consolidation. Best response rate was defined as the sum of CR and PR rates reached at any time during treatment by each patient. Overall survival (OS) was defined as the time from initiation of therapy to death from any cause and was censored at the date of last available follow up. Progression free survival (PFS) was measured from initiation of therapy to progression, relapse, or death from any cause and was censored at the date of last available follow up. Disease free survival (DFS) was calculated for CR patients from the first documentation of response to the date of relapse or death due to lymphoma or acute toxicity of treatment¹¹. Response was assessed using the International Working Group revised response criteria for malignant lymphoma^{11,12}. Safety and tolerability were evaluated by recording incidence, severity, and type of any AE according to the National Cancer Institute Common Terminology Criteria for AEs v4.0. A minimum of 12 months of follow up was required for the analyses to evaluate late Aes.

Demographics and patients' characteristics as well Aes were summarized by descriptive statistics. Continuous variables were reported as median (range) for non-normally distributed data and compared using the Student t-test or Mann Whitney U test. Categorical variables were reported as absolute and relative frequencies and compared using Fisher's exact test or Chi-squared test, as applicable. Correlations were tested among irAEs occurrence, effectiveness of ICIs and patients' survivals. Survival functions were estimated by using the Kaplan–Meier method. Statistical analyses were performed with Stata 11 (StataCorp LP, TX) and p values were set at 0.05.

Pt ID	irAE	Drug(s)	Grade	Action (ICI)	Outcome
#1	Thyrotoxicosis	Pembrolizumab	1	None	Resolved
#1	Hypothyroidism	Pembrolizumab	2	None	Controlled with drugs
#2	Acute renal failure	Pembrolizumab	3	Permanent suspension	Resolved
#2	Interstitial pneumonia	Pembrolizumab	1	Permanent suspension	Resolved
#3	Immune fever	Tislelizumab	1	None	Resolved
#4	Pancreatitis	Nivolumab (+ BV)	3	Permanent suspension of BV	Resolved
#4	Diabetes mellitus	Nivolumab (+ BV)	2	None	Controlled with drugs
#4	Thyrotoxicosis	Nivolumab (+ BV)	1	None	Resolved
#4	Hypothyroidism	Nivolumab (+ BV)	2	None	Resolved
#5	Hypothyroidism	Nivolumab (+ BV)	2	None	Resolved
#6	Acute hepatitis	Nivolumab (+ BV)	2	Permanent suspension	Resolved
#7	Hypersensitivity pneumonia	Nivolumab (+ BV)	1	None	Resolved
#8	Muscle pain	Nivolumab (+ BV)	1	Temporary interruption	Resolved
#9	Thyrotoxicosis	Pembrolizumab	1	None	Resolved
#9	Hypothyroidism	Pembrolizumab	2	None	Resolved
#9	Diffuse pain in the major joints	Nivolumab (+ BV)	2	None	Resolved
#10	Hypothyroidism	Nivolumab (+ BV)	2	None	Resolved

Table 1. Immune-related adverse events occurred during treatment with immune-checkpoint inhibitors. *BV* brentuximab vedotin, *ICI* immune checkpoint inhibitor, *irAE* immune-related adverse event, *pt* patient.

Ethical conduct of research statement. The study was approved by the local Ethical Committee (Comitato Etico Area Vasta Emilia Centrale di Bologna, IRCCS Azienda Ospedaliero-Universitaria di Bologna, approval id code 730/2019/Oss/AOUBo) and registered in the Italian Registry of Observational Studies. Patients provided signed informed consent, as applicable, in accordance with the Declaration of Helsinki.

Results

Thirty-two NHL patients (12 males and 20 females) were enrolled. They were treated between September 2014 and February 2019. Patients had PMBCL (N = 26), mycosis fungoides/Sézary syndrome (N = 5) and follicular T-helper lymphoma (N = 1).

Median age at diagnosis was 31 years (range, 19–61). Patients had a median of 3 previous therapies (range 1–9), including autologous stem cell transplantation (ASCT, N = 6) and brentuximab vedotin (BV, N = 5). Twenty-nine patients were refractory to first-line treatment and 29 to the last one.

Eighteen patients underwent pembrolizumab, 12 had nivolumab in combination with BV, 1 patient underwent nivolumab and 1 received tislelizumab, with a median of 5 cycles (1–52).

No dose reduction for ICIs have been necessary (only 1 reduction and subsequent discontinuation of BV) and 21 patients had an early drug discontinuation: 18 due to progression disease (PD, 5 of which death), 1 due to bridge to ASCT, 2 due to Aes (namely sepsis with heart failure, acute renal failure and interstitial pneumonia, and acute hepatitis).

Best response rate was 43.8% (31.6% CR rate), with 10 CR, 4 PR, 5 stable diseases (SD) and 13 PD. ORR was 37.5% (31.6% CR rate), with 10 CR, 2 PR, 2 SD and 18 PD.

No hematological toxicities occurred, while 15 patients developed at least 1 extra-hematological toxicity (overall 39 Aes). Ten patients (31.3%) developed at least 1 irAE for a total of 17 irAEs (two grade ≥ 3 and three judged as serious AE [SAE]): 1 patient developed 4 irAEs, 1 patient had 3 irAEs, 2 patients had 2 irAEs and 6 patients 1 irAE, respectively. Two out of these ten patients had an endocrinopathy (not the same irAE developed during ICI treatment) and none of them had familiarity for (auto)immune diseases. Five out of these ten patients achieved at least a PR (3 CR and 2 PR).

Complete irAEs description with grade in severity is reported in Table 1.

All irAEs resolved beside a post-thyroiditis immune-based hypothyroidism and diabetes mellitus which was not autoimmune (both chronic and controlled with therapy). One SAE which was constituted by multi-organ failure led to patient death due to heart failure even if his irAEs (acute renal failure and interstitial pneumonia which caused hospitalization) were resolved.

Median time to presentation of irAEs was 69 days (range 0–407) with a median resolution time of 16 days (range 0–98). No late irAEs (i.e. after end of treatment) occurred. No statistically significant difference in irAEs frequency resulted between different ICIs ($p = 0.181$), histologies ($p = 0.210$) and outcomes ($p = 0.158$ for best response; $p = 0.722$ for ORR; $p = 0.377$ for deaths). No correlations were found between patients' characteristics (age, gender, autoimmune diseases) and irAE occurrence.

Ten out of 17 (58.8%) irAEs were referred to endocrine glands. In particular, five patients developed sudden-onset hypothyroidism at different times (from 16 to 44 weeks after ICI starting). One PMBCL on pembrolizumab had an initial thyrotoxicosis at 6 weeks turning to overt hypothyroidism after 9 weeks. All the 5 subjects were asymptomatic. Two of them had positive anti-thyroid autoantibodies (anti-thyroid peroxidase and anti-thyroglobulin), whereas none had detectable anti-TSH (thyroid-stimulating hormone) receptors. All hypothyroid

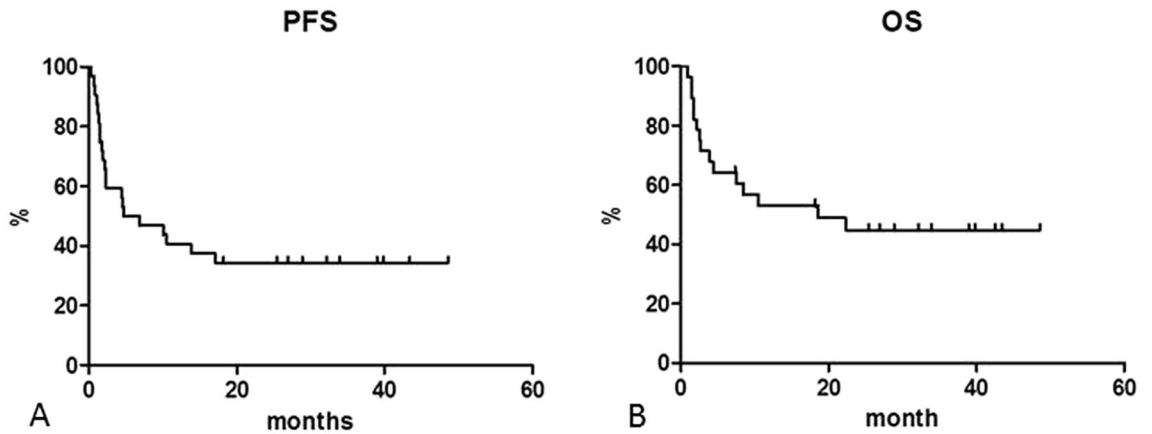


Figure 1. Progression free survival (PFS) (A) and overall survival (OS) (B).

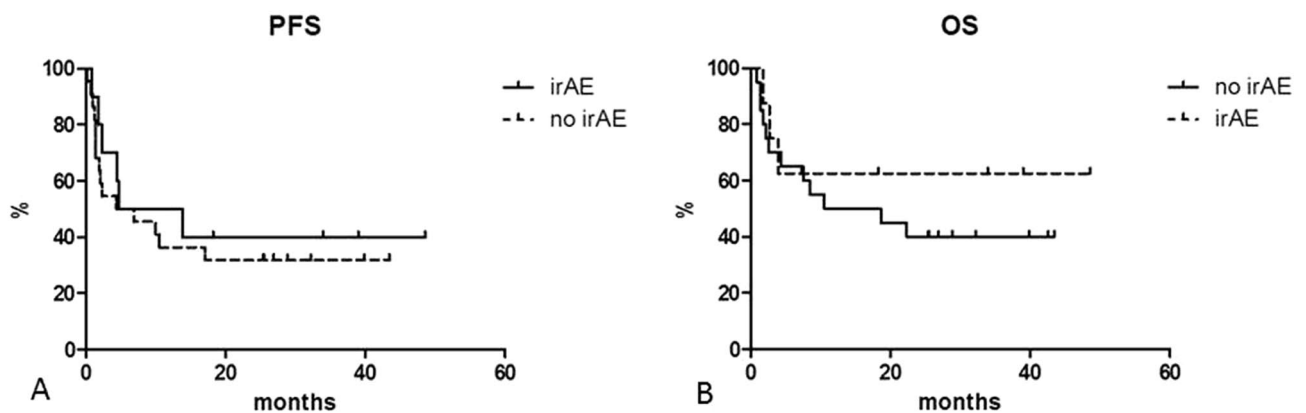


Figure 2. Progression free survival (PFS) for patients who developed an immune related adverse event (irAE) and for who did not ($p=0.5442$) (A) and overall free survival (OS) for patients who developed an immune related adverse event (irAE) and for who did not ($p=0.4718$) (B).

subjects started l-tyroxine therapy lifelong. At the last follow up, 3 out of the 5 patients with endocrine-irAE were in continuous CR, 1 still in PR and 1 had a relapse after an initial PR.

At a median follow up of 48.0 months, DFS was 100% at 24.0 months. PFS was 40.6% at 12 months, 34.4% at both 24.0 and 48.6 months (median reached at 5.8 months) (Fig. 1A). OS was 52.9% at 12 months. With 15 deaths, OS was 44.8% at both 24.0 and 48.6 months (median reached at 18.6 months) (Fig. 1B). We estimated PFS for patients who developed an irAE (40.0% at 24 months) and for who did not (31.8% at 24 months): the curves did not differ ($p=0.5442$) (Fig. 2A). OS for the two groups did not differ (at 24 months 40.0% and 62.5% for patients without and with irAE, respectively; $p=0.4718$), but median for who developed an irAE was not reached (Fig. 2B).

Discussion

Efficacy and safety findings coming from clinical trials indicate that ICIs have potential to provide substantial clinical benefit in heavily pretreated patients with NHL, particularly given the lack of effective alternatives. Currently, only pembrolizumab is approved for R/R PMBCL by FDA but other ICIs are under investigation worldwide as single agents or in combination.

Recognizing and characterizing treatment-related AEs represent a cornerstone of determining the value of NHL treatments. A shortage of high-quality and reliable AE data, even from clinical trials, has prompted a call for more rigorous standards of AE reporting^{13–16}. The advent of ICIs likely adds considerable challenge to this effort as the toxicities related to ICIs are peculiar and different from what previously observed with the other antineoplastic agents. In fact, irAEs may involve almost every organ and are unpredictable, sometimes permanent, and occasionally fatal^{17,18}.

The increase in immune response caused by ICI can result in both disease regression and irAEs and, in fact, some studies reported a connection between their occurrences. In details, irAEs occurrence was related to both a longer OS and tumor regression^{19–21}. In oncologic patients, namely affected by small cell lung carcinoma, an early occurrence of irAEs nivolumab-related was associated with better PFS and ORR²². This suggested that endocrine irAEs may be a symptom of an augmented immune response against neoplastic cells. In our study population, ICIs efficacy was not influenced by irAEs occurrence and patients' outcomes were preserved: improving or

worsening of response from best response to ORR; best and overall response rates did not significantly differ between patients who developed an irAEs and those who did not. PFS and OS at 24 months were higher in patients who developed an irAE (40% and 62.5%, respectively) than in those who did not (31.8%). These differences were not significant, but data supported the hypothesis that the highest activity of ICIs is associated with irAEs occurrence, which may be considered a clinical biomarker for ICI response¹⁰. To note, median OS for who developed an irAE was not reached.

A recent meta-analysis demonstrated that the frequency of each type of irAE depends on tumor type²³, thus specific data on NHL are needed. In our study there was no difference among different NHL but probably a larger sample size is needed to confirm this association also in lymphomas.

Now that single-agent and combination ICIs regimens are coming for NHL, the timeliness and feasibility of irAEs recognition and diagnosis is crucial for the management of lymphoma patients in terms of both safety and efficacy. Single-center experiences in a real-world context with immunotherapy showed a significant higher irAE rates than those reported in prospective clinical studies^{24–27}. To note that challenges in detection of irAEs seem to be caused by their heterogeneous manifestations, unpredictable timing, and clinical overlap with other conditions contribute^{16,28}.

While most toxic effects of conventional chemotherapy and molecularly targeted therapies are readily diagnosed through medical history, physical examination, and laboratory data, irAEs appear far more heterogeneous. Our data showed that medical history cannot predict irAE onset and we did not find any relationship with histology, type of ICI or patients characteristics (with the limitation of a small sample size). The lack of specific immune biomarkers contributes to the challenges of capturing irAEs by clinicians. The American Society of Clinical Oncology and the National Comprehensive Cancer Network published clinical guidelines for irAEs diagnosis and management, but lymphomas-adapted guidelines are needed^{7,29}.

Furthermore, to our knowledge, the accuracy of irAE diagnosis has not been evaluated and the observations in this regard in the literature are limited to a single report³⁰.

Whether or not it is safe or necessary to resume checkpoint inhibition after a clinically significant irAE remains unclear. In our patients, no dose reduction was needed although on the other hand irAEs lead to ICI temporary suspension in one patient and withdrawn for two other subjects. To note, after AE resolution, one patient with muscle pain (grade 1) was retreated without new irAE occurrence; for other patients, in whom irAE caused suspension (acute hepatitis grade 2, acute renal failure grade 3 and interstitial pneumonia grade 1), the withdrawn was permanent. The clinician decision depended on the type of toxicity i.e. the organ concerned, the irAE grade and the possibility of using drugs that control the event (e.g. l thyroxine for hypothyroidism or beta-blockers for thyrotoxicosis).

Limitations of this analysis include the single-center setting. The strength of the study is its prospective design. In addition, this is the first report on irAE occurrence and management in NHL treated with ICIs as single agent or in combination.

The occurrence of irAEs in NHL seems lower than in solid neoplasia, especially for grade ≥ 3 ones³¹. On the contrary, endocrine irAEs are confirmed as the most frequent (58.8% of all the irAEs), as previously reported also for solid tumors^{32,33}; thyroid dysfunction is the most common, which often presented as thyrotoxicosis. In our knowledge, therapy-related hypothyroidism is the unique irAEs characterized by well-defined laboratory values. In fact, the assessment of other relevant irAEs is complicated by the non-correlation with laboratory findings or by the fact that they may have non-immune causes.

Prompt consultation to the experts is of great importance and the grade of irAEs and patients' disease conditions need to be carefully evaluated to decide the optimal measures. As irAEs could affect various organs, a multidisciplinary approach is critical, and it is important to organize a cooperative system within a hospital.

To our knowledge, our data are the first one collected prospectively on irAEs occurring in NHL treated with ICIs. Further studies are required to master this particular issue with the aim to provide clinical practice guidelines. With the increasing use of immunotherapy in lymphomas therapeutic algorithms, physicians must be aware about the drug-related irAEs, their recommended management, monitoring and about the best actions to be taken to avoid treatment discontinuation and, consequently, loss of patients' response.

Data availability

The datasets used and analyzed during the current study are available from the corresponding authors on reasonable request.

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References

- Armand, P. *et al.* Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma. *J. Clin. Oncol.* **37**, 3291–3299 (2019).
- Kim, S. J. *et al.* PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. *Blood* **129**, 2437–2442 (2017).
- Ansell, S. M. *et al.* Nivolumab for relapsed/refractory diffuse large B-cell lymphoma in patients ineligible for or having failed autologous transplantation: A single-arm, phase II study. *J. Clin. Oncol.* **37**, 481–489 (2019).
- Younes, A. *et al.* Safety and activity of ibrutinib in combination with nivolumab in patients with relapsed non-Hodgkin lymphoma or chronic lymphocytic leukaemia: A phase 1/2a study. *Lancet Haematol.* **6**, e67–e78 (2019).
- Li, X. *et al.* Activity of pembrolizumab in relapsed/refractory NK/T-cell lymphoma. *J. Hematol. Oncol.* **1**, 15 (2018).
- Khodadoust, M. S. *et al.* Pembrolizumab in relapsed and refractory mycosis fungoides and sézary syndrome: A multicenter phase II study. *J. Clin. Oncol.* **38**, 20–28 (2020).

7. Brahmer, J. R. *et al.* Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J. Clin. Oncol.* **36**, 1714–1768 (2018).
8. Delaney, N. *et al.* Haematological immune-related adverse events induced by anti-PD-1 or anti-PD-L1 immunotherapy: A descriptive observational study. *Lancet Haematol.* **6**, e48–e57 (2019).
9. Martins, F. *et al.* Adverse effects of immune-checkpoint inhibitors: Epidemiology, management and surveillance. *Nat. Rev. Clin. Oncol.* **16**, 563–580 (2019).
10. Nayak, L. *et al.* PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. *Blood* **129**, 3071–3073 (2017).
11. Das, S. & Johnson, D. B. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. *J. Immunother. Cancer* **7**, 306 (2019).
12. Cheson, B. D. *et al.* Revised response criteria for malignant lymphoma. *J. Clin. Oncol.* **25**, 579 (2007).
13. Cheson, B. D. *et al.* Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *J. Clin. Oncol.* **32**, 3059–3068 (2014).
14. Schnipper, L. E. *et al.* Updating the American Society of Clinical Oncology value framework: Revisions and reflections in response to comments received. *J. Clin. Oncol.* **34**, 2925–2934 (2016).
15. Levit, L. A. *et al.* Streamlining adverse events reporting in oncology: An American Society of Clinical Oncology research statement. *J. Clin. Oncol.* **36**, 617–623 (2018).
16. Péron, J., Maillet, D., Gan, H. K., Chen, E. X. & You, B. Adherence to CONSORT adverse event reporting guidelines in randomized clinical trials evaluating systemic cancer therapy: A systematic review. *J. Clin. Oncol.* **31**, 3957–3963 (2013).
17. Sivendran, S. *et al.* Adverse event reporting in cancer clinical trial publications. *J. Clin. Oncol.* **32**, 83–89 (2014).
18. Ribas, A. & Wolchok, J. D. Cancer immunotherapy using checkpoint blockade. *Science* **359**, 1350–1355 (2018).
19. Wang, D. Y. *et al.* Fatal toxic effects associated with immune checkpoint inhibitors: A systematic review and meta-analysis. *JAMA Oncol.* **4**, 1721–1728 (2018).
20. Yang, J. C. *et al.* Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. *J. Immunother.* **30**, 825–830 (2007).
21. Downey, S. G. *et al.* Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. *Clin. Cancer Res.* **13**, 6681–6688 (2007).
22. Freeman-Keller, M. *et al.* Nivolumab in resected and unresectable metastatic melanoma: Characteristics of immune-related adverse events and association with outcomes. *Clin. Cancer Res.* **22**, 886–894 (2016).
23. Teraoka, S. *et al.* Early immune-related adverse events and association with outcome in advanced non-small cell lung cancer patients treated with nivolumab: A prospective cohort study. *J. Thorac. Oncol.* **12**, 1798–1805 (2017).
24. Khoja, L., Day, D., Wei-Wu Chen, T., Siu, L. L. & Hansen, A. R. Tumour-and class-specific patterns of immune-related adverse events of immunecheckpoint inhibitors: A systematic review. *Ann. Oncol.* **28**, 2377–2385 (2017).
25. Suresh, K. *et al.* Pneumonitis in non-small cell lung cancer patients receiving immune checkpoint immunotherapy: Incidence and risk factors. *J. Thorac. Oncol.* **13**, 1930–1939 (2018).
26. So, A. C. & Board, R. E. Real-world experience with pembrolizumab toxicities in advanced melanoma patients: A single-center experience in the UK. *Melanoma Manage.* **5**, 05 (2018).
27. Cho, J. Y. *et al.* Characteristics, incidence, and risk factors of immune checkpoint inhibitor-related pneumonitis in patients with non-small cell lung cancer. *Lung Cancer* **125**, 150–156 (2018).
28. Tournoy, K. G. *et al.* Does nivolumab for progressed metastatic lung cancer fulfill its promises? An efficacy and safety analysis in 20 general hospitals. *Lung Cancer* **115**, 49–55 (2018).
29. Chen, T. W., Razak, A. R., Bedard, P. L., Siu, L. L. & Hansen, A. R. A systematic review of immune-related adverse event reporting in clinical trials of immune checkpoint inhibitors. *Ann. Oncol.* **26**, 1824–1829 (2015).
30. Thompson, J. A. *et al.* NCCN Guidelines insights: Management of immunotherapy-related toxicities, version 1. 2020. *J. Natl. Compr. Can. Netw.* **18**, 230–241 (2020).
31. Hsiehchen, D., Watters, M. K., Lu, R., Xie, Y. & Gerber, D. E. Variation in the assessment of immune-related adverse event occurrence, grade, and timing in patients receiving immune checkpoint inhibitors. *JAMA Netw. Open* **2**, e1911519 (2019).
32. Cortellini, A., Buti, S., Agostinelli, V. & Bersanelli, M. A systematic review on the emerging association between the occurrence of immune-related adverse events and clinical outcomes with checkpoint inhibitors in advanced cancer patients. *Semin. Oncol.* **46**, 362–371 (2019).
33. Zhai, Y. *et al.* Endocrine toxicity of immune checkpoint inhibitors: A real-world study leveraging US Food and Drug Administration adverse events reporting system. *J. Immunother. Cancer* **7**, 286 (2019).

Author contributions

L.A., C.P., U.P., P.L.Z. and B.C. and designed the investigation, supervised the study and contributed to writing the paper. L.A. wrote the draft manuscript. L.A. analyzed data. L.A., B.C., C.P., V.L.P., U.P., F.B. and P.L.Z. collected and interpreted data. All the authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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