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Hot Topic

Real world data in the era of Immune Checkpoint Inhibitors (ICIs): Increasing evidence and future applications in lung cancer

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ABSTRACT

Immune checkpoint inhibitors (ICIs) targeting programmed death 1 (PD-1) and PD-ligand 1 (PD-L1) quickly subverted the standard of treatment in Non-Small Cell Lung Cancer (NSCLC), where they were first introduced in all comers previously treated advanced/metastatic NSCLC patients and subsequently in the first line of PD-L1 selected cases of metastatic and locally advanced disease.

Treatment algorithm is an evolving landscape, where the introduction of front-line ICIs, with or without chemotherapy, unavoidably influences the following treatment lines. In this context, medical oncologists are currently facing many unclear issues, which have been not clarified so far by available data.

Effectiveness and safety in special populations underrepresented in clinical trials - such as elderly, poor PS, hepatitis or human immunodeficiency virus-affected patients - are only a part of the unexplored side of ICIs in the real world. Indeed, pivotal randomized clinical trials (RCTs) often lack of external validity because eligibility criteria exclude some patient subgroups commonly treated in real-world clinical practice. Similarly, cost-effectiveness and sustainability of these innovative agents are important issues to be considered in the real-world. Though affected by several limitations, real-world evidence (RWE) studies allow to collect data regarding overall treated patients in clinical practice according to local authority regulations, overcoming the intrinsic limits of RCTs.

The present review focuses on RWE about ICIs in lung cancer treatment, with particular reference to special patient populations, and discusses potential application of real-world data in a potential innovative drug development model.

Introduction

During the course of last five years, the introduction of a new class of drugs, the immune checkpoint inhibitors (ICIs), has dramatically changed the treatment of lung cancer. Anti-PD1 (pembrolizumab and nivolumab) and anti-PD-L1 (atezolizumab and durvalumab) are able to avoid certain tumor immune-escaping mechanisms, thus restoring the antitumor response of patient's immune system [1]. ICIs were firstly introduced as first or second line treatment of patients with advanced stage disease, both in PD-L1 selected (pembrolizumab) and all comers [2–5]; later on, durvalumab was introduced as consolidation treatment in the algorithm of PD-L1 positive locally-advanced non-small cell lung cancer NSCLC [6]. Currently, several clinical trials in neoadjuvant and adjuvant setting are ongoing [7].

Different immunotherapeutic agents, with similar indication, target and safety profile, have been approved by regulatory agencies, thus contributing to the proliferation of "me-too drugs" in the current scenario [8]. In this context, little to no evidence is available to support the selection among available agents.

It is important to highlight that nowadays the approval process is based on the results of randomized clinical trials (RCTs). The majority of conclusive RCT randomly allocate patients to receive an interventional treatment or the standard of care, thus being able to prove the benefit of the investigational therapeutic agent. Patients' population is strictly defined by inclusion and exclusion criteria, in order to minimize the bias related to variables other than the interventional treatment itself. As a consequence, RCTs generate the strongest form of evidence and therefore represent the gold standard to evaluate the efficacy of an

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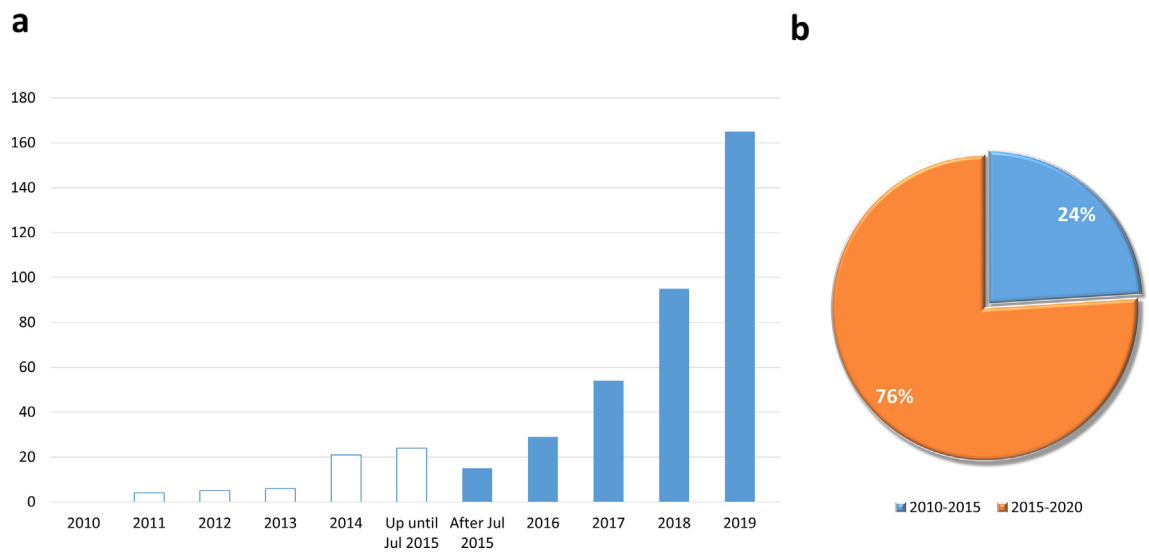

Fig. 1. Amount of real word evidence on ICIs between 2010 and 2020; a) Number of citations/year of real world evidence in lung cancer between January 2010 and January 2020; b) percentage of real world evidence on ICIs in lung cancer before and after July 2015.

intervention. However, translating this evidence in the real-life can be challenging, with a significant proportion of patients we deal with in daily practice being under-represented in RCT.

Since ICIs have become part of the new standard of care for lung cancer, oncologists have had to face the lack of data about subsets of patients usually excluded by pivotal clinical trials. Particularly, it is crucial to gain information about safety and effectiveness of ICIs in patients affected by chronic viral diseases and, more importantly, the ones having brain metastases or an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2 or worse.

Real world studies are emerging in medical oncology as a useful tool to collect data from daily clinical practice, thus driving clinical choices in special patients population; these studies may be enriched with budget impact analysis data and additional useful information for several stakeholders and possibly might become a part of regulatory agencies approval pathway in the next future.

The term real-world data (RWD) refers to population-level data gathered from multiple sources, such as existing registries, administrative databases, hospital records, disease-specific databases and insurance claims, in a post-market context. Real-world evidence (RWE) represents the evidence generated from the analysis of RWD, in the setting of pragmatism-oriented studies. RWE might be highly useful, as it could be informative about the features of patients who have access to health care and treatments for a certain disease (i.e. observational studies). On the other hand, it could also assess the efficacy of a certain medical intervention under usual conditions (i.e. pragmatic studies), outside the controlled setting of conventional clinical trials.

The widespread digitalization of source data is facilitating this kind of studies. Indeed, the advent of so-called electronic health records (EHRs) has simplified both the collection of wide range of data and the integration of patients' information coming from different data sets.

The aim of this review is to present a wide picture of RWE available since the advent of ICIs in thoracic oncology, focusing on their application particularly in the clinical management of special populations, and to discuss future application in the drug development process.

Materials and methods

We conducted a PRISMA-based systematic review with two systematic PICo searches (Supplementary Appendix). A systematic search of PubMed and Cochrane Library was performed, using the search terms 'real-world' and 'lung cancer' with all relevant synonyms and the time frame between January 2010 and January 2020.

A second systematic search of PubMed and Cochrane library was performed, using the search terms 'real-world', 'lung cancer' and 'immunotherapy' or 'nivolumab' or 'pembrolizumab' or 'atezolizumab' or 'durvalumab' with all relevant synonyms.

The first research was meant to evaluate the quantitative impact of ICI introduction in the RW studies in lung cancer. The second one focused on ICIs in particular sub-populations.

After removal of duplicates, titles and abstracts were screened by two researchers (A.P. and I.A.) independently and split in 'before' and 'after' ICI introduction, using the July 2015 as split point, and finally focusing on available data between July 2015 and January 2020.

Only English-language studies published in peer-review journals were considered. Studies that described only case reports, clinical trials, reviews and conference abstracts were excluded. Articles were read in full and a further selection was made based on relevance of these full texts. Discrepancies between the two researchers were discussed and resolved by consensus.

Results

Real world data on ICIs in lung cancer

The first literature search yielded 582 citations in PubMed and 101 citations in Cochrane library. After excluding duplicates and applying the selection criteria, 197 articles were excluded. Among the remaining articles, 60 were published in the 5-year time frame between 2010 and July 2015, whereas 372 in the following 5-year period between July 2015 and January 2020 (Figs. 1 and 2).

The second combined literature search yielded 157 citations; among them 120 citations were published after July 2015. Five results (4.2%) concern the locally advanced setting of treatment and 115 (95.8%) the treatment of stage IV NSCLC. After applying the selection criteria, nineteen articles were excluded (Fig. 2). Forty-seven final articles were selected according to the relevance of the full-text results.

Efficacy and safety a of ICIs in the real world

The vast majority of the real-world data about immunotherapy in lung cancer describes the activity, in terms of objective response rate (ORR), efficacy (in terms of overall survival, OS, and progression free survival, PFS) and the safety profile of the most common ICIs used in clinical practice (Table 1). Studies on pretreated NSCLC patients were all retrospective and showed outcomes comparable with those reported

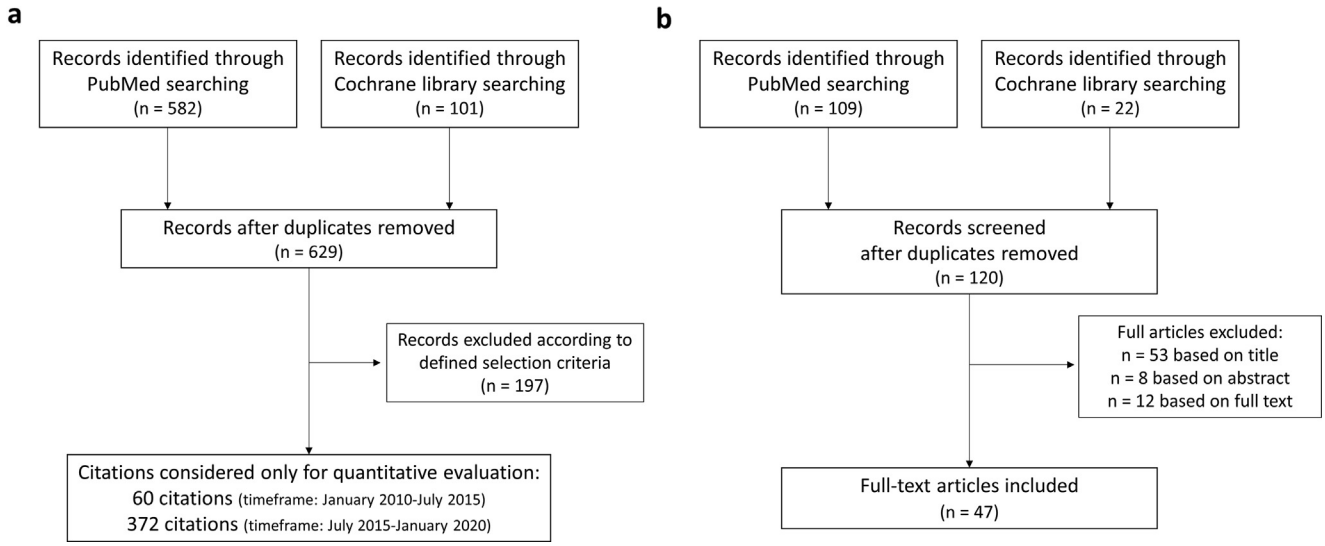

Fig. 2. Flow charts representing results of: a) systematic search of PubMed and Cochrane Library, using the search terms 'real-world' and 'lung cancer' in the time frame between January 2010 and January 2020; b) systematic search of PubMed and Cochrane library using the search terms 'real-world', 'lung cancer' and 'immunotherapy' or 'nivolumab' or 'pembrolizumab' or 'atezolizumab' or 'durvalumab' after July 2015.

in the pivotal RCTs, with median PFS and median OS ranging from 1.8 to 4.9 months and from 7.9 to 14.6 months, respectively [9–24]. Only one study showed a remarkable outcome for patients treated with nivolumab, with a median PFS exceeding 8 months and a median OS of over 15 months; however, this may be due to the small population ($n = 11$) considered for analysis [23]. There were no particular differences between real world experiences from Asian or non-Asian countries. The presence of EGFR or ALK druggable alterations, whenever tested for impact on outcome of non-squamous NSCLC patients, had a negative predictive role [9,10,19–22,25]. The rate of EGFR mutant NSCLC patients was consistent with pivotal trials (range: 5–21%), with the exception of the Taiwanese experience (41%) [22]. No new safety signals were observed; however, it is worth mentioning a slightly higher incidence of grade 3–4 treatment related pneumonitis in the Japanese and Portuguese studies (4.3% and 5.7%, respectively) [9,24]. Currently there are fewer RW studies in the first line treatment with pembrolizumab, they are retrospective and they deal with efficacy and safety as well [26–30] (Table 1). Results are in line with those obtained in RCTs; of interest however, median OS values in RW studies are closer to that observed in the Keynote 042 subpopulation of patients with PD-L1 TPS $\geq$ 50%[31], rather than that observed in Keynote 024 [5,32]. This may be due to patients characteristics, being the rates of never smokers included in these RW studies (range: 7.4–30.7%) more similar to the one of Keynote 042 (21%) [31]. Whenever clinical variables were tested for their impact on survival, ECOG PS 2 was the only one always affecting outcomes [26,28]. Safety profile was consistent with literature. Notably, Ksienski and colleagues performed logistic regression analysis in order to determine factors predicting grade 3 or higher immune-related toxicities within 3 months of starting pembrolizumab and found that patients with baseline ECOG PS $<$ 2 had higher risk of developing immune-mediated adverse events [26].

Budget impact of anti-PD1 and anti-PDL1 agents

In parallel to these clinical evaluations, the high incremental costs of ICIs have prompted particular attention towards treatment affordability. For the purpose of this review, we have selected studies directly involving real world patients and not cost effectiveness models derived from RCTs. Almazàn and colleagues performed an economical assessment of a retrospective series of patients treated with nivolumab as second line in 15 Spanish hospitals, using the cost per life-year gained (LYG) as variable [33]. LYG was calculated as the rate between the benefit in OS (months) and the incremental cost of nivolumab therapy for all patients and it turned out to be of €110,026.00. The profitability, as defined by WHO, should be lower than three times the gross domestic product of the country per year of life adjusted to disability. In Spain such value is €75,000.00: LYG largely exceeds this threshold, pointing out once more the need of selecting patients with higher potential benefit from ICI. In this context, a more recent study estimated the cost-effectiveness of pembrolizumab according to comorbidities, defined with Charlson scoring system [34], using a model that combines clinical trial and real-world patient data [35]. Authors evaluated the incremental cost-effectiveness ratios (ICERs) compared to a willingness-to-pay-threshold of $100,000.00/quality-adjusted life-year (QALY). When evaluating pembrolizumab, despite the survival improvement compared to chemotherapy alone, the treatment regimens were not cost-effective in any of the patient populations, mainly due to the shorter OS of real-world patients compared to that observed in clinical trials. ICERs were even higher for patients with relevant comorbidities, suggesting the need of price re-modulation in order to guarantee a fair cost-effectiveness, given the true effectiveness of pembrolizumab reported in the real-world setting [35]. In the context of economic evaluation, another interesting study focused on the budget impact of the switch from a weight-based to a fixed dose regimen of anti-PD-1 agents [36]. Authors calculated the difference between the costs in these two regimens in patients treated in France from January to April 2018, assuming a constant price for both nivolumab and pembrolizumab. The study reported a mean extra-cost attributable to flat-fixed dosing of €349 per infusion of nivolumab and €1,234 per infusion of pembrolizumab, addressing a new important issue in terms of need of price-adjustment for this innovative class of drug and demonstrate that fixed dosing is likely to have substantial economic impact.

Real world evidence on special populations

Elderly

Median age of lung cancer patients at diagnosis is 70 years [37], however, elderly patients are underrepresented in most RCTs: the over-75 population accounted for about 8% in the CheckMate 017 and 057 trials [2,3] and for about 10–15% in Keynote 042 and 024, respectively [5,31,38]. With their favorable safety profile, ICIs may represent a good option for elderly patients. On the other hand, immune-senescence might impact on the capability of an aged immune system to properly

Table 1
Summary of the main studies reporting about efficacy and safety of ICIs in the real world.

	Author (reference)	Sample size	Treatment	Median PFS (months)	Median OS (months)	ORR (%)	Main factors influencing outcome	Safety profile
Pre-treated setting								
R	Morita R. et al. [9]	901	Nivolumab	2.1 (95% CI: 1.9–2.4)	14.6 (95% CI: 12.3–15.9)	20.5	Negative impact on PFS and OS: - ECOG PS - Liver metastasis Negative impact on PFS: - EGFR sensitizing mutations	All grade irAE = 45.8% G3-4 irAE = 14.0% G5 irAE = N.I. Pulmonary irAE G3-4 = 4.3% ICI discontinuation rate = 17.9%
R	Kobayashi K. et al. [10]	142	Nivolumab	1.9 (95% CI: 1.6–2.2)	–	17.0	Negative impact on PFS: - EGFR sensitizing mutations Positive impact on PFS - Previous radiotherapy	All grade irAE = 45.1% G3-4 irAE = 13.3% G5 irAE = 1.4% Pulmonary irAE G3-4 = 2.1% Pulmonary irAE G5 = 0.7% ICI discontinuation rate = N.I.
R	Grossi F. et al. [40] *	1588	Nivolumab	3.0 (95% CI: 2.9–3.1)	11.3 (95% CI: 10.2–12.4)	18.0	Negative impact on OS: - ECOG PS - Liver metastasis	All grade irAE = 32.0% G3-4 irAE = 6.0% G5 irAE = 0.0% Pulmonary irAE G3-4 = < 1% ICI discontinuation rate = 5.0%
R	Crinò et al. [18] **	371	Nivolumab	4.2 (95% CI: 3.4–5.0)	7.9 (95% CI: 6.2–9.6)	18.0	Negative impact on OS: - ECOG PS - Liver metastasis - Bone metastasis	All grade irAE = 29.0% G3-4 irAE = 6.0% G5 irAE = 0.0% Pulmonary irAE G3-4 = < 1% ICI discontinuation rate = 9.0%
R	Manrique M. et al. [19]	188	Nivolumab	4.8 (95% CI: 3.6–5.9)	12.8 (95% CI: 9.1–16.6)	25.5	Negative impact on OS: - ECOG PS - CNS metastasis	All grade irAE = 78.0% G3-4 irAE = 4.8% G5 irAE = 0.0% Pulmonary irAE G3-4 = 1.1% ICI discontinuation rate = 4.8%
R	Khozin S. et al. [20]	1344	Nivolumab and pembrolizumab	–	8.0 (95% CI: 7.4–9.0)	–	Negative impact on OS: - EGFR sensitizing mutations - ALK translocation	–
R	Khozin S. et al. [21]	5257	Nivolumab, pembrolizumab and atezolizumab	3.2 (95% CI: 3.1–3.3)	9.3 (95% CI: 8.9–9.8)	–	Negative impact on PFS and OS: - EGFR sensitizing mutations - ALK translocation - Hepatic dysfunction Positive impact on PFS and OS: - Female sex - History of smoking	–
R	Lin S.-Y. et al. [22]	74	Nivolumab and pembrolizumab	1.8 (95% CI: not indicated)	7.9 (95% CI: not indicated)	32.0	Negative impact on PFS and OS: - ECOG PS Negative impact on PFS - EGFR sensitizing mutations Positive impact on PFS and OS: History of smoking	All grade irAE = 17.6% G3-4 irAE = 4.0 G5 irAE = 0.0% Pulmonary irAE G3-4 = 4.0% ICI discontinuation rate = N.I.

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Table 1 (*continued*)

	Author (reference)	Sample size	Treatment	Median PFS (months)	Median OS (months)	ORR (%)	Main factors influencing outcome	Safety profile
R	Abbas W. et al. [23]	11	Nivolumab	8.0 (95% CI: 1.5–14.5)	15.0 (95% CI: 6.9–23.1)	54.5	–	All grade irAE = 72.7% G3-4 irAE = 18.2% G5 irAE = 0.0% Pulmonary irAE G3-4 = 18.8% ICI discontinuation rate = N.I.
R	Figueiredo A. et al. [24]	219	Nivolumab	4.9 (95% CI: 3.9–6.1)	13.2 (95% CI: 9.9–16.5)	22.4	Negative impact on OS: - ECOG PS	All grade irAE = 76.4% G3-4 irAE = 16.0% G5 irAE = N.I. Pulmonary irAE G3-4 = 5.7% ICI discontinuation rate = 12.8%
R	Juergens R.A. et al. [25]	472	Nivolumab	3.5 (95% CI: 3.2–4.0)	12.0 (95% CI: 11.0–13.9)	–	Negative impact on OS: - ECOG PS - CNS metastasis Negative impact on PFS and OS: - EGFR sensitizing mutations	–
R	El Karak F. et al. [11]	110	Nivolumab and pembrolizumab	4.0 (95% CI: 2.6–5.4)	8.1 (95% CI: 2.8–13.4)	25.3	–	All grade irAE = 18.0% G3-4 irAE = N.I. G5 irAE = 0.0% Pulmonary irAE G3-4 = N.I. ICI discontinuation rate = N.I.
R	Ahn B.-C. et al. [12]	155	Nivolumab and pembrolizumab	3.1 (95% CI: 1.9–4.2)	10.2 (95% CI: 5.4–15.1)	23.9	Negative impact on OS: - ECOG PS - EGFR sensitizing mutations - ALK rearrangement - Liver metastasis	All grade irAE = 61.9% G3-4 irAE = 5.3% G5 irAE = 0.0% Pulmonary irAE G3-4 = 3.2% ICI discontinuation rate = N.I.
R	Nadler E. et al. [13]	718 (2L) 302 (3L)	Nivolumab and pembrolizumab	–	2L: 9.7 (95% CI: 8.3–13.0) 3L: 11.3 (95% CI: 7.8–14.4)	–	–	–
R	Brustugun O. T. et al. [14]	58	Nivolumab	–	11.7 (95% CI: not indicated)	–	–	All grade irAE = 31.0% G3-4 irAE = 5.0% G5 irAE = 0.0% Pulmonary irAE G3-4 = 0.0% ICI discontinuation rate = 6.9%
R	Weis T. M. et al. [15]	124	Nivolumab (65.3%) and atezolizumab (34.7%)	2.2 (95% CI: 1.7–2.8) for nivolumab 2.0 (95% CI: 1.8–2.7) for atezolizumab	8.4 (95% CI: 6.3–11.2) for nivolumab 6.5 (95% CI: 4.7-NR) for atezolizumab	14.3	Negative impact on PFS and OS: - ECOG PS	Nivolumab All grade irAE = 70.4% G3-4 irAE = N.I. G5 irAE = 0.0% Pulmonary irAE G3-4 = N.I. ICI discontinuation rate = 19.8% Atezolizumab All grade irAE = 65.1% G3-4 irAE = N.I. G5 irAE = 0.0% Pulmonary irAE G3-4 = N.I. ICI discontinuation rate = 14.0%
R	Fujimoto D. et al. [16]	613	Nivolumab	ND 1-year PFS = 18%	–	20.0	Negative impact on PFS: - ECOG PS - EGFR sensitizing mutations - ALK rearrangement - Never-smoking status	All grade irAE = N.I. G3-4 irAE = 11.1% Pulmonary irAE G3-4 = 4.6% G5 irAE = 1.3% ICI discontinuation rate = N.I.

First line setting

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Table 1 (*continued*)

	Author (reference)	Sample size	Treatment	Median PFS (months)	Median OS (months)	ORR (%)	Main factors influencing outcome	Safety profile
R	Ksienski D. et al. [26]	190	Pembrolizumab	3.7 (95% CI: 2.8–4.3)	24.3 (95% CI: 9.7-NR)	–	Negative impact on OS: - ECOG PS	All grade irAE = 34.7% G3-4 irAE = 8.4% G5 irAE = 0.0% Pulmonary irAE G3-4 = 0.5% ICI discontinuation rate = 12.1%
R	Tamiya M. et al. [28]	213	Pembrolizumab	8.3 (95% CI: 6.0–10.7)	17.8 (95% CI: 17.8-NA)	51.2	Negative impact on PFS: - ECOG PS - Steroid - PD-L1 TPS	All grade irAE = 76.4% G3-4 irAE = 18.3% G5 irAE = 0.5% Pulmonary irAE G3-4 = 0.9% ICI discontinuation rate = N.I.
R	Velcheti V. et al. [29]	611	Pembrolizumab	6.8 (95% CI: 5.3–8.1)	18.9 (95% CI: 14.9–25.5)	48.0	–	–

G = grading; irAE = immune-related adverse event; L = line; NI = not indicated; NR = not reached; OS = overall survival; PFS = progression free survival; PS = performance status; R = retrospective study.
* non-squamous cell advanced NSCLC population; ** squamous cell advanced NSCLC population.

respond to cancer and to be restored in its antineoplastic response after ICI administration [39]. Several retrospective works tried to shed some light on this topic, evaluating both outcomes (OS, PFS, time to treatment failure, TTF, and ORR) and safety of ICIs in an elderly population. All studies outlined that the benefit from ICI monotherapy was not statistically different between older and younger patients and that also tolerability was not affected by age [40–44]. Regarding treatment related adverse events, only Muchnik and colleagues found that the rate of immune-related colitis was higher for patients older than 80 [42]. This observation was not reported in CheckMate 153, a predominantly community-based phase IIIb/IV study designed to assess primarily the safety, but also the efficacy, of nivolumab monotherapy in previously treated patients with advanced NSCLC [45]. The setting of this trial more closely reflected the real world, as it used less stringent eligibility criteria, allowing the enrollment of older and ECOG PS 2 patients. Still, results from such studies support the use of ICIs for elderly patients.

ECOG performance status 2

The main pivotal trials of ICIs in lung cancer did not include patients with poor PS, limiting inclusion criteria to PS 0 or 1 according to ECOG classification, while PS 2 patients were included in a very limited number of clinical trials [45,46]. Although the proportion of PS 2 patients was very low (about 10% in CheckMate 153 and 12% in CheckMate 171), safety profile seems not to be affected by PS. Survival results suggest a very limited effectiveness of nivolumab in patients with poor PS, with halved OS data compared to PS 0-1 patients [45,46].

Both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) approved the four available ICIs, regardless of the PS of patients. Therefore, the use of ICIs in PS 2 patients in clinical practice has been allowed, with subsequent collection of real-world data. Three papers on RWD specifically addressed this population subset, evaluating nivolumab in previously treated NSCLC patients [16,18,25]. The largest series included 94 PS 2 pre-treated patients in a retrospective multicenter study in Japan, showing a disease control rate of 26% compared to 50% in patients with PS 0-1 [16]. The Italian experience of nivolumab expanded access program (EAP) included 22 patients with ECOG PS 2, showing worse survival outcome compared to those with PS 0 (HR 2.75, p = 0.0001) [18]. Data from a similar experience in Canada, within the EAP CheckMate 169, included 19% of patients with PS 2, with a 6-month OS rate of 47% compared to 64% in PS 0-1 patients 6. An updated analysis of the same data showed halved OS for PS 2 vs PS 0-1 patients (6.8 vs 12.9 months, p = 0.01) [25,47]. Similar experience in Spain confirmed PS 2 as an independent prognostic factor for OS with nivolumab [48]. Curiously, safety data seem not to be affected by PS through all these studies [16,18,25].

In the lack of solid data from RCTs, real world data suggest caution in the use of ICI in patients with poor PS, where the good safety profile may be not sufficient to justify high costs in absence of survival benefit [49].

In this context, trials evaluating efficacy and tolerability of ICIs in this subset of patients are currently ongoing. The first to have some results is the PePS2 trial, a phase II study assessing the safety and tolerability of pembrolizumab for the treatment of NSCLC patients with ECOG PS 2 [50]. Co-primary outcomes were a durable clinical benefit (DCB, i.e. disease control rate at 18 weeks), ORR and the rate of dose delay or discontinuation due to immune-related adverse event (irAE). Preliminary analyses performed in a subset of 60 patients, showed a DCB of 33%, an ORR of 30%, while the rate of irAE was 8%. These findings are quite encouraging, though survival results (median PFS of 5.4 and an OS of 11.7 months) should be considered carefully, as only 9 out of 60 patients included (15%) received first-line pembrolizumab, with no responses and PFS of 1.9 months.

Another phase II study (NCT02581943) randomized PS 2 NSCLC patients to receive pembrolizumab alone or combined with weekly carboplatin and paclitaxel. Co-primary objectives were ORR, PFS and OS, and circulating immune markers [51]. An interim analysis on 20 patients demonstrated a higher ORR was achieved in the combination arm (70% *versus* 20%), with a good tolerability profile. No grade 3–4 adverse events were recorded, even though it is important to note that four patients had to permanently discontinue carboplatin due to allergic reactions. Another phase II trial (NCT02879617), studying the efficacy and safety of durvalumab in PS 2, treatment-naïve, locally advanced or metastatic NSCLC patients, is currently ongoing. Of note, Facchinetti and colleagues recently published a retrospective study evaluating PS 2 patients treated with first-line pembrolizumab: in this study, median OS was 11.8 months in patients whose PS 2 was related to comorbidity compared to 2.8 months in those with PS 2 driven by lung cancer (HR = 0.5, p = 0.001) [52].

Finally, also two phase III trials started their accrual of PS 2 NSCLC patients in first line treatment: the IPSOS trial (NCT03191786), comparing first atezolizumab with a single agent chemotherapy by investigator choice (vinorelbine or gemcitabine), and the eNERGY trial (NCT03351361), comparing nivolumab and ipilimumab and a carboplatin based doublet.

Central nervous system metastases

Central nervous system (CNS) is a frequent metastatic site in NSCLC patients, with the rate of brain metastases (BM) being about 40%.

Patients with BM are often symptomatic, require treatment with corticosteroids and have a poor PS. For these reasons, this special population is under-represented in clinical trials, where patients with BM are generally included only when CNS disease is under control and does not require active treatment. The proportion of patients with inactive and asymptomatic BM in the main pivotal trials of immunotherapy in lung cancer ranges from six to 17.5% [2,3,5,53,54]. Moreover, such trials did not contemplate preplanned analysis of CNS metastasis subgroups.

With these premises, the data from RCTs showing no differences among chemotherapy and pembrolizumab or nivolumab in a second line setting [2,3,53]. On the other hand, patients with a history of asymptomatic, treated BM, had longer median OS with atezolizumab than with docetaxel [55] in second line of treatment, while chemotherapy plus pembrolizumab provided clinical benefit also for patients with stable BM, in first line setting [56]. Such analyses were performed *post hoc*, therefore they could not be considered conclusive. A non-randomized trial aimed to evaluate the activity of pembrolizumab in untreated brain metastases from melanoma or NSCLC [57]. A recent update showed BM response rate of 29.7%; all the responses were in the PD-L1 positive cohort [58]. However, it must be stressed that only 42, out of the 71 patients (59.1%) initially screened for the trial, were enrolled; eight of them (19.0%) had already received previous whole brain radiotherapy.

In this setting, a modest amount of real-world data is available. A recent publication has included 255 patients with BM treated with ICIs in a multi-centric prospective study [59]. The population in study included about 40% with active BM and 14% were symptomatic. Despite a lower disease control rate, and an increased incidence of brain progressive disease compared to patients without CNS metastasis, the presence of BM was not an independent factor for OS in multivariate analysis, when considering steroid treatment and PS [59]. Also, the administration of cranial radiotherapy, either whole brain or stereotactic radiotherapy, did not affect survival [59].

The Italian EAP with nivolumab included patients with CNS metastasis, showing no differences in OS both in the squamous and non-squamous population, when compared to the overall population OS [17,18,60]. Similar results derive from the French EAP with nivolumab, including n = 130 patients with BM [61].

With the exception of three reports including very small number of patients with BM [25,62,63], all the real-world published evidence is concordant with the European results described [48,64–66].

Overall, the amount of real-world data in NSCLC patients with CNS metastasis treated with immunotherapy provide stronger evidence than RCTs on the safety and efficacy of ICIs in this special population.

Patients with pre-existing autoimmune disorders

ICIs work acting on molecular pathways physiologically involved with the immune self-tolerance and are characterized by irAEs, which are *de facto* newly triggered autoimmune disorders. For this reason and for the consequent fear of causing unacceptable immune reactions and severe toxicities, patients with pre-existing autoimmune disease (AIDs), except subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, were excluded from clinical trials testing ICIs. However, patients affected by such disorders are at risk of developing malignancies, including lung cancer [67] and almost up to one fifth of all lung cancer patients suffers from an AID [68,69]. Given the limited treatment options for advanced stage lung cancer, real world evidence about ICIs treatment in subjects with AIDs under a close clinical monitoring could be clinically useful. Subsequently, several retrospective studies have been conducted in order to investigate the risk and benefit of the use of immunotherapy in this subset of patients. Notably, Leonardi and colleagues studied a group of 56 patients with advanced NSCLC and an AID, treated with an anti-PD-1 or an anti-PD-L1 [70]. They reported irAE incidence similar to the one of clinical trials; moreover, AID exacerbation occurred in a minority of patients, especially those who were symptomatic from their AID at the time of ICI initiation. A well-conducted retrospective real-world study has been recently conducted on a large series of patients (n = 751) with advanced solid malignancies treated with anti-PD-1 agents, evaluating safety and efficacy according to the history of pre-existing AIDs [69]. Two thirds of cases were represented by NSCLC patients. The incidence of irAEs of any grade was higher in patients with pre-existing AIDs, irrespective of AIDs being symptomatic or not; however no significant difference was observed regarding grade 3–4 irAEs, ORR, PFS or OS. It was also found that almost a half of patients with pre-existing AIDs experienced a flare of the autoimmune disorder, with a wide incidence range according to the subtype of AID: 10% for rheumatologic disorders, up to 100% for gastrointestinal/hepatic diseases [69]. According to these real-world findings, pre-existing AIDs should not represent an absolute contraindication to immunotherapy. Patients with an active autoimmune disorder may not represent the best candidates for ICIs, but clinicians should consider this treatment option case by case, in a close collaboration with rheumatologists and immunologists, especially when alternatives are both quantitatively and qualitatively limited.

Patients with chronic viral diseases

The majority of clinical trials regarding the use of ICIs in NSCLC treatment excluded patients with chronic viral infections such as human immune-deficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). The main concerns involve the possibility of viral reactivation, but also the efficacy and the safety of the treatment itself, considering also the antiviral therapy patients must continuatively undergo.

Real-world evidence about safety of NSCLC treatment with ICI in HIV positive patients comes from retrospective case series. Three case series, accounting for a total of 30 advanced NSCLC patients, showed no viral rebound during the course of therapy and no significant difference in the safety profile [71–73]. In this field, results from a prospective phase I study evaluating the safety of pembrolizumab in people with HIV and advanced cancer (n = 30), including 19 patients with non-AIDS-defining cancers includingNSCLC patients, were recently published [74,75]. Pembrolizumab showed an acceptable safety and no significant alterations in CD4 count were detected. Furthermore, durvalumab was also evaluated in a similar setting, in the phase II trial DURVAST [76]. Twenty patients were enrolled, including 14 NSCLC cases; once again no new safety events were detected and disease control rate reached 50% in the NSCLC cohort.

Regarding HBV- or HCV-positive NSCLC patients treated with ICI, evidence is scantier. A retrospective work collected 10 HBV-/HCV-positive NSCLC patients treated with immunotherapy and reported toxicity and efficacy rates were similar to those of patients without chronic viral infections [73]. Furthermore, ICI treatment had no repercussions on circulating viral load or on viral replication.

Discussion

Since 2013, when anticancer immunotherapy became the breakthrough of the year, a growing body of evidence showed long-term disease control and OS improvement with ICIs compared with standard chemotherapy, in several cancers. In thoracic oncology, anti-PD-1 and anti-PD-L1 drugs subverted the standard of treatment of lung cancer, where some drugs came into clinical practice with different indications, especially in the “unmet medical need” areas.

Marketing approval by regulatory agencies has recently been based, in some cases, on the evidence raised by early-phase trials, thus making the daily oncology practice a fast-evolving landscape. As a consequence, medical oncologists are currently facing many unclear issues which have been not clarified so far by available data.

Effectiveness and safety in special populations underrepresented in clinical trials - such as elderly, poor PS, hepatitis or human

Table 2
Summary of the main studies reporting about real world efficacy and safety of ICIs in special populations.

	Author (reference)	Patients	Treatment	Findings
Elderly patients				
R	Grossi F. et al. [40]	Over 75: 19% (overall population n = 371)	Nivolumab (100%)	Three groups considered: patients aged < 65, 65–75 and ≥ 75 years. No differences in terms of ORR. Non-significant trend for shorter PFS and OS for the over 75. No differences in terms of safety.
R	Galli G. et al. [41]	Over 70: 38% (overall population n = 290)	Anti-PD-1 (66.7%) Anti-PD-L1 (29.4%) Combo-ICI (3.9%)	Three groups considered: patients aged < 70, 70–79 and ≥ 80 years. No differences in terms of ORR, PFS and OS. No differences in terms of safety.
R	Muchnik E. et al. [42]	Over 70: 100% (overall population n = 75)	Nivolumab (86.7%) Pembrolizumab (8.0%) Other (5.3%)	Median TTF: 4.2 months. Median OS: 8.2 months. Median OS of ECOG PS 0–1 patients (n = 38): 13.7 months. Grade 3–4 irAE: 8%.
R	Corbaux P. et al. [43]	Over 70: 75% (overall population n = 304)	Anti-PD(L)-1 (100%)	Absence of statistically significant impact of age on OS and PFS was confirmed after adjustment on prognosis covariates. 2-year OS rate of older *versus* younger patients: 29% *versus* 27%. 6-month PFS rate of older *versus* younger patients: 40% *versus* 29% No differences in terms of safety.
R	Youn B. et al. [44]	Over 75: 43.4% (overall population n = 1256)	Nivolumab (92.0%) Pembrolizumab (8.0%)	Median OS: 9.3 months. Age was not significantly associated with the hazard of death.
R	Spigel D.R. et al. [45]	Over 70: 39% (overall population n = 1426)	Nivolumab (100%)	Over 70 *versus* overall study population: - Median OS of 9.1 *versus* 10.3 months. No differences in terms of safety.
R	Sabatier R. et al. [81]	Over 70: 100% (overall population n = 30)	Nivolumab (100%)	Median PFS 3.3 months. Median OS 7.1 months. All grade irAE: 50%. Grade 3–4 irAE: 13.3%
ECOG PS 2 patients				
R	Crinò L. et al [18]	ECOG PS 2: 6.0% (overall population n = 371)	Nivolumab	ECOG PS 2 *versus* PS 0–1 patients: - HR for death of 2.75, p < 0.0001.
R	Juergens R.A. et al. [47]	ECOG PS 2: 19% (overall population n = 161)	Nivolumab	ECOG PS 2 *versus* PS 0–1 patients: - 6-month OS rate of 47% *versus* 64%; - Median OS of 5.9 *versus* 9.1 months. Safety profile comparable to overall study population.
R	Fujimoto d. et al [16]	ECOG PS ≥ 2: 23% (overall population n = 613)	Nivolumab	ECOG PS 2 *versus* PS 0–1 patients: - DCR of 26% *versus* 50%; - 1-year PFS of 2.1% *versus* 11.7%. The incidence rates of severe irAEs were similar between those with good PS (0–1) and poor PS scores (2–4).
R	Garde-Noguera J. et al. [48]	ECOG PS 2: 22.3% (overall population n = 175)	Nivolumab	ECOG PS 2 *versus* PS 0–1 patients: - Median OS of 2.7 *versus* 7.8 months.
R	Facchinetti F. et al [52]	ECOG PS 2: 100.0% (overall population n = 153)	Pembrolizumab	Median OS was 11.8 months in patients whose PS 2 was related to comorbidity compared to 2.8 months in those with PS 2 driven by lung cancer (p = 0.001)
Patients with brain metastases				
P	Hendriks L.E.L. et al [59]	BM patients: 22.0% (overall population n = 1025)	Anti-PD-1 (96.3%) Anti-PD-L1 (3.7%)	BM *versus* without BM patients: - ORR of 20.6% *versus* 22.7%; - Median PFS of 1.7 *versus* 2.1 months; - Median OS 8.6 *versus* 11.4 months.
R	Crinò L. et al [60]	BM patients: 25.8% (overall population n = 1588)	Nivolumab	BM patients *versus* overall study population: - DCR of 40% *versus* 44%; - 1-year OS 43% *versus* 48%. Safety profile comparable to overall study population.
R	Molinier O. et al. [61]	BM patients: 22.0% (overall population n = 600)	Nivolumab	BM patients *versus* overall study population: - ORR 37% *versus* 37%; - Median OS 6.6 *versus* 9.5 months.
R	Henon C. et al. [64]	BM patients: 19.0% (overall population n = 271)	Anti-PD(L)-1	No difference was observed in terms of ORR and OS between BM *versus* non-BM population.
R	Gauvain C. et al. [65]	BM patients: 100.0% (overall population n = 43)	Nivolumab	Median intracerebral PFS: 3.9 months. Median PFS: 2.8 months. Median OS: 7.5 months.
Patients with autoimmune disorders				
R	Cortellini A. et al. [69]	AID patients: 11.3% (overall population n = 751; NSCLC patients n = 492)	Nivolumab (75.8%) Pembrolizumab (24.2%)	Among patients with pre-existing AIDs, incidence of irAEs of any grade was significantly higher. No significant differences were observed regarding grade 3–4 irAEs, ORR, median PFS and OS among subgroups.
Patients with chronic viral diseases				
R	Samri A. et al. [72]	12 HIV infected advanced NSCLC patients	Nivolumab	Favorable clinical outcome (3 Partial Response and 4 Disease Stability) No significant clinical side effects
R	Ostios-Garcia L. et al [71]	7 HIV infected advanced NSCLC patients	Pembrolizumab (71.4%) Nivolumab (28.6%)	Favorable clinical outcome (3 Partial Response and 2 Disease Stability) None of the patients experienced grade 3–4 irAE or immune reconstitution inflammatory syndrome None required dose interruption or discontinuation due to irAE
R	Shah N.J. et al [73]	12 HIV infected advanced NSCLC patients	HIV patients: - 8 treated with anti-PD-(L)1	HIV patients: - Any grade irAEs: 25% for both ICI monotherapy and ICI-chemotherapy - ORR in ICI monotherapy: 13%

(*continued on next page*)

Table 2 (*continued*)

Author (reference)	Patients	Treatment	Findings
	10 HBV/HCV infected advanced NSCLC patients	- 4 treated with chemo-immunotherapy HBV/HCV patients: - 7 treated with anti-PD-(L)1 - 3 treated with chemo-immunotherapy	- ORR in ICI-chemotherapy: 75% - No significant changes in HIV viral load and CD4 + T-cell counts HBV/HCV patients: - Any grade irAEs: 57% for ICI monotherapy and 33% for ICI-chemotherapy - ORR in ICI monotherapy: 14% - ORR in ICI-chemotherapy: 67% - No evidence of viral reactivation

AID = auto-immune disorder; BM = brain metastasis; ICI = immuno-checkpoint inhibitor; irAE = immune-related adverse event; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PS = performance status; P = prospective study; R = retrospective study.

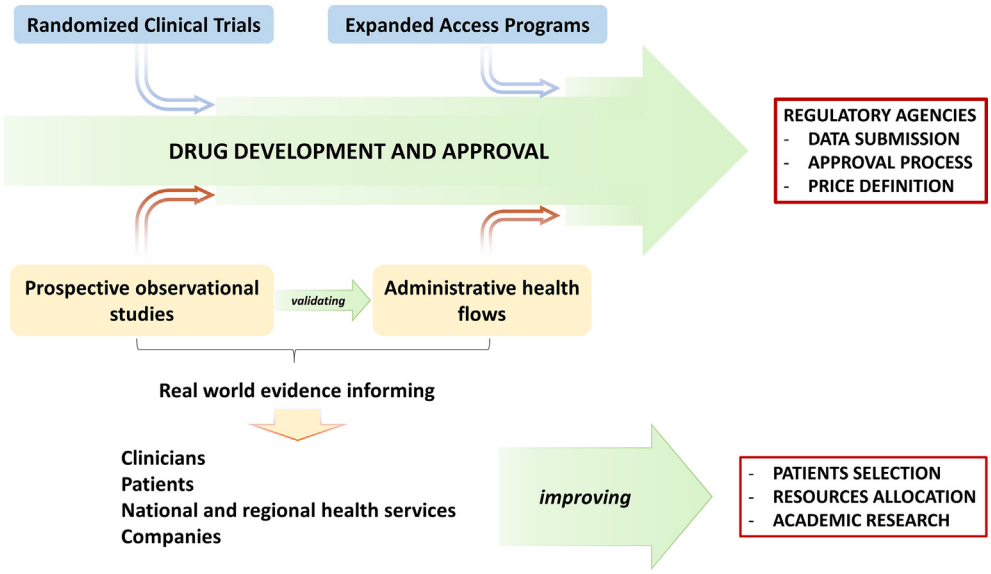

Fig. 3. A proposed integrated drug development model, where data from RCT and EAP are integrated with RWE in a dynamic process informing different stakeholders.

immunodeficiency virus-affected patients- are only a part of the unexplored side of ICIs in the real world. Activity in oncogene-addicted other than EGFR mutant and ALK rearranged NSCLC, the ideal treatment duration in first line, and the potential role of ICIs rechallenge in previously treated patients are also not yet defined by clinical evidence and may be potential research questions to be addressed by RW studies. Our literature search clearly showed how ICIs introduction in clinical practice raised some clinical issues needed to be solved, with a subsequent outbreak of RWE (Fig. 1). Indeed, between 2010 and 2020 publications on ICIs account for 36% of all RWE in lung cancer, and the ratio of evidence before and after July 2015 was 1–3, with 37 citations before and 120 after the data cut-off.

While available evidence supports the use of ICIs in elderly patients and in cases with brain metastases, some uncertainties about effectiveness in poor PS patients are still present, and more data about populations with some comorbidities (*e.g.* autoimmune disorders) is needed (Tables 1, 2).

There is no question about RCTs being the cornerstone for the best medical knowledge [77], but there is also a strong need to narrow the gap between conventional clinical trial data and the real-world of health care providers. Reliability of RWE depends on the main endpoints in specific settings, because some activity and efficacy data may be impaired by the lack of a control group and of standardized treatment and evaluation methods. Non-randomized observational studies do not allow to assess the benefit of a therapeutic approach considering that treatment choice and subsequent health outcome may be influenced by other concurrent conditions. Strength and limitations of RWE have been recently described [78], and should be kept under consideration in real world data applications and study planning. Indeed, we should remark that the application of administrative or clinical datasets or registries without an appropriate study design, planning and conduction does not produce any knowledge. In this context, prior identification of data to be systematically and prospectively collected about a target population from reliable sources may be simplified by electronic health records; however, this should be also integrated with an early definition of specific aims, according to research questions. Though observational RW studies should not be used to inform about efficacy of ICIs, possible aims may be to improve knowledge about toxicity and adverse effects in subgroups not included in RCTs and to get information about modes of use and patterns of care.

Available RWE is mostly made of retrospective studies making bias minimization more difficult, thus confirming that RW study methodology is still challenging.

The introduction of innovative high-cost drugs in the clinical practice, such as ICIs in lung cancer management, have risen some social and economical issues with subsequent heterogeneous measures across different countries for sustainability and affordability improvement.

Available health economics studies are based on efficacy data (e.g. progression free survival according to RECIST criteria) from pivotal clinical trials, while real world post-marketing data could allow a *payment by results* model construction, which could be extremely useful for a proper budget impact assessment though this could entail a price re-modulation or a reimbursement based on actual results by companies.

According to our literature review, while safety and efficacy real world data in the main patients population was in line with data from

RCTs, some criticism about ICIs cost-effectiveness and sustainability emerged [35,36].

Real world datasets and evidence from observational studies may be useful for epidemiological estimation about number of patients suitable for a specific agent and their real treatment duration by investigating time to treatment failure; both of them may be adopted as sources for an accurate place in therapy, and budget impact analyses for resources allocation planning by national and regional health service. Moreover, RWE is useful to depict the whole diagnostic-therapeutic pathway in oncology, enriched with long-term follow-up data about toxicities and treatments sequence.

Recently, both EMA and FDA have promoted the collection of real world data in the future post-marketing drug monitoring, regulatory and approval flow, thus prospecting a clinical research revolution [79,80].

Finally, in the next future RCT results should be integrated with RWE for a new drug development model where all different stakeholders are actively involved (Fig. 3).

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2020.102031.

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