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Original Research

Late-onset and long-lasting immune-related adverse events from immune checkpoint-inhibitors: An overlooked aspect in immunotherapy

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Abstract ***Background:*** Immune checkpoint inhibitors (ICIs) have revolutionised cancer therapy but frequently cause immune-related adverse events (irAEs). Description of late-onset and duration of irAEs in the literature is often incomplete.
Methods: To investigate reporting and incidence of late-onset and long-lasting irAEs, we reviewed all registration trials leading to ICI's approval by the US FDA and/or EMA up to December 2019. We analysed real-world data from all lung cancer (LC) and melanoma (Mel) patients treated with approved ICIs at the University Hospital of Lausanne (CHUV) from 2011 to 2019. To account for the immortal time bias, we used a time-dependent analysis to assess the potential association between irAEs and overall survival (OS).

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Results: Duration of irAEs and proportion of patients with ongoing toxicities at data cut-off were not specified in 56/62 (90%) publications of ICIs registration trials. In our real-world analysis, including 437 patients (217 LC, 220 Mel), 229 (52.4%) experienced at least one grade ≥2 toxicity, for a total of 318 reported irAEs, of which 112 (35.2%) were long-lasting (≥6 months) and about 40% were ongoing at a median follow-up of 369 days [194–695] or patient death. The cumulative probability of irAE onset from treatment initiation was 42.8%, 51.0% and 57.3% at 6, 12 and 24 months, respectively. The rate of ongoing toxicity from the time of first toxicity onset was 42.8%, 38.4% and 35.7% at 6, 12 and 24 months. Time-dependent analysis showed no significant association between the incidence of irAEs and OS in both cohorts (log Rank p = 0.67 and 0.19 for LC and Mel, respectively).

Conclusions: Late-onset and long-lasting irAEs are underreported but common events during ICIs therapy. Time-dependent survival analysis is advocated to assess their impact on OS. Real-world evidence is warranted to fully capture and characterise late-onset and long-lasting irAEs in order to implement appropriate strategies for patient surveillance and follow-up.

1. Introduction

Immune checkpoint inhibitors (ICIs) that target programmed cell death-1 (PD-1), programmed cell death-ligand 1 (PD-L1), or cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) have revolutionised cancer therapy. In the last five years, three PD-1 inhibitors (nivolumab, pembrolizumab and cemiplimab), three PD-L1 inhibitors (atezolizumab, avelumab and durvalumab) and one anti-CTLA-4 (ipilimumab) have been approved by the US Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) for various indications and disease settings. Although in many cases ICIs are not associated with relevant toxicities and are usually well-tolerated treatments, rare but severe immune-related adverse events (irAEs) can occur [1,2]. In a recent meta-analysis, including more than 18,000 patients, 66% of patients were found to develop at least one adverse event (AE) of any grade (G) and 14% of G3 or higher [3–7]. These above-mentioned irAEs can remain incompletely resolved or resolved with chronic sequelae, and exert a significant impact on patients and their caregivers [8].

Traditionally, safety assessments in clinical trials have primarily aimed to capture acute and life-threatening adverse events during short-course chemotherapy and for a limited time thereafter. With the advent of ICIs, however, there is a growing awareness that safety assessments need to capture chronic and late-onset toxicities that may develop several months or years from drug exposure. In this new scenario, less severe toxicities can constitute substantial threats to the quality of life (QoL) and compliance with therapy, thereby also affecting full treatment benefits [9]. Despite well-accepted international standards (Common Terminology Criteria for Adverse Events – CTCAE), reporting of toxicity in clinical trials of new anticancer agents remains difficult, especially in terms of duration of AEs, including long-lasting and chronic events [10]. Time of irAEs onset and duration of toxicities are mainly extrapolated from meta-analysis and reviews of the literature with a wide variability of settings. In some exceptional cases, the onset of rare events is described >50 weeks after ICI initiation [11,12]. In addition, publications of ICI(s) trial primary analysis are often based on a limited follow-up, further underestimating the occurrence and the duration of late-onset toxicity [13,14]. Intriguingly, it has been hypothesised that patients experiencing these irAEs might have a better outcome than patients without toxicities, likely reflecting a more competent/treatment-responsive immune system or cross-reactivity between tumour and host tissue [15–17]. Previous articles have investigated this issue with conflicting results, especially when a landmark approach was used to overcome the so-called 'immortal time bias' [18–20].

In order to describe the completeness of irAEs reporting, with particular attention to long-lasting and late-onset irAEs, we reviewed all published registration trials, which led to ICI's approval by Food and Drug Administration (FDA) and European Medicines Agency (EMA) up to December 2019. The identified lack of long-lasting and late-onset irAE prompted us to use the data obtained from a large database of electronic patient records at our Institution to provide one of the first real-world analysis in an unselected patient population. We then assessed the potential correlation between irAEs onset and overall survival (OS) using a time-dependent model to properly

account for the immortal time bias introduced by late-onset toxicities.

2. Methods

2.1. Review of ICIs registrative trials

FDA and EMA regulation lists were searched for approved ICIs up to December 2019, including any tumour type and stage of the disease. Namely, seven different treatments were included in this analysis: ipilimumab, pembrolizumab, nivolumab, avelumab, durvalumab, atezolizumab and ipilimumab–nivolumab combination. The corresponding registrational trial(s) was retrieved for each approval. A dedicated case report form (CRF) was used to collect data for each selected paper in an electronic database. For each study, the following information was recorded: date of publication, date of FDA and/or EMA approval, number of patients treated in the ICI arm, median follow-up (FU), number of patients ongoing at data cut-off and description of irAE duration. For all the relevant data, two investigators reviewed each selected paper. Any discrepancy was resolved by discussion with a third senior investigator. For all records, secondary publications with updated FU and data regarding toxicities duration were searched in PubMed, by using the name of the drug(s) and/or tumour type and/or the name of authors of the primary publication and/or the study acronym/code, when available.

2.2. Real-world data collection

Electronic health records (EHR) of adult patients with advanced melanoma (Mel) or lung cancer (LC) that were treated with ICIs in the Medical Oncology department at the University Hospital of Lausanne (CHUV) from February 2011 to December 2019 were retrieved using an application developed internally (Virtual Trial). This application preprocesses unstructured texts from the EHR and automatically assigns cancer diagnosis or TNMs using text-mining algorithms. A graphical user interface helps validate the predictions and visualise the data for patient selection. The application also includes text search functions that use regular expressions for pattern detection of irAEs. Clinicians diagnosed irAEs during treatment, and the related details were captured by four physicians independently using the aforementioned application. Any discrepancy between physicians was resolved by discussion with senior clinicians. A protocol for retrospective data analysis for scientific purposes was approved by the local ethics committee (CER-VD) on the 12th of February 2020.

Patients were excluded from the analysis if: (i) treated in a phase 1 trial; (ii) treated with an ICI combination, including an investigational ICI; (iii) treated in phase 2 or 3 study with approved ICIs but whose results are unpublished or in a double-blind phase 3 study where treatment allocation cannot be resolved; (iv) refused the general consent for the further use of coded personal data for research purposes; (v) have a FU $\leq$ 28 days or have been lost to FU (Online Suppl. Fig. 1). The following data were recorded: patients demographics, diagnosis, treatment setting, type of ICI(s) received, duration of each line of treatment, the incidence of any irAEs of G2 or higher, time to onset and duration of each irAE, use of steroids (topic and/or systemic) and of second-line immune-modulating agents. IrAEs were categorised by system organ class according to common terminology criteria for adverse events version 5.0 [CTCAE v5.0] (Online Supplementary material).

2.3. Statistical analysis

Descriptive statistics were computed in R and SPSS using built-in functions to assess patient, treatment and irAE characteristics. Graphs were produced using SPSS or the ggplot2 package in R. Comparisons between types of irAEs in LC and Mel were performed using Fisher exact tests for each category of irAEs. A log10 transformation was applied for normalisation of the onset time of irAEs. Pairwise comparison of irAE onset times was performed using the Tukey HSD test with p-value correction for multiple testing. The conditional probability of experiencing a second toxicity after a second ICI treatment was assessed using the Fisher exact test. The Kaplan–Meier time-to-event estimator was used to assess the cumulative probability of toxicities while on treatment, considering the first line only. If a subsequent line of treatment was given, the patient was censored at the time of the second line initiation and other potential irAEs associated with the second treatment line were not taken into account. In the case of the ipilimumab/nivolumab regimen, patients were censored after the end of the nivolumab maintenance. The time to onset of the irAE was defined as the time interval between ICI initiation (i.e. the first infusion) and the time at which the first abnormal clinical or laboratory findings related to a G2 or higher irAE occurred. Exploratory analysis of the association between the occurrence of adverse events and OS was performed independently in two subgroups (advanced lung cancer and advanced melanoma). Uveal melanoma and small-cell lung cancer (SCLC) were excluded, as well as (neo)adjuvant treatments (N = 44 and N = 16 for Melanoma and Lung, respectively). Only first line ICI-based treatments were retained, when patients received several lines of ICI-containing regimens (Online Suppl. Fig. 1). Kaplan–Meier curves were used to describe the survival probability of patients who experienced at least 1 adverse event compared to patients who did not. Using the survival and *survminer packages* in R, two Cox

models were applied: (1) a standard Cox model considering irAE occurrence as fixed variable and (2) a Cox model, including toxicity occurrence as a time-dependent covariate.

3. Results

3.1. Review of ICI registrative trials

We found 62 publications, corresponding to 27 different ICIs indications, involving 13′953 patients (Online Supplementary Table 1). Among 56 publications with available information, median follow-up (mFU) was 12.1 months (interquartile range [IQR] 9.1–15). The mFU time was particularly short for the studies leading to ICI approval by FDA fast-track procedure (10.2 months, IQR 5–11.9), compared to those approved by regular course (15.2 months, IQR 12–16.2, $p < 0.001$). In 51/62 publications (82.2%), treatment was still ongoing at data cut-off in a non-negligible proportion of patients (median 23.5%, range 1%–63%). Duration of irAEs and proportion of patients with ongoing toxicity at data cut-off were not specified in 56 publications (90.3%). In the remaining 6 publications, 3% up to 66% of patients had ongoing irAEs at data cut-off, including fatigue, endocrine dysfunctions, skin alterations, gastrointestinal, hepatic and neurological toxicities. Detailed results are reported in online Supplementary Table 2. Secondary publications reporting toxicity data were available in 25/62 cases (40.3%) and showed that even at longer follow-up (median 23 months, IQR 15.6–27.6) the proportion of patients with ongoing irAE was significant (median 13%, range 1%–23%). Among secondary publications, only 6/25 studies (24%) presented an update regarding the duration of irAEs, and in all cases, the above-mentioned toxicities were still ongoing.

3.2. Real-world patient and treatment characteristics

In total, 622 patients (342 lung cancers [LC] and 280 melanoma [Mel]) treated with ICIs were identified. Of these, 185 patients were removed due to exclusion criteria. 437 patients were included in the final analysis. Of these, 220 (50.3%) presented with Mel and 217 (49.7%) with LC. As some patients received more than one treatment line, we considered a total of 532 ICI treatments (242 for LC and 290 for Mel, of which 43 and 15 were in the context of a clinical trial, respectively). Most of the treatments were given in the metastatic setting (466, 88.6%). Nineteen (7.9%) LC patients received treatment for locally advanced disease in an adjuvant setting after surgery, or as consolidation after chemo-radiation and 47 (16.2%) Mel patients received adjuvant treatment.

The most frequent treatment was anti-PD1 ICI (n = 247, 46.4%) followed by combination of anti CTLA4-anti PD(L)1 (n = 116, 21.8%), anti-CTLA4 alone (n = 74, 13.9%), anti-PDL1 (n = 48, 9.0%) and combination of anti PD(L)1 and chemotherapy (CT, +/− bevacizumab) (n = 47, 8.8%).

The median treatment duration was 84 days [IQR 42–252]. The median duration of the different ICI and ICI-containing regimens reflected the indications and disease settings they were applied in. The longest treatments were the PDL1 monotherapies (median 237 days; [IQR 96–364]) and a combination of anti-PD(L)1 and CT (+/− bevacizumab) (median 160 days; [IQR 109–283]), followed by anti-PD1 monotherapy (126 days; [IQR 54–318]), a combination of anti-CTLA4 and anti-PD(L)1 (62 days; [IQR 21–158]) and anti- CTLA4 alone (62 days; [IQR 29–64]). Characteristics of patients and treatments included in the analysis are reported in Table 1.

3.3. Incidence of immune-related adverse events

For a total of 318 reported G ≥ 2 irAEs in our study population, 229 patients (52.4%) experienced at least one G ≥ 2 toxicity. Of these, 189 (59.4%) were G2, 110 (34.6%) G3, 17 (5.3%) G4 and 2 G5 fatal events were recorded (1 pneumonitis and 1 colitis). The most common irAEs were endocrine disorders (n = 71, 22.3%), followed by skin toxicity (n = 63, 19.8%) gastrointestinal toxicities (n = 57, 17.9%), pulmonary (n = 45, 14.2%) and hepatitis (n = 29, 9.1%). 140 toxicities lead to treatment discontinuation or temporary interruption (26.3%), out of which 44 (31.4%) occurred in LC and 96 (68.5%) in Mel patients. Of these, the majority were pneumonitis (n = 32, 22.9%) and colitis (n = 29, 20.7%). The regimen most frequently associated with irAEs was the anti-CTLA4-anti-PD(L)1 combination, with 69% of patients experiencing at least one irAE G ≥ 2, followed by anti CTLA4 (55%), anti-PD-L1 (50%), anti-PD1 (34%) and ICI + CT (28%). All toxicities and their relative incidence are listed in Table 2. Gastrointestinal irAEs and hepatitis occurred more frequently in the Mel group compared to LC (21% and 12% versus 11% and 2% respectively, $p < 0.05$), while pneumonitis and rheumatological irAEs were more frequent in LC (29% and 12% versus 8% and 4%, $p < 0.01$). Incidence of irAEs types in LC and Mel subgroups are represented in Fig. 1. Thirty-six patients were rechallenged with a second ICI line after having developed a G ≥ 2 toxicity during the first treatment and of these 13/36 (36%) had a second toxic event. Fifty patients received a subsequent ICI regimen without any previous irAE and 15/50 (30%) developed a G ≥ 2 irAE at this point. The difference in the conditional probability of making toxicity in these two subgroups turned out to be non-significant ($p = 0.6427$).

Table 1
Characteristics of patients and treatments included in the analysis.

Number of patients	Melanoma (n = 220)	Lung cancer (n = 217)	All (n = 437)
Median age, years [min–max]	66 [55–75]	65 [59–71]	66 [57–73]
Sex			
Female	89 (40.5%)	83 (38.2%)	172 (39.4%)
Male	131 (59.5%)	134 (61.8%)	265 (60.6%)
Number of patients with at least one irAEs ≥ G2	143 (65%)	86 (39.6%)	229 (52.4%)
Number of treatments[a]	Melanoma (n = 290)	Lung cancer (n = 242)	All (n = 532)
Treatment setting			
Adjuvant	47 (16.2%)	19 (7.9%)	66 (12.4%)
Metastatic	243 (83.8%)	223 (91.9%)	466 (87.6%)
Treatment types			
Anti-PD1	123 (42.4%)	124 (51.2%)	247 (46.4%)
Anti-PDL1	0	48 (19.8%)	48 (9.0%)
Anti-CTLA4	73 (25.2%)	1 (0.4%)	74 (13.9%)
Anti-CTLA4-antiPD(L)1	94 (32.4%)	22 (9.1%)	116 (21.8%)
Anti-PD(L)1-CT	0	47 (19.4%)	47 (8.8%)
Median treatment duration, days	64 [24–194]	141 [52–328]	84 [42–252]
Anti-PD1	138 [59–315]	118 [51–320]	126 [54–318]
Anti-PDL1	NA	237 [96–364]	237 [95–364]
Anti-CTLA4	62 [28–64]	750 [750-750]	62 [29–64]
Anti-CTLA4-antiPD(L)1	63 [21–173]	46 [23–75]	62 [21–158]
Anti-PD(L)1-CT	NA	160 [109–283]	160 [109–283]
Median follow-up, days	444 [243–901]	308 [169–553]	369 [194–695]
Anti-PD1	376 [194–573]	336 [167–598]	350 [179–593]
Anti-PDL1	NA	385 [235–591]	385 [235–591]
Anti-CTLA4	627 [241–1462]	1688 [1688-1688]	652 [244–1486]
Anti-CTLA4-antiPD(L)1	544 [269–907]	215 [108–367]	445 [240–875]
Anti-PD(L)1-CT	NA	258 [179–404]	258 [179–404]
Number of treatments stopped due to irAEs	96 (33.1%)	44 (18.2%)	140 (26.3%)
Anti-PD1	28 (29.2%)	20 (45.5%)	48 (34.3%)
Anti-PDL1	NA	9 (20.5%)	9 (6.4%)
Anti-CTLA4	25 (26.0%)	0	25 (17.9%)
Anti-CTLA4-antiPD(L)1	43 (44.8%)	8 (18.2%)	51 (36.4%)
Anti-PD(L)1-CT	NA	7 (15.9%)	7 (5.0%)

Data are reported as median values with [25th and 75th IQR] or as patient counts with (% of total per column). NA = not applicable.
[a] Some patients received more than one treatment line.

Table 2
Characteristics of the irAEs included in the analysis.

	Melanoma	Lung cancer	All
Any irAEs ≥ G2	220	98	318
irAEs G2	128 (58.2%)	61 (62.2%)	189 (59.4%)
irAEs G3	78 (35.5%)	32 (32.7%)	110 (34.6%)
irAEs G4	13 (5.9%)	4 (4.1%)	17 (5.3%)
irAEs G5	1 (0.5%)	1 (1.0%)	2 (0.6%)
Type of irAEs ≥ G2			
Skin	45 (20.5%)	18 (18.4%)	63 (19.8%)
Endocrine	53 (24.1%)	18 (18.4%)	71 (22.3%)
Pneumonitis	17 (7.7%)	28 (28.6%)	45 (14.2%)
Hepatitis	27 (12.3%)	2 (2.0%)	29 (9.1%)
Gastrointestinal	46 (20.9%)	11 (11.2%)	57 (17.9%)
Pancreatitis	5 (2.3%)	1 (1.0%)	6 (1.9%)
Rheumatological	8 (3.6%)	12 (12.2%)	20 (6.3%)
Neurological	8 (3.6%)	2 (2.0%)	10 (3.1%)
Nephrological	3 (1.4%)	2 (2.0%)	5 (1.6%)
Haematological	2 (0.9%)	1 (1.0%)	3 (0.9%)
Cardiac	2 (0.9%)	0	2 (0.6%)
Other	4 (1.8%)	3 (3.1%)	7 (2.2%)
irAEs ongoing at data cut-off or death	66 (30.0%)	62 (63.3%)	128 (40.3%)

Data are reported as patient counts with (% of total per column).

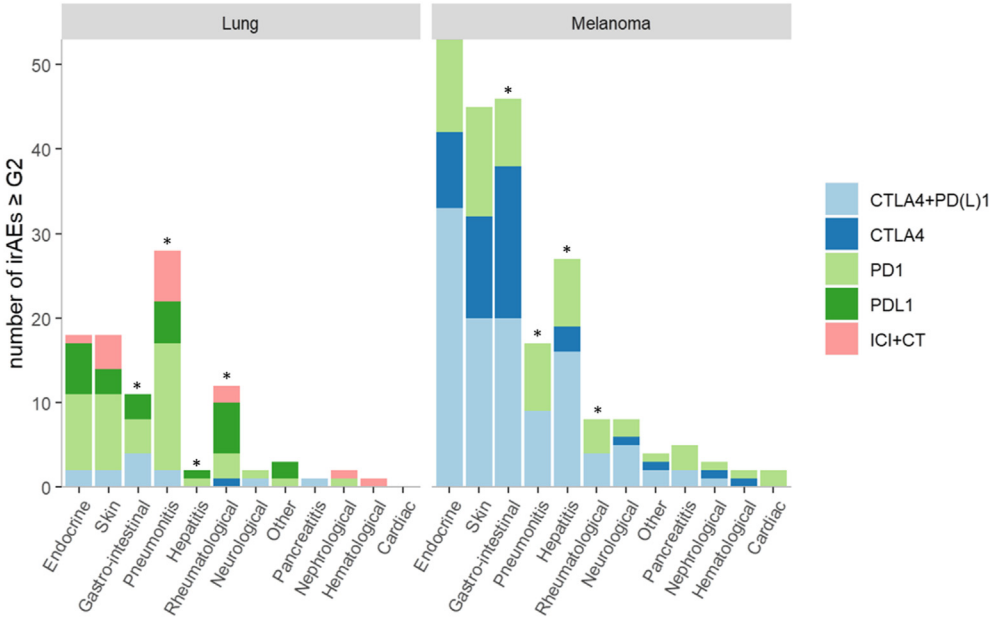

Fig. 1. Total number of specific irAEs G ≥ 2 according to cancer and treatment types. Symbol * indicates a significant difference between the two subgroups (Mel and LC): pneumonitis, rheumatological, gastrointestinal and hepatitis, all with $p < 0.05$ (using Fisher exact tests).

3.4. Onset and duration of immune-related adverse events

The median irAE onset time was 63 days [IQR 29–122] after the initiation of an ICI treatment. Comparisons between categories of irAEs onset time showed in LC a trend for skin toxicities to appear sooner than endocrine irAEs ($p = 0.053$) and pneumonitis ($p = 0.06$) (Fig. 2). The distribution of irAEs onset times was more homogenous in Mel with no statistically significant difference found. In total, 6.9% of all irAEs started one year after treatment initiation. All median times to onset and duration of irAEs are described in Supplementary Table 3. Regarding treatment type PD1, PD-L1 and ICI + CT were more prone to result in late-onset irAEs, possibly be explained by the longer treatment duration (Table 1). However, relatively small numbers in each subgroup preclude drawing statistical significance.

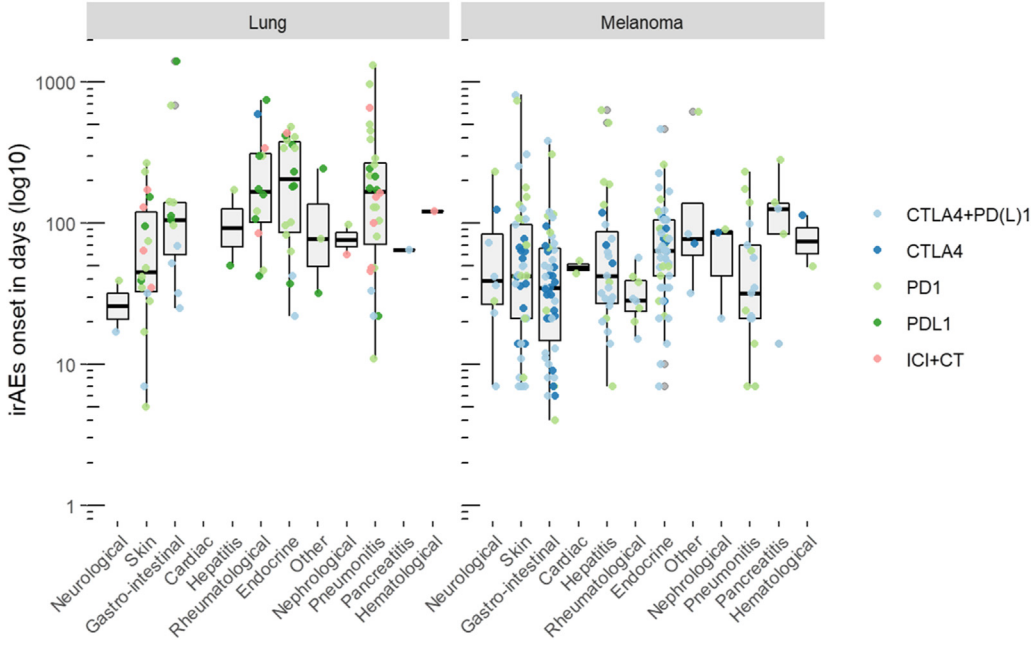

Fig. 2. **Boxplots displaying irAEs onset time on a logarithmic scale according to toxicity type.** Toxicities are presented in ascending order according to the global median onset time. Points show individual onset times per treatment type. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The cumulative probability of onset of first toxicity since treatment initiation was 42.8%, 51% and 57.3% at 6, 12 and 24 months respectively (Fig. 3A).

With an mFU of 369 days [IQR 194–695], we observed a median duration of all irAEs of 98 days [IQR 28–279]. In particular, median time to resolution for endocrine irAEs was not reached and it was 93 days for pulmonary, 44 days for skin and 39 days for gastrointestinal toxicities (Supplementary Fig. 1). Of the 318 irAEs recorded, 112 (35.2%) were long-lasting (duration $\geq$ 6 months) and 128 (40.3%) were ongoing at our data cutoff or patient death. Of these, the majority were endocrine irAEs (n = 69, 53.9%), skin toxicities (n = 20, 15.6%), rheumatological (n = 14, 10.9%) and pneumonitis (n = 11, 8.6%). We then calculated the cumulative probability of ongoing toxicity for patients still on ICI treatment and found that this probability remains relatively stable with only a slight increase over time (risk of 42,8% at 6 months, 38,4% at 12 months and 35,7% at 24 months, respectively) (Fig. 3 B).

3.5. Correlation between irAEs and OS

We then investigated whether the onset of any irAE(s) correlated with overall survival (OS) benefit in our study

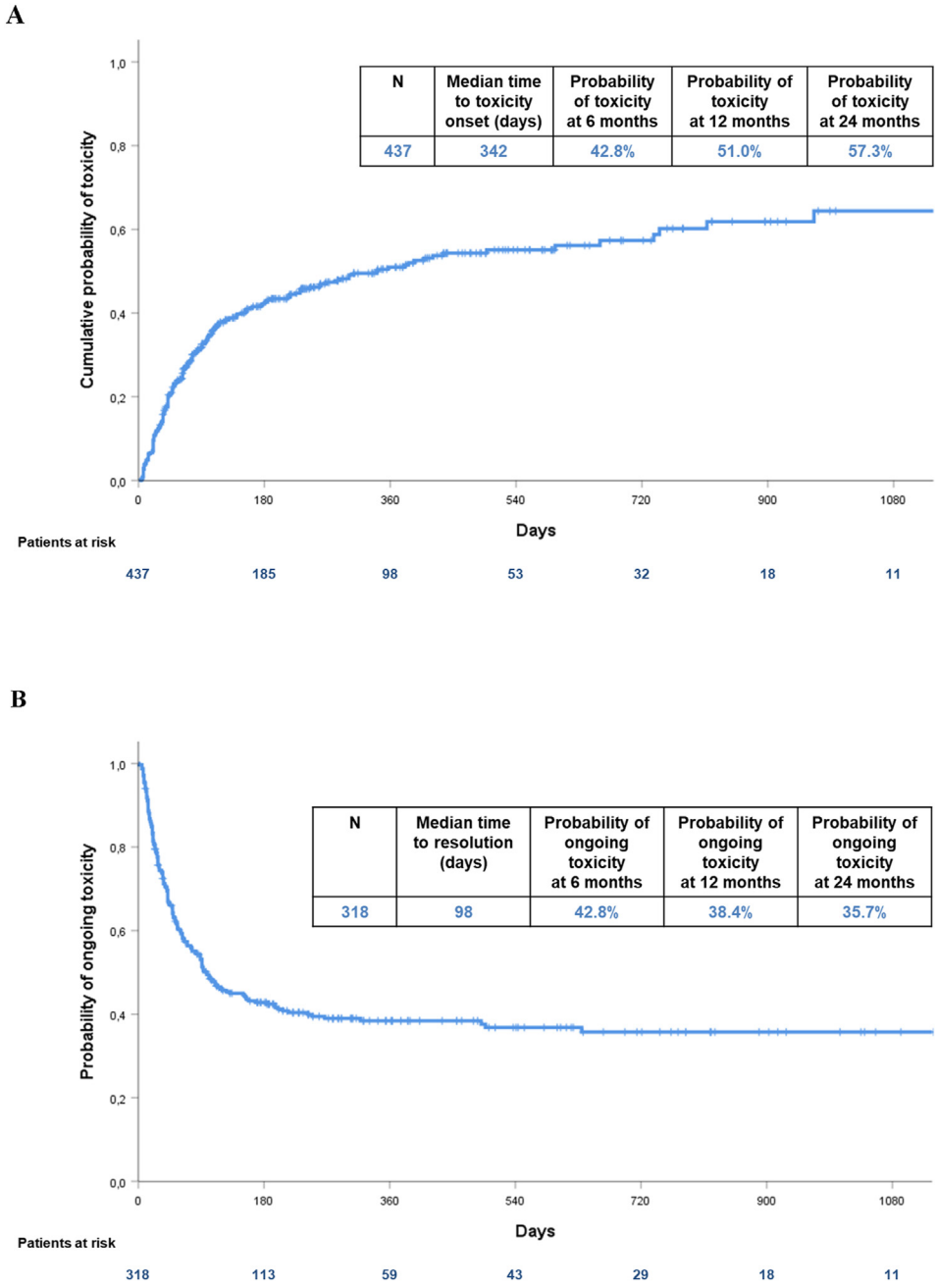

Fig. 3. Kaplan-Meyer curves representing the cumulative probability of toxicity since treatment start (A) and probability of ongoing toxicity since toxicity onset (B) in our study population.

population (Mel and LC cohorts). Standard Cox model resulted in an apparent statistical significant benefit in OS for both LC and Mel subgroups of patients who developed a toxicity G ≥ 2 (HR 0.53 [95%CI 0.33–0.86], p = 0.0069 and HR 0.56 [95%CI 0.36–0.88], p = 0.013, respectively, Fig. 4A and C). By contrast, the corrected Cox model, including toxicity as time-dependent covariate failed to retain the significant difference between the two subgroups (HR 1.11 [95%CI 0.68–1.80], p = 0.67 and HR 0.74 [95%CI 0.47–1.16], p = 0.19) (Fig. 4B and D).

4. Discussion

A comprehensive analysis of irAEs in clinical trials is critical, as the results constitute an important reference for clinicians. However, the need to quickly provide potentially curative treatments to patients has prompted regulatory agencies to develop fast track approval programs, which, although necessary, have the drawback of potentially underestimating late-onset adverse events, as well as the long-term impact of chronic toxicities.

In our systematic review of pivotal trials leading to ICI approval, the information regarding the duration of irAEs and the proportion of patients with ongoing toxicity at data cut-off was not specified in 90% of the studies. Moreover, median follow-up was relatively short and in more than 80% of the studies, treatments were still ongoing at data cut-off in a significant proportion of patients. We believe that accurate evaluation and description of toxicity is essential to define treatment value. Toxicity is among the parameters included in the ASCO value framework [21,22]. Specifically, in the case of unresolved symptomatic toxicities one year after treatment completion, 5 points should be subtracted from the clinical benefit score. Similarly, the NCCN and ESMO Magnitude of Clinical Benefit Scale (MCBS) include safety among the five key value measures, and the total score should be decreased for significant chronic or long-term toxicities [23,24]. Consequently, if the information is lacking in the

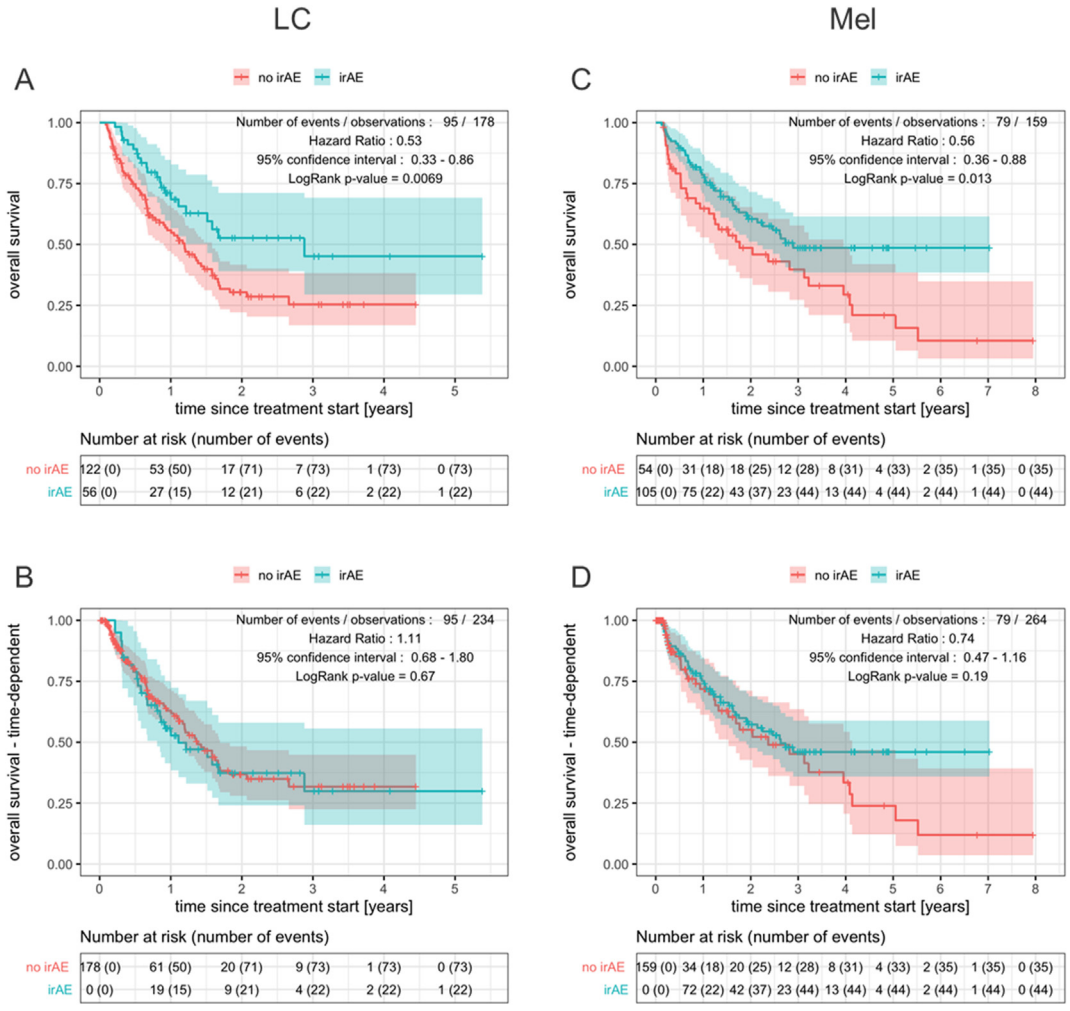

Fig. 4. **Correlation between Overall Survival (OS) and immune-related toxicities (irAEs).** (A, B): advanced/metastatic lung cancer cohort. C, D: advanced/metastatic melanoma cohort. (A, C): OS according to standard Cox model considering irAE occurrence as a fixed variable; (B, D): OS considering irAE onset as a time-dependent covariate.

publication, the score cannot be accurately calculated, and the value of treatment can be overestimated. Indeed, in several tumours, immunotherapy is associated with a significant increase in the chance of long-term survival and this unprecedented benefit reasonably outweighs the uncommon risks of long-term toxicities. However, this issue will be more relevant following ICI approvals in the adjuvant setting, where the threshold of patients' willingness to accept the risk of long-term toxicity may probably be lower compared to the advanced disease setting.

As already highlighted for haematological malignancies, the need to revise principles for monitoring safety and tolerability in pre-marketing trials and post-marketing follow-up studies is urgent for new standard-of-care treatments, including ICIs [25]. Nevertheless, the need for efficient drug development, combined with the financial constraints of prolonged patient monitoring within trials, increases the relevance and need for more extensive use of real-world evidence for long-term post-marketing surveillance. In our real-world data analysis, the cumulative incidence of any irAEs G $\geq$ 2 was 52%, and one-third of our patients experienced at least one G $\geq$ 3 adverse event, in line with the findings of the recent systematic review by Wang and colleagues [3]. These numbers can be important to share with patients before they begin treatment with ICIs. Incidence of toxicities according to treatment type in our series was consistent with results from 3 previous studies: the anti-CTLA4-anti-PD(L)1 combination is the most toxic treatment, followed by anti CTLA4, while anti-PD1 shows the best safety profile for irAEs [1,26,27]. Furthermore, organ-specific irAE distribution according to treatment type and differences between melanoma and lung cancer were in accordance with previous reports (i.e. higher incidence of pneumonitis in lung cancer and gastrointestinal toxicities in melanoma) and mainly dependent on the agents used [1]. Interestingly, the conditional probability of developing toxicity during a subsequent line of ICI treatment did not differ between patients who experienced an irAE during the first line and patients who did not. However, this finding could be explained by the selection bias in re-challenging patients who already had severe toxicity with first-line ICI(s). As per guidelines, only patients with moderate toxicity (G2) and completely resolved ones have been rechallenged with a second ICI line [4,6].

Of note, the present study yielded three important findings regarding ICI use and irAEs in the real-life setting among patients with melanoma and lung cancer. First, we found that the time to onset of irAEs varies considerably and is widely distributed over time, with late-onset toxicities that can appear up to 2 years after the first-treatment initiation. Even if a trend for a longer time to onset was observed for endocrine irAEs and pneumonitis compared to skin and GI irAEs, no statistically significant difference was found. Furthermore, the cumulative probability of onset of first toxicity in our study population was 42.8%, 51% and 57.3% at 6, 12 and 24 months respectively. These numbers are even more relevant if we consider the mFU of ICI pivotal trials (12 months), meaning that a significant proportion of late-onset irAEs could not be captured in these trials. These results underline once more that patients receiving ICI(s) should be regularly educated about the probability of developing irAEs and monitored for treatment-related complications since we show that late-onset irAEs are more common than previous evidence suggested.

Second, in our cohort, about 35% of irAEs lasted $\geq$6 months, and about 40% were ongoing at our data cutoff or patient death. The probability of ongoing toxicity from the onset was 42.8%, 38.4% and 35.7% at 6, 12 and 24 months respectively. The potential occurrence of long-lasting skin, endocrine, rheumatological, neurological or nephrological toxicities is a relevant issue for both patients and caregivers, which definitely warrants discussion during medical visits. This point is even more relevant considering that in our study we captured only irAEs of G2 and above, meaning that these toxicities, by definition, could potentially lead to the need for life-long treatment with a meaningful impact on patient quality of life (Qol). We found no statistical association between patients baseline characteristics (age and sex) and irAEs onset and/or frisk of long-lasting toxicities.

Third, we demonstrated that a rigorous accounting of toxicities onset, including late-onset ones, is critical to assess the potential impact of irAEs on OS. While an association between irAE development and response to ICI(s) has been advocated in many retrospective studies [28–30], in our series, no statistical association exists between irAE occurrence and OS, both for advanced/metastatic melanoma and LC. In fact, while comparing OS between patients who experienced irAEs and patients who did not, HR from the standard Cox model appears to be highly significant (suggesting better outcome for patients experiencing toxicity), but the difference is not significant when the toxicity is correctly considered as a time-dependent covariate, see Fig. 4. This could be explained by the well-known 'immortal-time bias': patients who experienced late-onset toxicities have a guaranteed survival up to the onset of that toxicity. Of note, in the Mel cohort, the survival curve for patients who experienced an irAE shows a distinctive plateau after the 3-year mark (Fig. 4D, 23 patients at risk). This could suggest a potential correlation of irAE with long-term ICI benefit in a specific sub-group of Mel patients. However, caution should be taken for the interpretation of these results, as patients receiving different treatments were pooled together in this survival analysis. Unfortunately, subgroup analysis according to irAE or treatment types led to insufficient numbers to reach sufficient statistical power, precluding conclusions as to whether a specific ICI regimen or irAE is associated with a better prognostic.

However, some limitations of this study need to be stated. First of all, our study focused only on melanoma and lung cancer. Second, the use of text-based search functions to screen for irAEs in electronic medical records that are not always populated by medical terms from MedDRA (Medical Dictionary for Regulatory Activities). In addition, the retrospective nature of the study and the difficulty of irAE grading outside of clinical trials could potentially lead to an underestimation of irAEs. Last but least, the potential confounding effect of immunosuppression on OS should be taken into account. As the immunotherapy field is rapidly advancing, we recognise that further studies, ideally multicentre prospective ones, are urgently needed to validate our findings across different tumour subtypes and also in the adjuvant setting [28,31,32].

In conclusion, we demonstrated that in the immunotherapy era, initial clinical trial reports leading to ICI approval should imperatively be followed by studies with long-term follow-up of the same patients, as incomplete reporting of duration and resolution of toxicities certainly underestimates the clinical relevance of irAEs. In this context, real-world evidence represents an indispensable complement to clinical trials, as it provides data on large numbers of patients on long time scales at a fraction of the cost of clinical trials. In addition, real-world evidence can help assess the generalisability of clinical trial findings to unselected patient populations that are more faithful to real-life situations. To our knowledge, this study is one of the first and largest real-world data analysis evaluating the risk of late-onset and long-term irAEs in unselected patients. The reported evidence is a seminal example of how real-world data can be harnessed to guide clinical decision making.

Authors' contributions

EG, AW, BH, MAC, DMM, OM conceived the study and carried out study design and coordination of data entry and analysis. EG, AW, MI, DJ, GMB, GCL participated in data entry. BH, LS, OB, KO, MANN, PS, OM, GC patient care and data collection. EG, LM, GV, MA, MDM carried out the systematic revision of the literature. CM, PS, TE, WA, GR, MAC developed Virtual Trial tool and assured data quality. WA, MAC, MDM statistical analysis. MAC, DMM, OM study supervision. All authors read and approved the final manuscript.

Ethics committee approval

A protocol for retrospective data analysis for scientific purposes was approved by the local ethics committee (CER-VD) on the 12th of February 2020 at the University Hospital of Lausanne (CHUV).

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Conflict of interest statement

EG, AW, MI, BGM, CLG, SL, BCO, MC, SP, ET, RG, LM, MC declare no conflicts of interest.

HB received advisory board or consultant fees from MSD, BMS, Astrazeneca, Roche.

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GV received advisory board or consultant fees from GSK-Tesaro, Amgen, PharmaMar, Roche, Astrazeneca, Clovis.

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MO and HZ declare research support and honoraria from Roche, BMS, MSD, Astra-Zeneca, GSK and Novartis.

NNMA declared an advisory role for Astrazeneca.

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GC has received grants, research support and/or is coinvestigator in clinical trials by BMS, Celgene, Boehringer Ingelheim, Roche, Iovance and Kite; has received honoraria for consultations or presentations by Roche, Genentech, BMS, AstraZeneca, Sanofi-Aventis, Nextcure and GeneosTx.

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Appendix A. Supplementary data

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