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ORIGINAL RESEARCH

Challenges and knowledge gaps with immune checkpoint inhibitors monotherapy in the management of patients with non-small-cell lung cancer: a survey of oncologist perceptions

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Available online 12 January 2023

Background: Immune checkpoint-inhibitors (ICIs) are changing outcomes in different cancer settings, notably for patients with non-small-cell lung cancer (NSCLC). There are, however, still important gaps of evidence for clinical practice when using these novel treatments. In this study, we assessed physicians' opinion and experience on challenges for clinical practice with ICIs monotherapy in NSCLC.

Methods: A survey was conducted on experienced physicians treating patients with NSCLC with ICIs. Two rounds of pilot tests were carried out for validation among a group of experts.

Topics under analysis were in relation to treatment of elderly populations, performance status, brain metastases, use of steroids or antibiotics, the effects of gut microbiome, autoimmune diseases, human immunodeficiency virus infection, solid organ transplants, use of anti-programmed cell death protein 1 versus anti-programmed death-ligand 1 drugs, atypical tumour responses, predictors of response, duration of treatment and a final open question on additional relevant challenges.

Results: Two hundred and twenty-one answers were collected, including 106 (48%) valid answers from experts for final analysis (physicians who have treated at least 20 patients with NSCLC with ICIs). The vast majority agreed that the selected topics in this study are important challenges ahead and more evidence is needed. Moreover, predictors of response, treating brain metastasis, shorter duration of treatment, the effects of gut microbiome and concomitant use of steroids were voted the most important topics to be further addressed in prospective clinical research.

Conclusions: This survey contributed to understanding which are the main challenges for clinical practice with ICIs monotherapy in NSCLC. It can also contribute to guide further clinical research, considering the opinions and experience of those who regularly treat NSCLC patients with ICIs.

Key words: immunotherapy, immune checkpoint inhibitors, NSCLC, clinical challenges

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are changing practice rapidly as cancer therapeutics across several tumour types, both as single agents and in combination with other treatments. Importantly, clinical trials research and subsequent drug approvals with ICIs have been particularly prominent in non-small-cell lung cancer (NSCLC),[1,2] which is the major cause of cancer-related death worldwide.[3] The evidence gained by these pivotal trials, however, has certain limitations considering unmet real-world population needs.[1,4]

Elderly patients, with a poorer Eastern Cooperative Oncology Group (ECOG) performance status, brain metastases, patients with comorbidities such as human immunodeficiency virus (HIV) infection, solid organ transplant, or prior autoimmune diseases (AIDs) have been excluded from pivotal trials, despite representing a substantial proportion of patients with cancer.[1,5-15]

Additionally, assessing ICI response could be challenging, considering its mechanism of action and some possible

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interactions with concomitant medications such as steroids, other anti-inflammatory medications or antibiotics.

Notably, some patients treated with ICIs could be long-term responders in some metastatic setting scenarios and the appropriate moment for treatment discontinuation without affecting survival is still unclear.[16] Moreover, the so-called atypical responses [hyperprogression (HPD) or pseudoprogression (PPD)] could occur with rates and by mechanisms still to be fully understood.[17]

Real-world studies could bring complementary evidence from a broader population.[18] Nevertheless, the retrospective and non-randomization nature of these studies, patient selection, lower control on data collection and validation correlate with several bias and confounding factors.[7]

Nowadays, oncologists are accumulating experience with ICIs in NSCLC worldwide, more than in any other tumour type.[1] Thus, they are obtaining important knowledge from a real-world context, which can be considered complementary information to clinical trials and real-world studies data. Such broader experience could be valuable to better understand the important unmet needs with these novel treatments and to develop further clinical research to tackle some of the most relevant questions ahead more efficiently.

This study aims to assess, via a survey, physicians' opinion and experience on challenges for clinical practice with ICIs monotherapy in NSCLC.

MATERIALS AND METHODS

Survey preparation

A collaborative survey was developed within the multinational research network Oncodistinct (www.Oncodistinct.net) and cooperative oncology centres in different countries. It used a previously published comprehensive review on 'challenges for clinical practice with immune checkpoint inhibitors' as background information.[19] Between May and August 2019, a first questionnaire draft was constructed by authors, and two rounds of pilot test were carried out among a group of 12 experts for validation. A total of 35 questions consisting of Likert rating scales of agreement, multi-choice options or short text open boxes were considered (Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2022.100764).

Questions

Questions were focused on the aforementioned challenges with ICIs monotherapy in NSCLC, and included as topics: elderly patients, performance status, brain metastases, concomitant use of steroids or antibiotics, the effect of gut microbiome, concomitant AIDs, HIV, solid organ transplants, use of anti-programmed cell death protein 1 (anti-PD-1) versus anti-programmed death-ligand 1 (anti-PD-L1) drugs, atypical tumour responses or predictors of response and duration of treatment. An open question was also included asking about additional relevant challenges.

Conduction

The survey was shared by email and social media (Facebook™, Twitter™ and Youtube™) to oncologists using 'SurveyMonkey'. It was open to collect answers between September 2019 and February 2020. Responders were also asked to spread the questionnaire among their network, in a snowball approach. No geographic restrictions were included. The survey was anonymous, but an option field was included requesting an email address to track answers and avoid duplications. In addition, only one answer per Internet Protocol address (IP) was valid to avoid duplications.

Final analysis

Answers from participating physicians who fully completed the questionnaire and who have treated at least 20 patients with ICIs were included in the final analysis. Results are presented using descriptive statistics methodology, namely counts and percentages.

RESULTS

Results on experience and opinions towards important challenges for clinical practice with ICIs in NSCLC are presented on Table 1, Figure 1 and Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2022.100764.

Demographics

A total of 221 answers were collected, which included 106 (48%) completely valid answers for final analysis: fully completed questionnaire from physicians who have treated at least 20 patients with NSCLC with ICIs. Detailed demographic information from respondents is provided in Table 1.

Most answers included for final analysis were from medical oncologists (66%; $n = 70$), 23% were from pneumologists ($n = 24$) and 11% were from the rest of the participants. There was a male predominance (64%) and half of the responders (50%) were between 36 and 50 years old. The majority were Europe-based doctors (80%), followed by 12% in North America. Half of the doctors work in academic centres, 28% in research cancer centres and 17% in regional hospitals.

Regarding physician's experience in treating NSCLC patients with ICIs: 76% self-reported an experience of >5 years, 22% between 1 and 5 years and only 2% <1 year.

The collected results are reported in three different sections: (i) patient-related questions, (ii) patients with prior comorbidities and concomitant medication and (iii) questions regarding treatment outcomes.

Patient-related questions. The majority (74%) of clinicians believe that both safety and efficacy of ICIs are equivalent in elderly populations (>70 years old) when comparing with younger patients. Almost all (94%) agree to treat ECOG PS 0-2 NSCLC patients with ICIs, 36% with ECOG PS 3 and only 6% consider it reasonable in ECOG PS 4 patients.

Table 1. Demographics and clinical background

Total answers % (total number)	
Total	100 (221)
Valid (completely answered)	48 (106)
Not valid	52 (115)
Uncompleted survey	30 (66)
Low experience[a]	39 (87)
Demographics and clinical background from the 106 valid answers % (total number)	
Speciality	
Oncologist	66 (70)
Thoracic oncologists	23 (24)
Oncologists in training	8 (9)
Others	3 (3)
Gender, % (*n*)	
Male	60 (64)
Female	39 (41)
Other	1 (1)
Age, % (*n*)	
36-50	50 (53)
25-35	28 (30)
51-70	22 (23)
Region, % (*n*)	
Europe	80 (85)
North America	12 (13)
Other	8 (8)
Type of institution, % (*n*)	
Academic	50 (53)
Cancer centre	28 (30)
Regional	17 (18)
Other	5 (5)
Years of experience treating NSCLC patients, % (*n*)	
>10	42 (44)
5-10	34 (36)
1-5	22 (23)
0-1	3 (3)
Number of NSCLC patients treated with ICIs, % (*n*)	
21-50	40 (42)
51-100	22 (23)
101-200	24 (25)
>200	15 (16)

ICI, immune checkpoint inhibitor; NSCLC, non-small-cell lung cancer.
[a]Self-reporting treatment on <20 NSCLC patients with immune checkpoint inhibitors.

In patients with brain metastases, 81% of responders believe that ICIs monotherapy could be efficacious in asymptomatic cases, whereas only 30% agree to treat brain metastases in symptomatic patients.

Comorbidities and concomitant medication. Regarding patients with previous diagnosis of AIDs, 77% of responders would treat patients with ICIs only in cases of low severity situations. Seventy-four percent think that the safety profile is worse in this group of patients, but 65% believe in similar efficacy for this population compared with patients without AIDs.

In patients with controlled HIV defined as having >250 CD4 cells/μl and undetectable HIV viral load, nearly 60% believe in similar ICI safety and efficacy. For uncontrolled HIV patients, around half of the responders are uncertain if there are differences in safety or efficacy with ICIs (50% and 52%, respectively) compared with the non-HIV population.

The majority refused to treat patients with NSCLC and heart (69%), lung (67%) or liver (59%) organ transplant with ICIs. For kidney transplant, however, only 42% disagreed to consider treatment.

Considering the steroid dose threshold (equivalent to prednisone mg/day) with the risk to reduce efficacy of ICIs in NSCLC, 37% answered 0-10 mg, 34% 11-30 mg, 11% >30 mg and 15% responded they do not know the answer to this question. Finally, 48% of oncologists thought that antibiotics could reduce the efficacy of ICIs and 61% believed that modulating gut microbiota might be a strategy to increase the efficacy of ICIs.

Treatment outcomes. Overall, 62% mentioned that they already diagnosed a 'hyperprogression' status whereas the corresponding percentage for 'pseudoprogression' was 81%. The majority of responders would not interrupt treatment before 24 months, including in patients with stable disease (90%), partial response (85%) or with a complete response (72%).

Around a quarter believe that there are both safety and efficacy differences between anti-PD-1 and anti-PD-L1 drugs (24% and 23%, respectively). After interruption of treatment due to severe toxicity with ICIs, 62% disagree to shift treatment to another ICI (from anti-PD-1 to anti-PDL1 or vice versa). Predictors of response were considered the most important challenge ahead for clinical practice and research, with a total of 63% answers. Finally, 52% ($n = 56$) of responders raised other additional challenges not directly questioned in this survey (Supplementary Material, Supplements 1 and 2, available at https://doi.org/10.1016/j.esmoop.2022.100764).

DISCUSSION

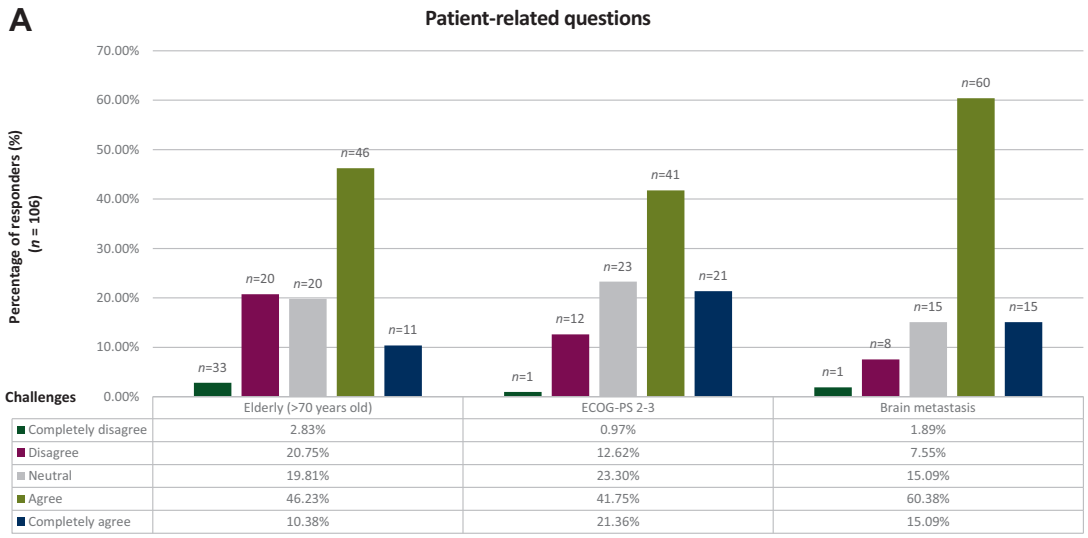
Overall, most responders agreed that the selected topics in this study are important challenges ahead and more evidence is needed for better clinical decision making.

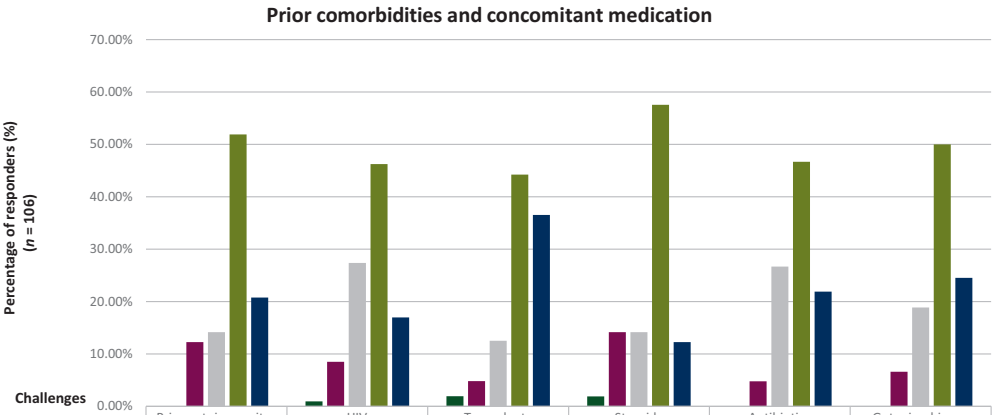
Currently, there are no firm data suggesting lower efficacy or higher toxicity with ICIs based only on patient age, and that is aligned with most doctors' (74%) opinion on this survey, who also believe that there are still important gaps of evidence in this topic.

In a retrospective study from 615 patients (191 ≥70 years old and 424 <70 years old) treated with ICIs, the rate of immune-related adverse events (IrAEs) grade ≥2 was higher in the older group (33% versus 25%, $P = 0.03$).[20]

Other studies, however, did not find such deleterious toxic effects.[21-23] Comparable overall survival (OS) across ages was also reported in clinical trials[23-25] and from real-world studies.[26] A Food and Drug Administration analysis of four randomised clinical trials confirmed that efficacy was similar in older patients, including those ≥70 years old, compared with the younger population.[23]

The CheckMate-153 study was designed to assess nivolumab in previously treated patients with advanced NSCLC. An analysis on 1426 patients, of whom 556 (39%) were ≥70 years old showed similar median OS (9.1 months versus 10.3 months) and toxicity profiles compared with younger patients.[25]





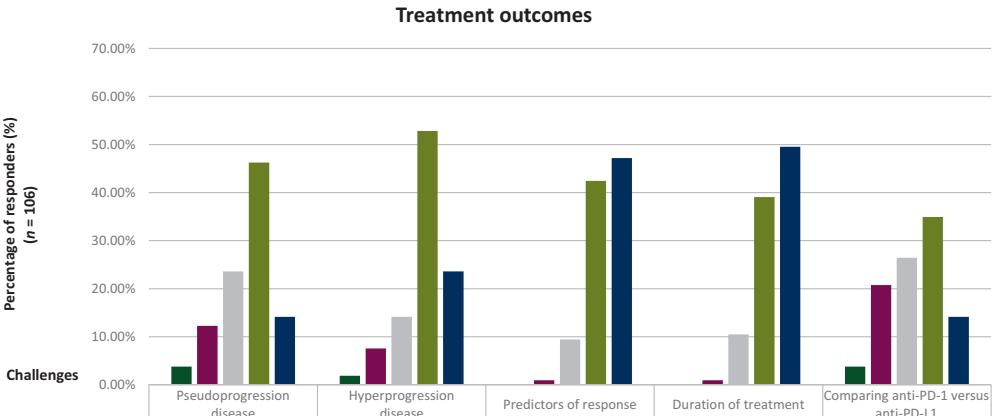


Figure 1. Physicians' opinion and experience on challenges with immune checkpoint inhibitors in non-small-cell lung cancer. (A) Opinion on gaps of evidence for clinical practice with ICIs in NSCLC. (B) Previous prescription of ICIs in challenging scenarios in patients with NSCLC. (C) Opinion on priorities (voting up to 5) to be addressed in further prospective clinical research.

ECOG PS, Eastern Cooperative Oncology Group performance status; HIV, human immunodeficiency virus; ICI, immune checkpoint inhibitor; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

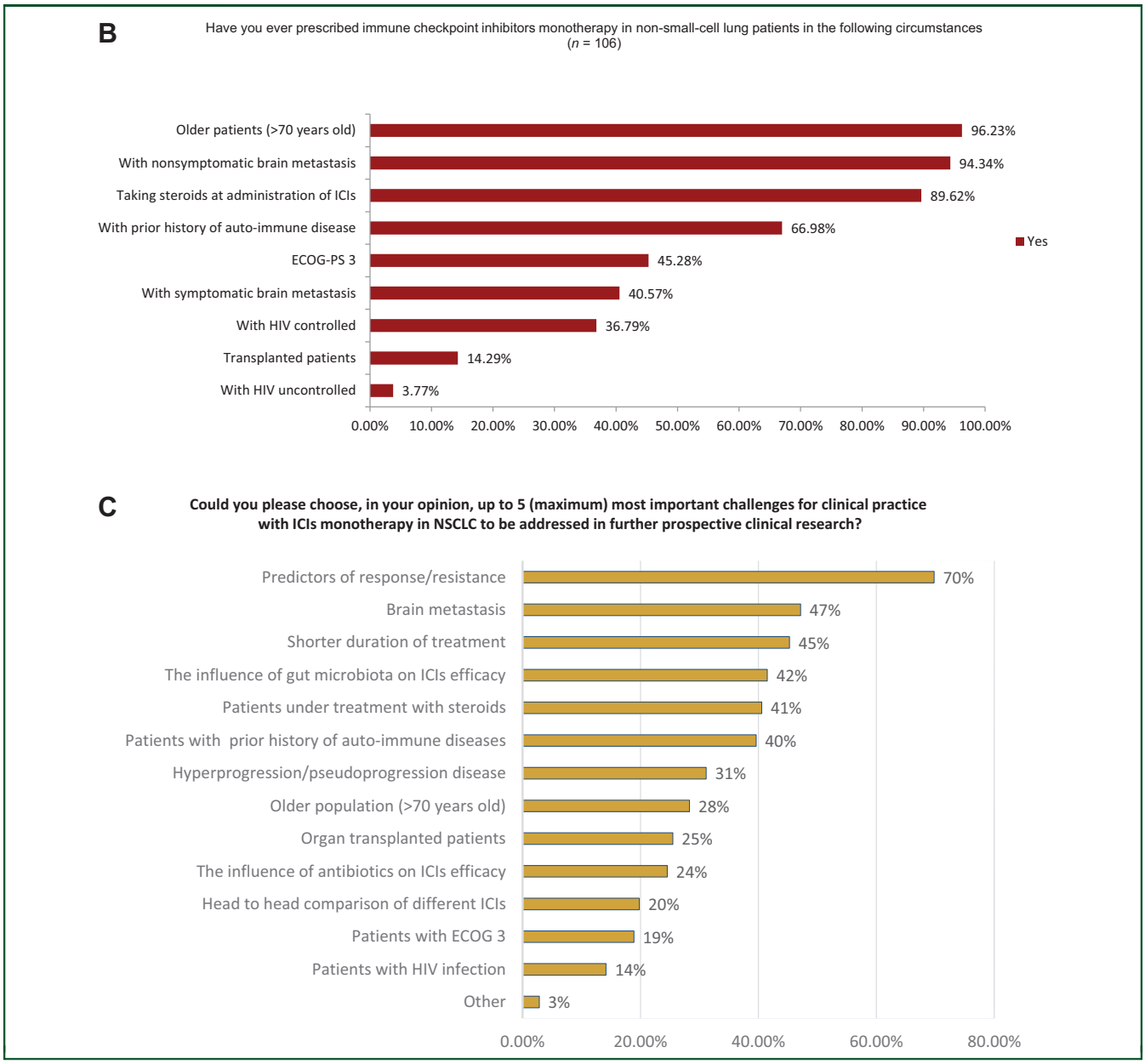


Figure 1. Continued.

The majority (63%) of responders agree that there are important gaps of evidence when using ICIs in ECOG PS 2-3 patients, and almost all (94%) agree to treat the ECOG PS 0-2 population. In Checkmate-817, the safety of nivolumab + ipilimumab was similar for patients with ECOG 2 versus ECOG <2,[27] and in the PePS2 trial the efficacy and tolerability of pembrolizumab in patients with NSCLC and ECOG 2 was not inferior to the ECOG 0-1 cohort.[28] In the CheckMate-171 and Checkmate-153 trials, however, nivolumab showed worse efficacy in ECOG 2 population compared with ECOG 0-1.[24,25]

Noticeably, the international guidelines are not consensual in this regard. For instance, the European Society for Medical oncology (ESMO) allows ICIs for patients with advanced NSCLC and ECOG PS 2[29] whereas the American Society of Clinical Oncology (ASCO) restricts such indications only for ECOG PS 0-1 patients.[30] Both guidelines excluded ECOG PS 3 patients from their recommendations due to lack of evidence, however 45% of responders in this survey had prescribed ICIs in the ECOG PS 3 population.

Treating brain metastasis with ICIs was voted the second most important challenge for further research, just after predictors of tumour response. Currently, ESMO guidelines consider that there is limited evidence demonstrating safety and efficacy of ICIs in patients with brain metastases.[29] Clinicians clearly differentiate symptomatic brain metastasis from non-symptomatic cases. A review conducted by Caponnetto et al.[31] found a 16%-33% intracranial objective response rate (ORR) from three anti-PD-1 studies in NSCLC, in patients with asymptomatic and previously untreated brain metastases. A 29% intracranial ORR (11/37) was found in a phase II trial of pembrolizumab in NSCLC with PD-L1

Table 2. Ongoing clinical trials addressing challenges for clinical practice with immune checkpoint inhibitors on patients with stage IV NSCLC

Identification	Phase and (patients enrolment)	Treatment tested	Key eligibility	Primary outcome(s)	Trial status
Elderly population					
NCT03293680	II (82)	Pembro	> 70 Years old, ECOG 0-1;	OS at 12 months	Active, not recruiting
NCT03977194 ELDERLY	III (500)	Atezo + chemo	70-89 Years old; ECOG 0-1	OS at 11 months	Recruiting
Elderly and ECOG 2-3 population					
NCT03191786 IPSOS	III (453)	Atezo	>70 Years old; ECOG 2-3; comorbidities; asymptomatic brain metastasis	OS up to 3.5 years	Active, not recruiting
NCT03351361 eNERGY	III (217)	Nivo + ipi	First line; <70 years old; ECOG 2	OS up to 3 years	Active, not recruiting
ECOG 2, brain metastasis, comorbidities					
NCT02869789 Checkmate 817	III/IV	Nivo + ipi	First line; ECOG 2; asymptomatic untreated brain metastases; comorbidities (hepatic, renal impairment, or HIV); high tumour mutation burden	High-grade AEs	Active, not recruiting
Patients with brain metastasis					
NCT02696993	I-II (88)	Nivo + RT ± ipi	Brain metastasis Exclusion: leptomeningeal disease	Intracranial PFS up to 4 months	Recruiting
NCT02886585	II (102)	Pembro	Brain metastasis >5 mm; ECOG 0-1; leptomeningeal disease (cohort C)	ORR; OS; extracranial ORR	Recruiting
NCT03526900 ATEZO-BRAIN	II (43)	Atezo + chemo	Asymptomatic brain metastasis; ECOG 0-1 Exclusion: leptomeningeal disease; neurological symptoms; >4 mg of dexamethasone	PFS at 12 weeks	Active, not recruiting
NCT04967417	II (50)	Pembro + chemo	First line; asymptomatic brain metastasis; intracranial lesion ≥10 mm; ECOG 0-1	Intracranial response rate	Not yet recruiting
Patients with pre-existing autoimmune diseases					
NCT03656627	I (7)	Nivo	Stable AIDs	DLT	Active, not recruiting
NCT03816345	I (312)	Nivo	AID; HIV positive-controlled allowed	AEs; DLT; ORR	Recruiting
HIV positive					
NCT03304093 CHIVA2	II (16)	Nivo	HIV 1 or 2 positive; HIV viral load <200 copies/ml; any CD4 cell count	DCR	Active, not recruiting
NCT02408861	I (96)	Nivo + ipi	HIV-associated relapsed or refractory classical Hodgkin's lymphoma or solid tumours; HIV viral load <75 copies/ml; CD4+ cell >100 cells/mm^3	MTD	Recruiting
NCT02595866	I (60)	Pembro + antiretroviral medications	HIV and cancer; CD4+ cell >50 cells/ul	Rate of AEs	Recruiting
NCT04499053	II (18)	Durva + chemo	Viral infections (HIV, chronic HBV, HCV)	Rate of AEs Radiological response	Recruiting
Gut microbiome effects					
NCT05008861	I (20)	Gut microbiota + ICIs	Having SD after at least 2 doses of ICIs	FMT-related AEs ICI-related AEs	Not yet recruiting
NCT04521075	I-II (42)	Nivo + FMT	Metastatic or inoperable melanoma, MSI-H, dMMR or NSCLC	FMT-related AEs ORR	Recruiting
NCT04951583 FMT-LUMINATE	II (70)	ICI + FMT	NSCLC and melanoma	ORR	Recruiting
NCT03637803	I-II (132)	Pembro + live biotherapeutic product MRx0518;	Solid tumours progressing on ICIs	AEs and time to treatment discontinuation	Recruiting
NCT04601402	I (93)	Avelumab + GEN-001 (live biotherapeutic product);	Solid tumours progressing on ICIs	AEs and ORR	Recruiting

AE, adverse event; AID, autoimmune disease; atezo, atezolizumab; DCR, disease control rate; DLT, dose-limiting toxicity; dMMR, deficient mismatch repair; Durva, durvalumab; ECOG, Eastern Cooperative Oncology Group; FMT, faecal microbiota transplant; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICI, immune checkpoint inhibitor; Ipi, ipilimumab; MSI-H, microsatellite instability-high; MTD, maximum tolerated dose; Nivo, nivolumab; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; RT, radiotherapy; SD, stable disease.

≥1% and untreated brain metastases.[32] Patients with neurological symptoms or requiring corticosteroids were excluded from this study, and no clinical activity was observed on tumours not expressing PD-L1.[32] A meta-analysis of 12 studies including 566 NSCLC patients with brain metastases and who were treated with ICIs reported an intracranial response of 16.4% and disease control rate (DCR) of 45%.[33]

Interestingly, in the CHECKMATE 204 clinical trial in melanoma patients, an important intracranial response of nivolumab and ipilimumab was observed, not only in asymptomatic patients (58% response) but also in

symptomatic patients (22% response).[34] To our best knowledge, the evidence of ICIs in symptomatic brain metastasis is very scarce. More data on patients with different neurological symptoms, locations of brain metastases, steroid treatment or brain disease burden might also be important to address.

Data currently available seem to be aligned with clinicians' perception that ICIs could be used in patients with AIDs, but under certain conditions.

In a systematic review, from 123 patients treated with ICIs and pre-existing AIDs, 50% had an exacerbation of their AID, and new IrAEs occurred in 34% but with 90% recovery.[35] In another retrospective study from 522 patients with controlled AIDs treated with ICIs, only 6%-16% suffered a flare of their disease.[36] A retrospective study on NSCLC patients treated with ICIs was carried out to compare outcomes in patients with or without AIDs. From the 2425 patients identified, 22% ($N = 538$) had a concomitant AID and no difference in efficacy or incidence of AEs was observed.[37]

Moreover, in another study, an association between a flare of AID and better response with ICIs was found.[38]

AIDs are a very heterogeneous entity, and further research with ICIs could be important in discriminating results by type of disease, severity or concomitant treatment used.

Most practitioners believe that controlled HIV will not interfere with the efficacy and safety of ICIs, but they are less confident for non-controlled HIV patients. A systematic review retrieving 73 cancer cases in HIV patients treated with ICIs found a good tolerability profile, with only 8.6% (6/70) grade $\geq$3 toxicity and a 30% ORR observed in NSCLC patients.[39]

A phase II trial assessed durvalumab (anti-PD-L1) in 20 HIV+ cancer patients with solid tumours. None of the patients had serious adverse events, and clinical benefit was observed in 45% of patients.[40] Importantly, plasma viremia remained negative, suggesting no viral reactivation during ICI therapy.[40] Data for uncontrolled HIV patients are insufficient; accordingly, half of doctors mention they do not know the clinical behaviour of ICIs in this population and only a minority (18%) believed in similar results compared with non-HIV patients.

Nowadays, with HIV disease controlled by antiretroviral treatments, the inclusion of HIV patients in most cancer trials[41] is safe and recommended and ICIs should not be an exception.

The decision to treat a solid organ transplanted patient with ICIs is complex, with few data available and many uncertainties. Although colleagues identified this as an important challenge, they showed a very defensive behaviour and admitted a lack of knowledge of clinical decisions. Some (21%) would consider treating kidney transplanted patients, but only a few (5%-9%) would consider treatment within other organ transplants (heart, lung, liver). These differences could be explained by an alternative (dialysis) that could be offered to kidney transplanted patients if rejection occurs, and not to other organ transplants. A review of 39 cases across tumour types treated with ICIs found an allograft rejection of 41% (11/23 renal, 4/11 hepatic and 1/5 cardiac transplantations) with a death rate due to allograft rejection of 46% (18/39).[42] Importantly, the tumour response rate was 47% in the total population and 40% in patients who had allograft rejection.[42] Another systematic review retrieved 48 transplanted patients with cancer (19 liver, 29 kidney) treated with ICIs.[43] The DCR was 35% (21% for liver and 45% for kidney transplants) and allograft rejection was 37% in liver and 45% in kidney transplanted patients. Notably, a clinical response with durable graft tolerance was observed in 21% of cases.[43] Finally, another systematic review reported results in 83 solid organ recipients (54 kidney, 24 liver and 6 heart transplantation) in different solid tumours treated with ICIs. A 40% allograft rejection rate due to immunotherapy was observed, with similar results across organs and ICI types.[44] In multivariable analysis the use of steroids (versus other immunosuppressants), <8 years since transplant and prior episodes of rejection were associated with a higher risk of rejection.[44] In this complex scenario, the benefit—risk is to be considered carefully for decision making.

A total of 7 out of 10 responders agree there are still important gaps in evidence for clinical practice taking steroids and ICIs concurrently, although 90% already prescribed those treatments alongside, suggesting the extent of the need, even when practising with low levels of evidence. Published data to date appear somehow contradictory and insufficient for final conclusions.

If in some retrospective studies patients taking steroids had a lower progression-free survival (PFS) or OS,[45-49] in others such a deleterious effect was not observed.[50,51] A systematic review and meta-analysis found that patients taking ICIs and steroids had worse survival compared with those not taking steroids, but when used to manage side-effects it did not negatively affect OS.[52]

Regarding a dose threshold, a retrospective analysis of 90 patients treated with $\geq$10 mg daily prednisone equivalents showed poorer PFS [hazard ratio (HR) 1.31, $P < 0.03$], and OS (HR 1.66, $P < 0.001$) compared with a lower dose of steroids (<10 mg prednisone).[46]

In fact, there are still many questions ahead: it is unclear if steroids reduce the efficacy of ICIs or if an eventual difference could be driven by a more aggressive disease or comorbidities on those taking corticotherapy. In addition, the timing of administration of steroids possibly has some influence in patient outcome and needs to be elucidated. Moreover, some could also be using steroids following IrAEs, which was suggested as a predictor of better benefit with ICIs, thus a possible confounder.[53-56] More studies are needed to better understand these questions.

Most of the responders considered that the correlation between antibiotics, gut microbiome and ICIs' efficacy is an important challenge ahead. Some studies reported lower outcomes for NSCLC patients taking ICIs and antibiotics concomitantly,[47,57-61] but the exact reasons for such an association are not clear. Antibiotics could be administered following an infectious complication of a more aggressive

tumour, which could explain such an association. In addition, these drugs can change the gut microbiome profile, leading to dysbiosis (less diverse and less stable microbiota), which has been associated with lower outcomes on patients treated with ICIs.[62-66] In fact, manipulating gut microbiota or faecal transplant from responders was shown as a promising strategy to boost efficacy of ICIs,[63,67-70] and this possibility is being explored in several clinical trials (Table 2) and observational studies (NCT04107168). Recently, the concomitant use of proton pump inhibitors has also been associated with lower efficacy of ICIs, possibly also due to their influence on gut microbioma.[71,72]

Doctors could be underestimating HPD and also overestimating PPD.

Importantly, the biological mechanisms of HPD are not yet fully understood: it is uncertain if HPD could be induced by ICIs, or if it is just tumour aggressiveness.[73] In a retrospective study, from 406 NSCLC patients treated with ICIs, the rate of HPD was 14% (defined as increase in tumor growth rate >50% on first evaluation after starting treatment) and the rate of PPD disease was 5%. From the 56 patients treated with chemotherapy, 5% had HPD and 0% had PPD.[74] Another retrospective study in 220 NSCLC patients found a 17% rate of HPD.[75] In a pooled analysis of three metastatic NSCLC trials, the rate of PPD following ICI treatment was <2%.[76] These differences between evidence published and doctors' perception could be explained by unawareness of real data, lack of consensual definitions and perhaps unbalanced focus given to PPD and HPD on many congresses and publications.[73,77]

The overwhelming majority of doctors (90%) in this survey agree that the duration of treatment is an important challenge. Deciding the appropriate time in treatment is important to avoid IrAEs, hospital visits and to reduce 'financial toxicity'. Most ICI trials were designed to keep treatment during clinical response and good tolerability, or in some cases up to 24 months. In fact, in this survey most doctors would never stop treatment before 24 months even after a complete response.

In a retrospective study conducted in 96 patients who completed 24 months of ICI treatment, long-term PFS after treatment discontinuation was demonstrated.[78] In CheckMate153, patients with advanced NSCLC received nivolumab during 1 year, and after they were randomised to either continue or stop treatment. The median PFS [24.7 months versus 9.4 months; HR, 0.56 95% confidence interval (CI) 0.37-0.84], and OS [not reached versus 28.8 months; HR, 0.62 95% CI 0.42-0.92] were significantly longer with continuous versus 1-year fixed-duration treatment.[79]

In a multicenter retrospective study assessing 54 patients with NSCLC with clinical benefit after at least 18 months of treatment with ICIs, treatment discontinuation was proven a reasonable option.[80] The 24-month OS and PFS after treatment interruption were 84% and 63%, respectively.[80]

In a single-centre study, all four NSCLC patients who had complete response after four administrations of pembrolizumab and interrupted treatment, remained in complete response with a median follow-up after treatment cessation of 10 months (6-15 months).[81]

Comparing anti-PD-1 versus anti-PD-L1 drugs was not considered a major priority by clinicians. This suggests that, although there are only few data available, oncologists do not believe in clinically relevant differences between these treatments. Two meta-analyses assessing indirect comparison between anti-PD-1 and anti-PD-L1 inhibitors in NSCLC did not find significant efficacy differences,[82,83] and the safety profile from a systematic review was also found to be similar.[84]

Predictors of response were considered the most important challenge ahead by physicians. In fact, despite important clinical efficacy, only 30%-40% patients with NSCLC benefit from ICIs.[85,86] PD-L1 expression has been assessed in most NSCLC trials, and there is a proven correlation between higher expression and ICIs clinical benefit, with some approvals and guidelines recommendations depending on its value.[29,30] Its predictive value alone, however, remains low.[87] Beyond PD-L1, tumour mutational burden was also prospectively assessed in clinical trials; however, its value is still debatable in predicting the OS and the strongest results are needed to qualify its predictive role.[30,88] The immunogenicity from specific neoantigens might be more relevant rather than the total number of mutations, but that is still an important question to be answered. Microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) correlates with stronger responses with ICIs, and it is already validated in several tumour subtypes, but its frequency is <1% in NSCLC.[89] Also, some other genetic features such as epidermal growth factor receptor (EGFR) and LKB1 mutations have been associated with lower responses with ICIs in NSCLC.[90-92]

Finding more clinical useful predictors of response is certainly one of the most important research topics with ICIs in NSCLC, and other biomarkers such as extended genetic/mutations assessment, liquid biopsies, gut microbiome profile, assessment of immune-regulation genes, major histocompatibility complex/human leukocyte antigen (MHC/HLA), neutrophil to lymphocyte ratio or lactate dehydrogenase (LDH) level are under active research or their combination in different scores.[85,93,94] It is possible that a conjugation of different biomarkers in a score, rather than one isolated, could help to improve the prediction of benefit with ICIs, but so far this is a priority unmet need.

Some doctors mentioned ICI toxicity, posology or price/accessibility as additional relevant challenges (Supplementary Material, Supplements 1 and 2, available at https://doi.org/10.1016/j.esmoop.2022.100764). Despite different international guidelines available to manage IrAEs, such as from ESMO, ASCO or the Society for Immunotherapy of Cancer (SITC), virtually any human tissue could suffer from ICI toxicity and with different grades of severity. Thus, there are still many uncertainties in this regard, and it

is complex to collect high levels of evidence in all those cases. Additionally, doses and schedules of treatment were approved following clinical trials design, but it is still important to address whether different posology schemes (particularly lower doses and number of administrations) could be used, keeping efficacy, and sparing some clinical and financial toxicity.

To our best knowledge, this is the first and larger international survey addressing these challenging questions on doctors treating NSCLC patients. For this analysis, the 106 valid answers collected comprise a good representation of the very specific target population — oncologists who treat NSCLC patients and have relevant experience with ICIs.

This survey has some limitations. Selection bias eventually occurred, considering dissemination started directly from the authors. National and international societies, however, were contacted to share the survey and additionally, each responder was asked to spread the survey among his network. Reporting opinion could be subjective and does not necessarily represent extensive experience on each topic. In this regard, only answers from those who self-reported to have treated >20 NSCLC patients with ICIs were included for analysis. Also, to mitigate such limitations, some core questions were repeated at different moments to capture trends and reduce subjectivity. Some definitions might not be completely consensual, and two pilot tests were conducted not only to validate the relevance of each question, but also to optimise clear definitions, where needed.

In conclusion, this survey contributed to understanding what the main challenges for clinical practice with ICIs monotherapy in NSCLC are, and it was also an opportunity to review the best evidence available for current clinical decisions in each identified challenging scenario.

These results may also contribute to guide further clinical research, not only in NSCLC, but also in other solid tumours treated with ICIs. There are several clinical trials ongoing (Table 2) addressing some of these unmet needs and more research is important to progressively reduce these gaps of evidence for optimal clinical decisions.

Finally, some of these conditions may occur simultaneously in the same patient. In addition, ICIs are now commonly used concomitantly with radiotherapy, small molecules or chemotherapy. Thus, future surveys should consider those emerging combined challenges for clinical practice, and different perspectives across geographies, aiming to help physicians to provide best care for patients with NSCLC and other solid tumours.

ACKNOWLEDGEMENTS

The authors would like to thank all medical doctors who provided some of their precious time responding to this survey, sharing their experiences and opinions. Without their contribution this work was not possible.

FUNDING

None declared.

DISCLOSURE

GM reports support for advisory board/consultation positions for AstraZeneca, Roche, Novartis, Lilly and Pfizer. AP reports honoraria and/or advisory fees from: AstraZeneca, Bristol Myers Squibb (BMS), Roche/Italfarma. MS reports honoraria and/or advisory fees from: Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Janssen, Lilly, Novartis, Pfizer, Roche, Sanofi Aventis, Siemens Healthineers, Takeda. He also declares research support (institutional) from: Amgen, BMS, Dracen Pharmaceuticals, Janssen, Novartis, Pfizer, Siemens Healthineers. AA took part in advisory boards for Amgen, AstraZeneca, Bayer, Daiichi, EISAI, Genomic Health, Hengrui, Innate, Ipsen, Leo Pharma, Lilly, Merck, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Seattle Genetics. He received speaker fees from Amgen, AstraZeneca, Bayer, Daiichi, Eisai, Genomic Health, Ipsen, Leo Pharma, Lilly, Merck, MSD, Novartis, Pfizer, Seattle Genetics. He received research grants from BMS, Roche. All other authors have declared no conflicts of interests.

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