Real-world effectiveness of immunotherapies in pre-treated, advanced non-small cell lung cancer Patients: A systematic literature review

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Real-world effectiveness of immunotherapies in pre-treated, advanced non-small cell lung cancer Patients: A systematic literature review

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ABSTRACT

Background: Clinical trials have shown immunotherapy (IO) to be more effective than chemotherapy in pre-treated, advanced non-small cell lung cancer (NSCLC). However, there is a lack of understanding of its effectiveness in clinical practice, and among patient groups that are often underrepresented in trials. We aimed to summarize the existing real-world evidence (RWE) on the survival outcomes of IO in second- or higher line in advanced NSCLC.

Methods: We conducted a systematic review of real-world observational studies that reported overall survival (OS) estimates with IO, primarily nivolumab, pembrolizumab or atezolizumab, in adult, previously treated advanced or recurrent NSCLC patients. Meta-analysis was conducted using random-effect models to pool 1- and 2-year OS rates across studies. Additional subgroups were examined among patients treated with IO, including the elderly, those with poor performance status (PS) and those exhibiting metastasis.

Results: In total, 66 studies were included, of which 46 (70%) included a nivolumab-specific study arm. Pooled 1-year and 2-year OS rates with nivolumab monotherapy were 45.6% (95% CI; 43.4–47.8) and 28.0% (95% CI; 24.8–31.4), respectively, compared to 43.9% (95% CI; 39.1–48.8) and 20.4% (95% CI; 14.7–27.6) in the mixed immune checkpoint inhibitors (ICI) group. OS rates with nivolumab were slightly lower in elderly compared to non-elderly populations. Poor PS was associated with worse survival rates, with a pooled one-year OS estimate of 27.1% in PS $\geq$ 2 vs 51.6% in PS $<$ 2. The pooled 2-year OS rate with nivolumab in patients with and without brain metastases was 22.1% and 26.1% respectively, and this difference was significant in 36% of individual studies.

Conclusions: While the OS benefits of IO seen in real-world studies among pre-treated, advanced NSCLC patients are consistent with pivotal clinical trials, these tend to vary for the more vulnerable patient groups, such as patients with poor PS, which are often excluded from trials. Further research is needed to investigate findings in patients with brain and liver metastases.

Abbreviations: ATE, atezolizumab; BSC, best supportive care; CI, confidence interval; CNS, central nervous system; DUR, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; EC, European Commission; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HR, hazard ratio; ICI, immune checkpoint inhibitors; IO, immunotherapy; NIV, nivolumab; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; PD-1, programmed death receptor-1; PEM, pembrolizumab; PFS, progression-free survival; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PS, performance status; RCT, randomized controlled trials; RWE, real-world evidence; SLR, systematic literature review.

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1. Introduction

Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers. Patients with NSCLC typically present at an advanced stage of disease (stage IIIB to IV). Immune checkpoint inhibitors (ICIs) are a revolutionary development in oncology and multiple immunotherapy (IO) agents have been approved for the treatment of previously treated advanced NSCLC patients. ICIs of programmed death-1 (PD-1), nivolumab and pembrolizumab, or programmed death ligand 1 (PD-L1), atezolizumab, have proven more effective in the second-line treatment of advanced or metastatic NSCLC in IO-naïve patients in comparison to single agent chemotherapy, which was widely used until recently [1]. In 2015, nivolumab received approval from the US Food and Drug Administration (FDA) and the European Commission (EC) for second-line treatment of advanced squamous NSCLC, regardless of PD-L1 expression levels on tumour cells. Nivolumab was subsequently approved for second-line treatment of advanced non-squamous NSCLC in the US (October 2015) and the European Union (June 2016), with PD-L1 expression conferring improved efficacy. In July 2015 and October 2015, respectively, the EC and the FDA granted approval for pembrolizumab as second-line treatment for patients with PD-L1 positive (≥1%), advanced NSCLC. Atezolizumab received approval from the FDA and the EC in October 2016 and September 2017, respectively for second-line treatment of advanced NSCLC, regardless of PD-L1 status.

In CheckMate 017 (NCT01642004), a randomized phase 3 trial among previously treated patients with advanced squamous NSCLC regardless of PD-L1 expression level, median overall survival (OS) with nivolumab was 9.2 (95% confidence interval (CI); 7.3–13.3) months compared to 6 (95% CI; 5.1–7.3) months with docetaxel [2]. Similarly, in CheckMate 057 (NCT01673867), a randomized phase 3 trial among previously treated patients with advanced non-squamous NSCLC, median OS with nivolumab was 12.2 (95% CI: 9.7, 15.0) versus 9.4 (95% CI; 8.0–10.7) months with docetaxel, with PD-L1 expression providing increased efficacy [3]. In the KEYNOTE-010 trial of previously treated, ≥1% PD-L1 positive, advanced NSCLC patients with squamous or non-squamous histology, median OS was 10.4 (95% CI: 9.4, 11.9) months for pembrolizumab 2 mg/kg and 12.7 (95% CI:10.0, 17.3) months for pembrolizumab 10 mg/kg, versus 8.5 months (95% CI: 7.5, 9.8) for docetaxel [4]. In the OAK trial that enrolled advanced NSCLC patients regardless of histology and PD-L1 status, median OS was 13.8 (95% CI; 11.8–15.7) months for atezolizumab versus 9.6 (95% CI; 8.6–11.2) months for docetaxel [5]. Moreover, evidence from these trials suggests that IO can provide long-term, sustained benefit in previously treated advanced NSCLC, with the respective 5-year OS rates with nivolumab and pembrolizumab approximately five and three times that attained with docetaxel [6,7] and a 4-year rate with atezolizumab of 1.8 times that with docetaxel [8].

As traditional randomized controlled trials (RCTs) have restrictive eligibility criteria, the differences in patient characteristics between clinical trials and the real world highlight the need to examine how RCT findings translate to real-world settings. Real-world evidence (RWE) provides valuable context for clinical trial findings, with broader populations and the inclusion of patients typically excluded or underrepresented in clinical trials. In pre-treated patients with locally advanced or metastatic NSCLC, patients often underrepresented in RCTs include the elderly, patients with poor performance status (PS), brain/liver metastases and autoimmune disorders. In a recent systematic review of the literature, Pasello et al [9] summarized the growing RWE on immunotherapy use in NSCLC, emphasizing the importance of RWE particularly in the context of populations excluded from the pivotal immunotherapy trials. While the findings support immunotherapy use in elderly patients and in those with brain metastases, they also highlight the uncertainties in effectiveness among patients with poor performance status who demonstrated worse survival outcomes with immunotherapy as compared to those with better performance status [9].

The objective of the present review of the literature was to identify and summarize the existing RWE, highlighting the OS outcomes with IO in previously treated patients with locally advanced or metastatic NSCLC. OS was defined as the time from the initiation of IO therapy to death from any cause. Secondary objectives were to report OS in specific patient populations of interest including the elderly, those with poor PS and those with brain metastases, to validate the findings reported by Pasello et al [9] and offer further insights. To the existing pool of evidence, our review additionally contributes an understanding of the survival benefit of IO stratified by histology, PD-L1 expression and liver metastases, thereby complementing data from clinical trials where these groups may be underrepresented. Further, this review of RWE provides early insight into the long-term survival outcomes associated with IO in the real-world setting.

2. Methods

A systematic literature review (SLR) of observational studies involving IO-based regimens used in patients previously treated with first-line anticancer therapy for locally advanced, metastatic or recurrent NSCLC was conducted. Systematic searches were run in MEDLINE® Epub Ahead of Print and MEDLINE® In-Process (OVID SP), and EMBASE (OVID SP). The search strategy included free-text and controlled vocabulary terms for NSCLC and the interventions of interest, combined with real-world study designs, and relevant synonyms (see **Appendices A and B**). This search for peer-reviewed publications included studies published between January 1, 2015 and August 28, 2019 (date of search). No limit was placed on geography and language of publication. Abstracts from eleven international and thirty-four local conferences held between 2017 and August 2019 were searched electronically or manually for unpublished studies. Since key studies describing IO use were presented at some congresses held between August 2019 and December 2019, such as the European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer World Conference on Lung Cancer (IASLC WCLC), data from these conferences were extracted and included once available. Authors were contacted when additional information was needed.

Studies were eligible for inclusion in the SLR if they included adults (18 years of age and older) who were previously treated with first-line anti-cancer therapy for locally advanced (stage IIIB or IIIC), metastatic (stage IV) or recurrent NSCLC. Key interventions of interest were IOs, specifically: nivolumab, atezolizumab or pembrolizumab; however studies with unspecified ICIs were also eligible for inclusion. The sample size of the overall study population was to be ≥ 60, to allow for more generalizable real-world findings, however the subpopulations of interest for which OS was reported, could have a sample size lower than 60. Studies that additionally comprised patients receiving IO treatment in the first-line were included only if this patient group constituted ≤ 10% of the study population. Since OS was the effectiveness outcome of interest, studies had to have at least reported OS to be eligible for inclusion. Further, comparative or non-comparative (single-arm) observational studies were eligible for inclusion.

All studies were independently reviewed according to the eligibility criteria by two experienced systematic literature reviewers, followed by consensus. The first screening involved review of titles and abstracts. After removal of studies that did not pass this initial screening, full-text articles were then reviewed. Key data for all studies that met the inclusion criteria for the SLR were extracted, including study design, baseline patient characteristics and effectiveness endpoints (OS, PFS, response rate). Data were extracted as available in the publication/abstract and for the following key subgroups of interest: histology, PD-L1 expression, age, Eastern Cooperative Oncology Group (ECOG) PS, and presence of brain metastases and liver metastases. While baseline data for smoking status and driver mutations (such as epidermal growth factor receptor or EGFR) were extracted, inadequate reporting of OS estimates for these variables precluded the analysis of outcomes in these

subpopulations. The data extraction was independently verified and validated by a second extractor against a clean copy of the publication or conference abstract. While median OS and OS rates (1-year, 2-year and 3-year), were the focus of this review, data on other endpoints, including PFS and response rates, were also extracted and will be explored in a future update of the present SLR.

2.1. Data synthesis and analysis

Where appropriate, forest plots were generated and *meta*-analyses were conducted to summarize OS for the overall study populations and subpopulation groups of interest. To combine the 1-year and 2-year OS probabilities across studies, a random-effects *meta*-analysis for proportions was performed using the meta package in R. To calculate pooled estimates, a random intercept logistic regression model with the logit transformation was used. To assess the presence of heterogeneity, the Q-statistic and Q-test, the I^2 statistic, and the between-study variance tau^2 were calculated. Results from groups with<3 estimates were not *meta*-analysed and were described narratively. We did not pool estimates of median OS as the use of *meta*-analysis to summarize median OS data, especially in single-arm studies, is not well established. Traditional *meta*-analysis methods for continuous outcomes are not appropriate, because they do not take into account censoring and the fact that median OS might not be reached in some studies, and because the underlying data typically does not follow a normal distribution [10].

3. Results

3.1. Study attrition results

In total, 739 records from the database search for peer-reviewed studies, and 197 abstracts from conference proceedings were identified and reviewed for potential inclusion. After applying the eligibility for the current study, a total of 72 articles were included in the SLR, reflecting 66 unique studies comprising 57, 016 pre-treated, advanced NSCLC patients (Fig. 1).

3.2. Study-specific details and baseline characteristics

Study design and baseline patient characteristics are summarized in Table 1. The most common settings for the studies were the USA (21%) or France (15%) and the study periods ranged from 2006 to 2019, with 49 studies (74%) conducted in 2015 and later. There were 57 single-arm observational studies and nine comparative effectiveness studies. There was a lot of variation across studies in the line of treatment in which IO was administered, as well as in the proportion of patients who received the treatment in second line or later lines (17% to 100%). Considering the variations observed across studies in the ICI agents used, treatment

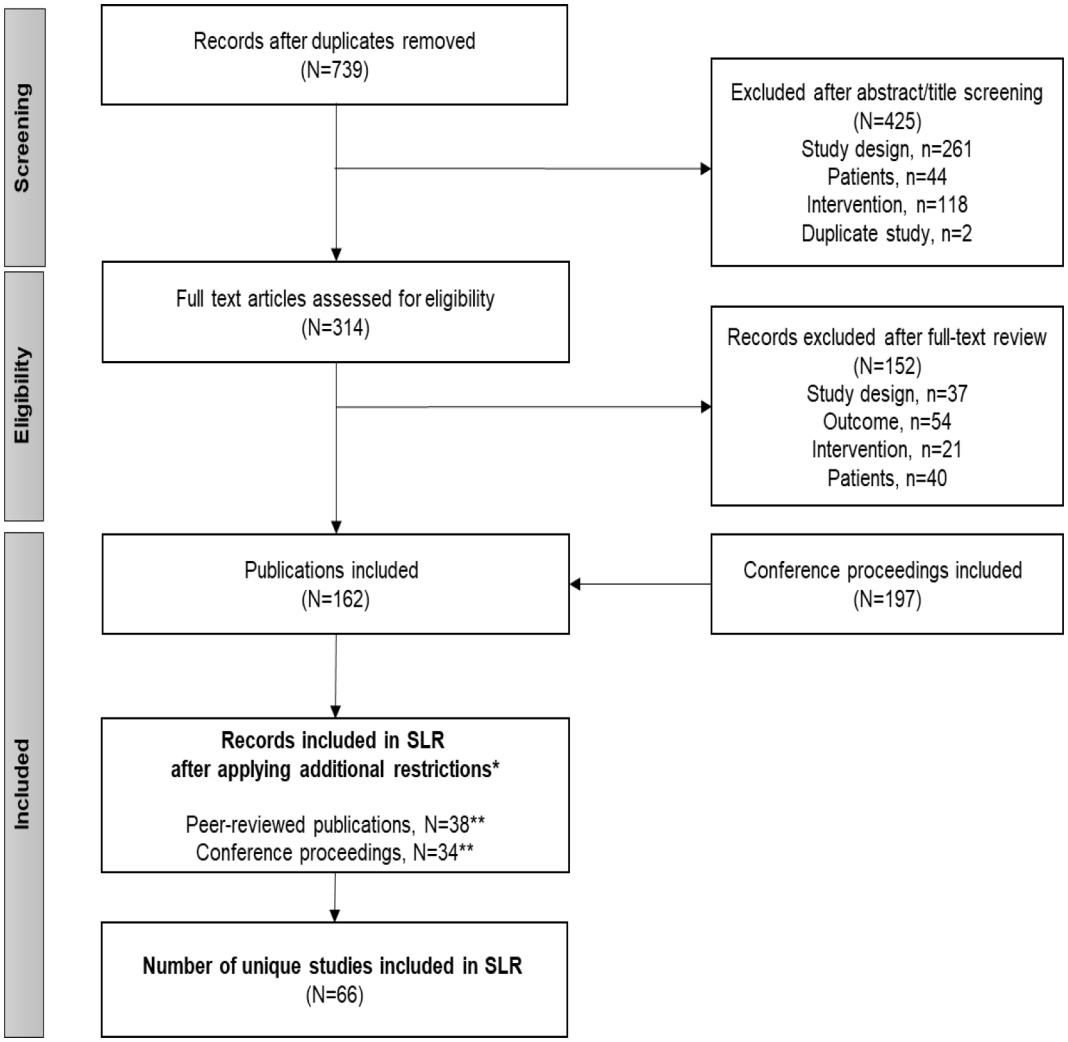

Fig. 1. PRISMA Diagram. *Sample size of overall study population must be ≥ 60; studies that comprised patients receiving IO in the first-line were included only if this patient group constituted ≤ 10% of the study population; studies should have at least reported OS. **includes primary and secondary publications. Abbreviations – SLR: Systematic literature review, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1
Baseline and study characteristics of all included studies (n = 66).

First Author, Year	Country	Study Period	Sample Size (N included)	Median age (years)	Male (%)	Current/former smokers (%)	Histology	PD-L1 expression (%)				ECOG PS (%)					CNS or liver metastases	Proportion of patients who failed one prior line treatment (%)
								+ve	-ve	Other	Unk	0	1	2	3	4		
Baas, 2019[27]	Netherlands	2015–2016	248	63.0	55.0	81.0	Mixed	–	–	–	–	84.0*	–	16.0^	–	–	Yes: CNS	100.0
Bagley, 2017 [45]	USA	2015–2016	175	68.0	46.0	84.0	Mixed	–	–	–	–	17.0	58.0	22.0	3.0	–	Yes: Both	54.0
Barlesi, 2019 [37]	France	2016–2017	1,420	66.0	69.4	89.6	Mixed	64.9ж	–	–	–	82.9	–	13.6	3.5¥	–	Yes: CNS	73.6
Campredon, 2019 [53]	France	2015–2017	105	61.0	68.6	–	–	–	–	–	–	–	–	–	–	–	No	–
Correale, 2018 [54]	Italy	2015–2018	98	–	–	–	–	–	–	–	–	–	–	–	–	–	No	–
Costa, 2019[55]	Portugal	2015–2016	115	62.0	63.5	–	Mixed	–	–	–	–	–	–	–	–	–	No	29.6
Costantini, 2019 [15]#	France	2015–2016	303	65.0	69.0	91.7	Mixed	10.0	11.0	–	79.0	67.0*	–	23.0**	–	–	Yes: Both	40.0
Crino, 2019[24]#	Italy	NR – 2017	1,588	66.0	65.0	70.8	Non-squamous	–	–	–	–	41.0	51.0	7.0	0	0	Yes: Both	24.0
Dudnik, 2018[16]#	Israel	2015–2016	260	67.0	68.0	76.0	Mixed	–	–	–	–	46.0*	–	46.0**	–	–	Yes: Both	64.0
Dumenil, 2018 [42]	France	2015–2016	67	68.5	69.0	86.6	Mixed	–	–	–	–	73.0*	–	27.0	–	–	Yes: CNS	–
Fujimoto, 2018[56]	Japan	2016–2017	613	66.9£	71.0	78.6	Mixed	–	–	–	–	77.0*	–	15.0	8.0¥	–	No	33.0
Garde-Noguera,2018[43]	Spain	2015–2016	175	61.5	73.1	89.1	Mixed	–	–	–	–	80.5*	–	19.5	–	–	Yes: Both	37.1
Geier, 2018[57]	France	2015–2016	259	62.0	72.2	85.7	Mixed	–	–	–	–	77.2*	–	22.8**	–	–	Yes: CNS	61.4
Giannicola, 2019[58]§	Italy	2015–2018	92	66.0£	81.5	–	Mixed	–	–	–	–	–	–	–	–	–	No	–
Girard, 2017[59]	France	2015–2015	902	64.18	69.7	86.7	Mixed	2.7	6.1	–	–	–	–	–	–	–	Yes: CNS	27.3
Gobbini, 2019 [47]	France	2010–2018	144	63.0	67.0	87.0	Mixed	–	–	–	–	80.0*	–	17.0**	–	–	No	–
Grangeon, 2019[60]	France	2013–2017	270	61.0	65.6	88.5	–	–	–	–	–	93.2*	–	6.8	–	–	Yes: CNS	–
Grossi, 2018[46]	Italy	2015–2015	371	68.0	80.0	83.0	Squamous	–	–	–	–	36.0	58.0	6.0	–	–	Yes: Both	44.0
Hakozaki, 2018 [39]	Japan	2016–2017	90	68.0	63.3	–	Mixed	–	–	–	–	71.1*	–	14.4	14.4	–	No	–
Juergens, 2018 [19]#	Canada	2015–2017	472	66.0	43.0	53.8	Mixed	–	–	–	–	85.6*	–	8.9**	–	–	Yes: CNS	44.3
Junker, 2019[34]	Denmark	2015–2019	224	67.7	53.0	90.6	Mixed	47.0¤	11.0	–	42.0	24.0	61.0	15.0	–	–	No	82.0
Kambartel, 2018[61]	Germany	2015–2017	243	–	–	–	–	–	–	–	–	–	–	–	–	–	No	100.0
Kasherman, 2017[62]	Australia	2015–2017	77	69.0	–	–	Mixed	–	–	–	–	–	–	–	–	–	No	91.0
Katsura, 2019[28]	Japan	2015–2018	99	71.0	70.7	76.8	Mixed	–	–	–	–	22.2	21.2	7.1	32.3	17.2	No	49.5
Khozin(a), 2019 [63]	USA	2011–2017	1,344	69.0	55.6	88.0	Mixed	49.1	33.0	4.46*	13.4	–	–	–	–	–	No	49.8
Khozin(b), 2019 [64]	USA	2011–2017	5,257	69.0	53.6	89.0	Mixed	27.4	30.0	0.3**	42.3∋	–	–	–	–	–	No	51.0
Ksienski, 2018 [11]	Canada	2015–2017	271	66.0	50.6	87.5	Mixed	31.4¤	9.9ł	–	58.7	69.0*	–	31.0**	–	–	Yes: Both	58.7
Laktionov, 2019 [65]	Russia	–	176	61.5	64.0	69.9	Mixed	–	–	–	–	81.0*	–	19.0**	–	–	Yes: CNS	48.9
Lee, 2019 [36]	Korea	2016–2018	83	60.0	–	–	Mixed	20.0¤	17.0	–	–	–	–	–	–	–	No	100
Lefebvre, 2019 [30]	France	2010–2017	176	60.0	–	–	Mixed	–	–	–	–	–	–	–	–	–	No	100
Levra, 2019[38]	France	2015–2017	10,452	63.8£	71.0	–	Mixed	–	–	–	–	–	–	–	–	–	Yes: CNS	–
Majem Tarruella, 2018 [66]	Spain	2015–2017	665	61.0	73.0	88.1	Mixed	–	–	–	–	85.1*	–	14.7^	–	–	Yes: Both	–
Manrique, 2018 [44]	Spain	2015–2017	188	58.0	77.0	91.0	Mixed	–	–	–	–	8.0	82.0	10.0	0	0	Yes: CNS	62.0
Mazieres, 2019 [67]	European (10 countries)	2017–2018	551	–	–	–	Mixed	66.8	33.2	–	–	–	–	–	–	–	No	41.0
Merino Almazan, 2019 [68]	Spain	2016–2017	221	64.5	83.7	68.8	Mixed	–	–	–	–	28.1	56.6	13.6	–	–	Yes: Both	65.2
Mielgo Rubio, 2018[69]	Spain	2015–2018	168	65.0	79.8	–	Mixed	15.5¤	8.9	–	75.6	72.0*	–	28.0**	–	–	No	–
Moezi, 2017[70]#	USA	2014–2017	383	67.5	53.3	88.5	Mixed	1.3	2.6ł	–	96.1	13.6	59.5	19.8**	–	–	No	–
Molife, 2019[29] Φ	USA	2014–2017	4,054	65.8	52.5	88.1	Mixed	34.5	41.5	–	29.5	–	–	–	–	–	No	–
Moor, 2018[71]	Australia	–	214	67.0	–	–	–	–	–	–	–	64.0*	–	36.0^	–	–	No	100.0
Nadler, 2018[21]#	USA	2012–2016	10,689	68.0	54.4	84.3	Mixed	0.5	0.7	–	98.8	7.0	59.0	18.0	1.6	–	No	–
Nadler, 2019[72]#	USA	2015–2017	188	70.3	57.4	89.9	Mixed	5.9	7.4	–	86.7	82.0*	–	12.0**	–	–	No	66.0
Nakaya, 2018[26]	Japan	2015–2016	101	69.0	77.0	83.2	Mixed	–	–	–	–	84.0*	–	16.0**	–	–	No	18.0
Naqash, 2018[73]	USA	2015–2017	61	63.0	60.7	–	Mixed	–	–	–	–	–	–	–	–	–	Yes: Both	–
Oya, 2017[33]	Japan	2015–2017	124	66.0	70.0	78.2	Mixed	41.1¤	30.6	–	28.2	88.0*	–	10.0	2.0	–	No	17.0
Prelaj, 2019[74]	Italy	2013–2019	193	65.0	62.0	78.0	Mixed	–	–	–	–	36.0	52.0	12.0	–	–	Yes: Both	61.0
Raez, 2018[75]	USA, Peru	–	216	65.0	54.0	–	Mixed	–	–	–	–	–	–	–	–	–	No	–
Ramos Garcia, 2018[76]	Spain	–	129	–	–	–	–	–	–	–	–	–	–	–	–	–	No	–
Ramos Sousa, 2019 [77]	Brazil	2006–2018	87	–	–	–	–	–	–	–	–	–	–	–	–	–	No	–

(*continued on next page*)

Table 1 (*continued*)

First Author, Year	Country	Study Period	Sample Size (N included)	Median age (years)	Male (%)	Current/former smokers (%)	Histology	PD-L1 expression (%)				ECOG PS (%)					CNS or liver metastases	Proportion of patients who failed one prior line treatment (%)
Ratnayake, 2019 [22]	Australia	2015–2016	85	65.0[ε]	62.4	88.2	Mixed	–	–	–	–	62.4*	–	35.3**	–	–	Yes: Both	85.6
Ravanelli, 2019 [78]	Italy	–	104	67.0	66.35	79.8	Mixed	–	–	–	–	60.58	39.42	–	–	–	No	–
Ren, 2019[79]	China	2016–2019	148	–	–	–	–	–	–	–	–	–	–	–	–	–	No	64.9
Rossi, 2019[20]	Italy	2015–2017	65	68.0	68.0	92.3	Mixed	–	–	–	–	68.0*	–	32.0**	–	–	Yes: CNS	78.0
Schouten, 2018 [41]	Netherlands	2015–2016	248	–	54.8	80.7	Mixed	–	–	–	–	24.6	59.3	13.3	2.8[¥]	–	Yes: CNS	74.6
Schwartzberg, 2019 [14]	USA	2011–2017	6,597	66.9[ε]	54.6	88.6	Mixed	25.2[Φ]	–	–	–	25.2	48.6	21.6	4.5	0.1	No	100.0
Sebastian, 2019 [35][#]	Germany	2016–2019	660	66.5	62.0	81.7	Mixed	48.6	41.2	–	10.1	27.0	47.0	12.0**	–	–	Yes: Both	74.0
Shamai, 2018[17][ט]	Israel	2015–2016	77	68.0	55.85	40.3	Mixed	–	–	–	–	0	52.0	45.0	3.0	–	Yes: Both	56.0
Sherman, 2019 [18][#]	Israel	2015–2016	270	67.0	67.0	77.0	Mixed	–	–	–	–	46.0*	–	47.0**	–	–	Yes: CNS	66.0
Sinclair, 2018[80][#]	USA	2010–2017	98	–	–	–	Mixed	–	–	–	–	–	58.2	20.4	–	–	No	62.2
Stenehjem, 2019 [81][#]	USA	2015–2018	3,019	68.5[ε]	55.0	90.6	Mixed	11.9	12.3[ו]	–	75.8	53.0*	–	20.6**	–	–	Yes: CNS	84.0
Svaton, 2018[82]	Czech Republic	2015–2016	120	–	59.2	81.7	Mixed	–	–	–	–	25.0	75.0	–	–	–	No	39.2
Tanaka, 2019[31]	Japan	–	67	–	–	–	–	–	–	–	–	–	78.6[Ψ]	–	–	–	No	–
Tournoy, 2018 [40]	Belgium	2016–2016	267	66.0	72.3	92.1	Mixed	–	–	–	–	16.1	60.3	23.6	0	0	Yes: Both	51.7
Velcheti, 2019 [12][#]	USA	2016–2018	281	68.0	56.0	–	Mixed	100.0	–	–	–	57.0*	–	18.0	–	–	Yes: CNS	–
Weis, 2019[13]	USA	2015–2017	124	65.6[***]	50.0	83.9	Mixed	9.7	13.7	–	76.6	16.9	57.3	25.8**	–	–	No	69.3
Yang 2018[25]	USA	2014–2015	320	–	–	–	Squamous	–	–	–	–	–	–	–	–	–	No	100.0
Zhang, 2019[23]	China	2016–2018	65	59.0[ε]	75.4	–	Mixed	–	–	–	–	90.8*	–	9.2**	–	–	Yes: Both	81.5

A dash (-) denotes that the data were not reported by the authors. 'Mixed' histology indicates mixed patient populations with different histologic subtypes.

All values highlighted in **bold** indicate back-calculated values for the overall population derived using the data for subgroups/treatment arms as reported in the study. Median/mean age in bold represents the computed mean of subgroup values.

[ε]Mean age, [***]Unclear if mean or median reported, *includes PS 0–1, **includes PS 2–4, ˆIncludes PS 2 or 3, [¥]includes PS 3 or 4, [Ψ] Reported only in elderly subpopulation (n = 14), [#]ECOG PS not reported/unknown for a certain proportion of the study population, [ט] ECOG PS reported at cycle 1 of nivolumab treatment, [§]Entire study population has PS < 2, [Φ] Denominator for PD-L1 status percentages (%) is the tested population (N = 982 for Molife, 2019, N = 1,032 for Schwartzberg, 2019, N = 405 for Sebastian, 2019), [Ж] PD-L1 expression status was assessed only in 14.9% of patients, [ת] Calculated by combining groups PD-L1 > 50% and > 1%-<50%, [ב] Includes patients with no PD-L1 status interpretation reported and those with unknown/pending results, [ת] Only reported for patients with PD-L1 > 50%,*Unsuccessful or indeterminate PD-L1 test, [**]Equivocal results for PD-L1 test, [ו]defined as PD-L1 < 1%.

Abbreviations – PD-L1: Programmed death-ligand 1, ECOG PS: Eastern Co-operative Oncology Group performance status, CNS: Central nervous system, +ve: PD-L1 status positive, -ve: PD-L1 status negative, Unk: PD-L1 status unknown, NR: Not reported.

groups were broadly re-categorised into three different groups for the purpose of this review: nivolumab monotherapy (representing nivolumab-specific study arms); other ICIs (comprising unspecified ICIs, mixed ICIs including or not including nivolumab, pembrolizumab monotherapy, atezolizumab monotherapy); and non-IO comparators. Most of the studies (n = 47) included a study arm of nivolumab monotherapy and an additional eight studies included mixed ICIs including nivolumab, adding up to 35,168 patients. In studies with a nivolumab-specific arm, median follow-up time ranged from 3.5 to 26.1 months. Pembrolizumab was included in ten studies either as a separate treatment arm or among other ICIs (i.e., mixed ICIs). While two of these studies assessed pembrolizumab as a separate arm [11,12], the study by Ksienski et al [11] comprised > 10% patients receiving pembrolizumab in first line and therefore, this specific treatment arm of the study was excluded from the analyses (reference to the additional restrictive criteria defined under Methods). Atezolizumab was included in four studies as an option in which ICIs were given, and in one study that reported atezolizumab monotherapy as a study arm [13]. Of the 66 included studies, 10 studies assessed outcomes for treatment with unspecified ICIs and one study [14] evaluated treatment with either unspecified ICI or chemotherapy.

The study patients' median age ranged from 58 to 74 years whereas the minimum and maximum age for study participants ranged from 17 [15] to 99 years [16–18]. In 51 studies (77%), the majority of study participants were men. Current or former smokers constituted the greater proportion of study population in all included studies, ranging from 53.8% to 92.3% [19,20], except in a study by Shamai and colleagues (40.3%) [17]. Of the 57 studies that reported tumour histology, the majority comprised of mixed populations with varying histologic subtypes (including squamous cell carcinoma, adenocarcinoma, large cell carcinoma, or others). In 50 studies, a higher percentage of patients presented a non-squamous histology. PD-L1 expression was only reported in 19 studies with the proportion of patients positive for PD-L1 expression ranging from 0.5% [21] to 100% [12]. ECOG PS was reported in 46 studies (69.7%), of which 43 studies included patients with poor PS (≥2). The proportion of patients in the group with better PS (<2) was consistently higher than for poor PS, except in one study [18] that reported comparable proportions (46% and 47% respectively). Data on the presence of central nervous system (CNS) metastases were reported in 31 studies (47%), with the proportion ranging from 5% [22] to 40% [23] of the overall study population. Data on the presence of liver metastases were reported in 16 studies, with the proportion ranging from 10% [22] to 39% [11,24].

3.3. Os

For all but one study [25] included in the SLR, median OS for nivolumab monotherapy ranged from 4.2 months [22] to 17 months [26] (Fig. 2). The study by Yang et al (2018) [25] reported median OS since the initiation of the first-line treatment and was, therefore, excluded from the forest plot. As described in Table 2 and Fig. 3, the pooled estimate for the 1-year OS rate related to nivolumab treatment was 45.6% (95% CI; 43.4–47.8). The pooled estimate for the 2-year OS rate associated with nivolumab treatment was 28% (95% CI; 24.8–31.4) (Table 2 and Fig. 4). Only two studies reported the 3-year OS rate with nivolumab treatment as 12.8% and 17.0% respectively [18,27]. The 1-year and 2-year OS rates from the *meta*-analysis for non-IO comparator arms were 30.2% (95% CI; 20.6–41.9) and 23.9% (95% CI; 19.8–28.4), respectively. Within the non-IO group, the shortest median OS of 1.1 months was reported in a small Japanese subpopulation (N = 36) receiving only best supportive care [28], while the longest median OS of 29.3 months was reported in a subpopulation of a US Flatiron Health database study that received sequential targeted-/IO-based treatment [29] (Fig. 2).

The median OS for mixed ICIs including nivolumab, pembrolizumab, atezolizumab, durvalumab, and unspecified ICIs, ranged from 4.6 months [30] to 29.6 months [31] (Fig. 2). The pooled estimate for mixed ICIs was calculated as 43.9% (95%CI; 39.1–48.8) for 1-year OS rate (Table 2 and Fig. 3), and as 20.4% (95%CI; 14.7–27.6) for 2-year OS rate (Table 2 and Fig. 4). In addition, Nadler et al [21] reported a 3-year survival rate of 17.2% with IO treatment, not specifying the specific agents included. The median OS for pembrolizumab monotherapy as reported by one study was 13.5 months [12] and the 1-year OS rate was 53.6% [12] in a PD-L1 positive population that excluded patients with<6 months of follow-up. Two-year and 3-year OS rates were not reported for pembrolizumab monotherapy. Only one study [13] reported median OS and 1-year OS rate for atezolizumab monotherapy as 6.5 months and 34.6%, respectively. In the same study [13], the 2-year OS rate for atezolizumab was not reached and the 3-year survival rate was not reported.

3.4. Histology

When results were available by histology specifically (n = 57), median OS for patients with squamous histology treated with nivolumab ranged from 5.5 months [32] to 15.5 months [33]. The pooled estimate for nivolumab-specific study arms for squamous NSCLC was 41.8% and 24.7% for 1-year and 2-year survival, respectively (Supplementary **Figure S1,** Table 2). Only one study including patients treated with either nivolumab or pembrolizumab [34] assessed outcomes stratified by histology and reported a median OS of 13.2 months among squamous histology patients.

Median OS for patients with non-squamous histology treated with nivolumab ranged from 5.8 months [16] to 19.3 months [35]. The pooled estimate for nivolumab-specific study arms for non-squamous NSCLC was 46.6% and 32.2% for 1-year and 2-year survival, respectively (Supplementary **Figure S2,** Table 2). The only study to include patients treated with either nivolumab or pembrolizumab and assess outcomes by histology [34] reported a median OS of 12.9 months for patients with non-squamous histology. None of the studies with IO treatment arms reported on 3-year survival rate for patients with either squamous or non-squamous histology. Pooled estimates for other treatment groups by histology were not calculated due to having < 3 estimates.

3.5. PD-L1 expression

Median OS for the PD-L1 positive population treated with nivolumab monotherapy as reported in four studies, ranged from 8.2 months [32] to 18.1 months [36], and from 5.5 months [32] to 9.1 months [37] in the PD-L1 negative population, as reported in three studies. One study [34] reported median OS for the PD-L1 positive population treated with either nivolumab or pembrolizumab, for PD-L1 expression > 1% to < 50% and PD-L1 expression > 50% as 13.7 and 16.7 months, respectively. Only one study [12], which excluded patients with a follow-up of < 6 months reported median OS and 1-year OS rate for a PD-L1 positive population treated with pembrolizumab monotherapy as 13.5 months and 53.6%, respectively.

For PD-L1 positive NSCLC, the pooled 1-year survival for nivolumab-specific study arms was 46.3% (Table 2); 2-year OS rates only reported in one study [32] were 26.0% and 23.0% for patients with squamous and non-squamous histology, respectively. For the PD-L1 negative population, 1-year OS rates associated with nivolumab were reported in two studies [32,33], of which one [32] reported the rates as 21.0% and 32.0% in squamous and non-squamous populations, respectively. The second study [33] reported a 1-year OS rate of 30.1% with nivolumab for PD-L1 negative patients across histologies. The pooled 1-year OS rate with nivolumab was 27.8% (Table 2). Two-year OS rate for PD-L1 negative advanced NSCLC patients with non-squamous histology, reported in one study, was 14.0% [32]. Pooled estimates for other treatment groups by PD-L1 status were not calculated because of an insufficient number of estimates.

3.6. Populations of interest

3.6.1. Elderly populations

For patients treated with nivolumab, elderly populations (≥75 years old) had a median OS ranging from 4.7 to 12.1 months [16,19], and those < 75 years of age had median OS ranging from 6.3 to 15.5 months [16,33]. Eight studies compared the OS benefit of nivolumab between the two subgroups (≥75 years vs. < 75 years) but none reported a significant difference. In the two studies where elderly patients received either nivolumab or pembrolizumab, median OS was very similar at approximately 14 months [31,34]. Yet, in the same two studies, the non-elderly population (<75 years old) had a median OS ranging from 12.8 to 29.6 months [31,34]. Of these two studies, only Junker and colleagues [34] compared the elderly and non-elderly populations but observed no difference in OS between the two age groups [Hazard ratio (HR) 1; p = 0.37].

The pooled 1-year OS rate associated with nivolumab treatment was 39.6% in the elderly and 43.2% in non-elderly populations (Table 2). The 2-year OS rate associated with nivolumab treatment as reported in two studies, ranged among the elderly population from 16.0% (in a squamous NSCLC population) to 26.0% [38], and from 20.0% (in a squamous NSCLC population) [32] to 34.0% [19] in the non-elderly population. The pooled 2-year OS rate associated with nivolumab treatment was 21.3% in the elderly and 25.5% in the non-elderly population (Table 2). Pooled estimates for other treatment groups by age were not calculated because of an insufficient number of estimates.

3.6.2. Poor ECOG PS

Fifteen studies compared survival benefit of nivolumab therapy in patients with poor PS (≥2) to those with PS < 2. Of these, ten studies reported a statistically significant HR (p < 0.05) with all ten reporting a shorter OS (i.e., increased risk of death) in patients with PS ≥ 2. Median OS for those with PS ≥ 2 ranged from 2.6 to 7 months [33,39] and 7.3–15.5 months [33,40] in those with PS < 2. Only one study [34] of the two that included nivolumab or pembrolizumab reported on PS subgroup data and reported a significantly shorter OS in those with poor PS (HR 4.2, PS ≥ 2 vs PS 0; p > 0.0001). The study by Weis et al [13] was the only study to report on those who received nivolumab or atezolizumab and observed a 49% lower risk of death (i.e., longer OS) in those with PS 0 compared to PS ≥ 2 (p = 0.03). No study that assessed pembrolizumab monotherapy or atezolizumab monotherapy reported survival by ECOG PS.

The 1-year OS rate for patients with PS ≥ 2 treated with nivolumab ranged from 0% (n = 15) in one study [33] to 76.6% [41], and from 36.0% to 100.0% in those with PS < 2 [33,40]. The 2-year OS rate for patients with PS ≥ 2 treated with nivolumab was 14.0% [32] and ranged from 19.0% to 34.0% in those with PS < 2 [19,32]. The 3-year survival rates for patients with PS ≥ 2 available from one study were 6% and 8.3%, respectively, among those with squamous and non-squamous histology. The 3-year survival rate for patients with PS < 2 was 14.1% as reported in one study [18], and 14.5% and 18% in squamous and non-squamous subpopulations, respectively, in another study by Stenehjem et al [32]. The pooled 1-year OS rate associated with nivolumab treatment in patients with ECOG PS ≥ 2 was 27.1%, and 51.6% in those with PS < 2 population (Table 2). The pooled 2-year OS rate for nivolumab specific study arms for the ECOG PS < 2 was 26.4%. The pooled 2-year estimate for ECOG PS ≥ 2 was not calculated due to an insufficient number of estimates.

3.6.3. CNS metastases

Median OS was reported in ten studies assessing nivolumab treatment, which ranged from 3.1 to 14.8 months [42–44] in patients with CNS metastases and 5.1 to 13.1 months [19,44] in those with no CNS metastases. Although median OS for the two groups were reported to be in the similar range, eleven studies compared the OS benefit conferred by nivolumab monotherapy in patients with and without CNS metastases, of which four reported a significantly shorter OS (p < 0.05) in those presenting with metastases. No study that included subgroup data for CNS metastases reported on any ICI treatment other than nivolumab monotherapy.

One-year OS rate with nivolumab as reported in six studies for patients with CNS metastases ranged from 31.0% to 61.5% [44] compared to 28.4% to 52.1% [19,44] in those without CNS metastases. The pooled 1-year OS rate associated with nivolumab treatment in patients with and without CNS metastases was quite similar at 41.9% and 40.0%, respectively (Table 2). Two-year OS rates only reported in two studies were 10.0% [32] and 30.6% [24] for those with CNS metastases, and ranged from 19.0% [32] to 39.0% [19] among those without CNS metastases as reported in four studies. The pooled 2-year survival associated with nivolumab treatment in patients with and without CNS metastases was 22.1% and 26.1%, respectively (Table 2). Pooled estimates for other treatment groups by presence of CNS metastases were not calculated because of an insufficient number of estimates.

3.6.4. Liver metastases

Median OS was reported in four studies [16,23,40,45] for patients with liver metastases and treated with nivolumab ranging from 3.6 months [45] to 7.5 months [23]. For patients without liver metastases, median OS with nivolumab treatment was reported in four studies [16,23,40,45] and ranged from 5.8 [16] to 20.7 months [23]. Three out of the four studies [16,23,40,46] that compared OS between patients (receiving nivolumab treatment) with and without liver metastases reported a significant association between presence of metastases and worse survival (p < 0.05). No study reported OS outcomes by presence of liver metastases for treatment groups other than nivolumab.

One-year OS rate for patients without liver metastases treated with nivolumab ranged from 35.6% [45] to 63.8% [23], and the respective pooled estimate was calculated to be 43.4% (Table 2). Two-year OS rate associated with nivolumab treatment in patients without liver metastases was reported to be 40.1%, as reported from only one study by Zhang et al [23]. While 1-year OS reported in three studies for NSCLC patients with liver metastases treated with nivolumab ranged from 14.0% to 39.1% respectively [23,40], the 2- and 3-year rates were either not reached or not described by any study. The pooled 1-year OS rate associated with nivolumab treatment in patients exhibiting liver metastases was 23.8% (Table 2). Pooled estimates for 2-year OS rates by presence of liver metastases were not calculated due to an insufficient number of estimates (i.e., <3 estimates).

3.7. IO rechallenge

Two studies were identified which assessed survival following IO rechallenge [38,47]. These studies reported a similar median OS of 18.1 (95% CI; 14.6–21.6) months and 18 (95% CI; 12–25.2) months, respectively, after IO rechallenge. Only one of these studies [38] further reported on 1-year and 2-year OS rates, which were 55% and 33.5%, respectively.

4. Discussion

Treatment with IO has been considered a breakthrough in recent years, and has shown favourable outcomes for pre-treated advanced NSCLC in pivotal clinical trials when compared to conventional chemotherapy [2–5]. This SLR was conducted to obtain insight into survival outcomes associated with IO use in previously treated patients with locally advanced or metastatic NSCLC in the real-world setting. While the approval of IOs were based on pivotal RCTs supporting the efficacy and safety of their treatment in advanced NSCLC patients, RWE is essential to assess whether the findings in the trials are also evident in routine clinical practice outside of the trial setting.

The present SLR confirms the beneficial effects of IO on OS for the second-line treatment of locally advanced or metastatic NSCLC, in real-

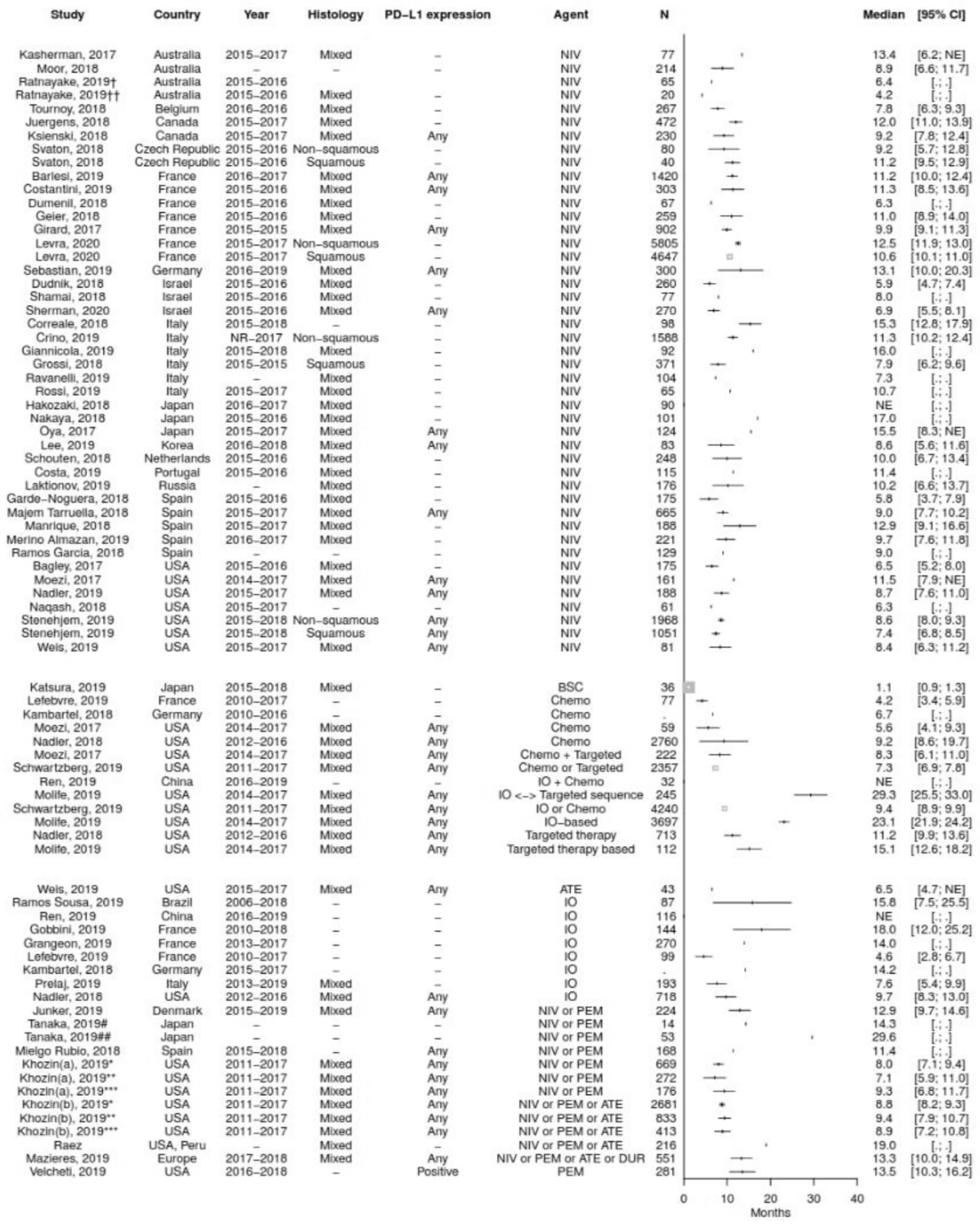

Fig. 2. Forest plot showing median overall survival (OS) in months. †Subgroup treated with nivolumab with concurrent radiotherapy or prior radiotherapy; ††Subgroup treated with nivolumab monotherapy with no history of radiotherapy; #Elderly subpopulation (≥75 years); ##Non-elderly subpopulation (<75 years); *treatment received in second line; **Treatment received in third line; ***Treatment received in fourth and subsequent lines. Abbreviations – PD-L1: Programmed death-ligand 1, IO: Immunotherapy, NIV: Nivolumab, ATE: Atezolizumab, PEM: Pembrolizumab, DUR: Durvalumab, BSC: Best supportive care, CI: Confidence interval.

world study populations. The highlights of this study indicate global RWE related to IO use, with most of the evidence coming from the US and Europe. While the search was conducted to assess outcomes for nivolumab, pembrolizumab and atezolizumab, most of the evidence base reported on nivolumab treatment (55 of the 66 studies containing nivolumab treatment), which was anticipated considering it was the first immunotherapy agent to be approved for this indication, with an early access program in several countries For the overall population, the pooled estimates generated from this SLR for 1-year and 2-year OS rate associated with nivolumab treatment in RWE studies were 45.6% and

Table 2
Meta-analysis results for survival rate as 1-year and 2-year.

	1-year OS rate								2-year OS rate					
	Number of estimates	Treatment group	Pooled estimate (%) (95% CI)	Q statistics			I^2 (%)	tau^2	Number of estimates	Pooled estimate (%) (95% CI)	Q statistics			I^2 (%)	tau^2
				Q	df	p-value					Q	df	p-value		
Overall population	32	Nivolumab	45.6 (43.4; 47.8)	233.38	31	<0.0001	88.5	0.0478	15	28.0 (24.8; 31.4)	171.73	14	<0.0001	95.4	0.0931
Overall population	9	Mixed ICIs	43.9 (39.1; 48.8)	47.94	8	<0.0001	84.3	0.0696	6	20.4 (14.7;27.6)	73.92	5	<0.0001	93.9	0.2253
Overall population	8	Non-IO	30.2 (20.6; 41.9)	106.34	7	<0.0001	99.2	0.4838	4	23.9 (19.8; 28.4)	65.03	3	<0.0001	95.7	0.0553
Histology															
Non-squamous	9	Nivolumab	46.6 (43.1; 50.1)	83.32	8	<0.0001	85.8	0.0305	5	32.2 (27.0; 37.9)	63.03	4	<0.0001	95.6	0.0724
Squamous	8	Nivolumab	41.8 (34.9; 49.0)	58.20	7	<0.0001	93.3	0.1400	3	24.7 (18.1; 32.6)	30.82	2	<0.0001	94.1	0.1032
Age															
≥ 75 years old	8	Nivolumab	39.6 (34.8; 44.6)	25.00	6	0.0003	68.2	0.0450	3	21.3 (17.0; 26.4)	11.69	2	0.0029	77.3	0.0462
< 75 years old	7	Nivolumab	43.2 (39.4; 47.1)	25.88	7	0.0005	73.1	0.0334	3	25.5 (19.9; 32.1)	17.97	2	0.0001	88.5	0.0680
PD-L1															
Positive	3	Nivolumab	46.3 (34.2; 59.0)	10.94	2	0.0042	80.5	0.1536	–	–	–	–	–	–	–
Negative	3	Nivolumab	27.8 (21.9; 34.5)	4.31	2	0.1158	33.6	0.0255	–	–	–	–	–	–	–
ECOG PS															
≥2	10	Nivolumab	27.1 (17.8; 39.0)	39.60	9	<0.0001	91.1	0.6151	–	–	–	–	–	–	–
<2	14	Nivolumab	51.6 (44.4; 58.8)	49.93	13	<0.0001	92.6	0.2493	5	26.4 (21.4; 32.1)	29.57	4	<0.0001	83.2	0.0731
CNS metastases															
Present	7	Nivolumab	41.9 (38.7; 45.2)	11.64	6	0.0706	0.0	0.0000	3	22.1 (13.4; 34.2)	10.89	2	0.0043	87.1	0.2090
Absent	6	Nivolumab	40.0 (33.9; 46.3)	38.37	5	<0.0001	90.3	0.0848	4	26.1 (19.3; 34.2)	58.68	3	<0.0001	94.0	0.1371
Liver metastases															
Present	3	Nivolumab	23.8 (14.9; 35.7)	4.71	2	0.0947	57.6	0.0923	–	–	–	–	–	–	–
Absent	4	Nivolumab	43.4 (34.4; 52.9)	13.15	3	0.0043	77.2	0.1121	–	–	–	–	–	–	–

A dash (-) indicates that no *meta*-analysis was conducted due to < 3 estimates.
Mixed ICIs include nivolumab, pembrolizumab, atezolizumab, durvalumab, and IOs where the agent was not specified.
Abbreviations – OS: Overall survival, PD-L1: Programmed death-ligand 1, ECOG PS: Eastern Co-operative Oncology Group performance status, CNS: Central nervous system,.
df: degrees of freedom.

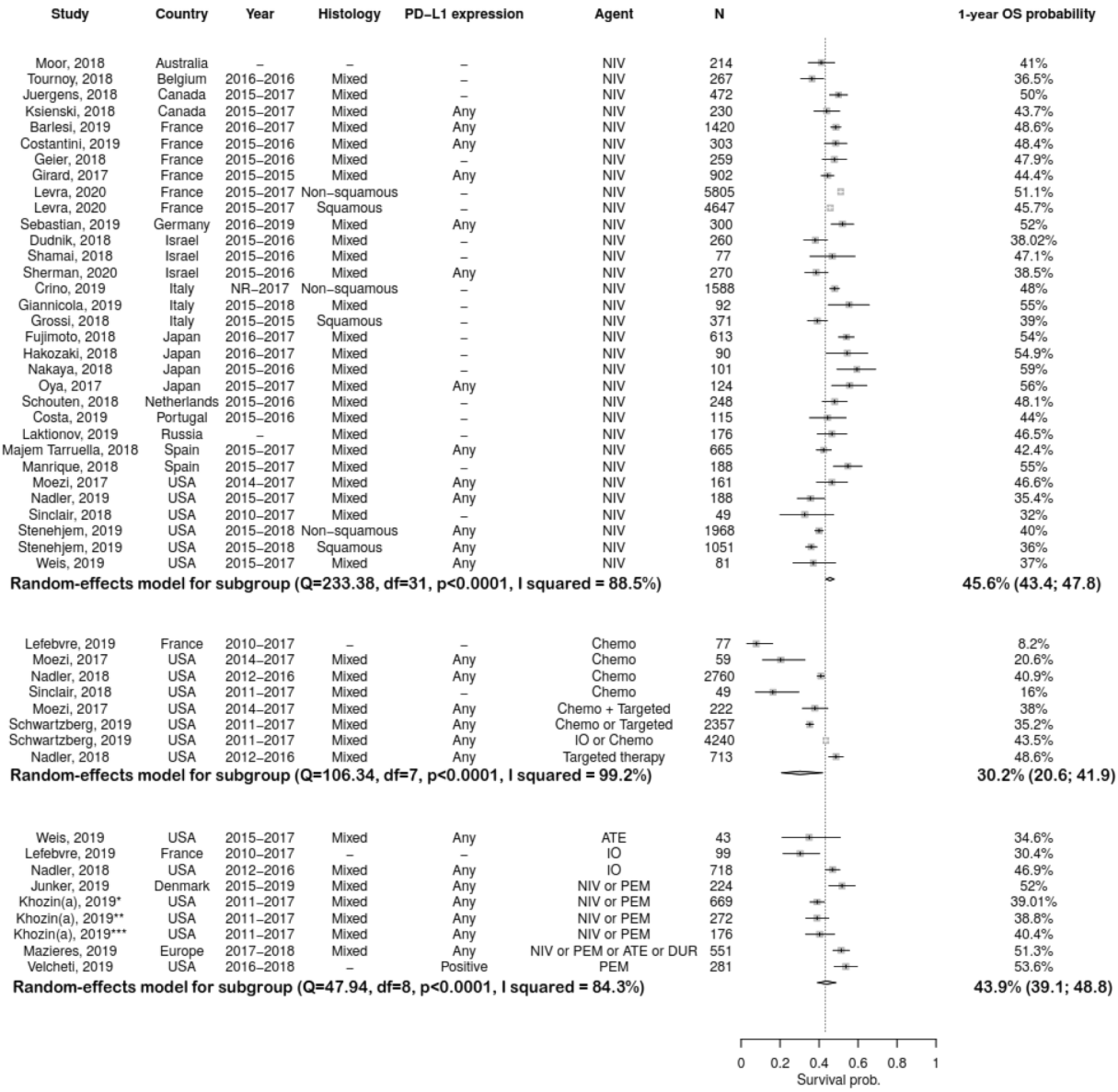

Fig. 3. Summary of meta-analysis for 1-year OS probability. The dotted vertical line represents the average 1-year survival rate across the three treatment groups. The square boxes denote the estimate and the solid horizontal lines denote the 95% CI. The size of the square boxes correspond to the weight of the study and are proportional to the precision of estimates. Abbreviations – OS: Overall survival; PD-L1: Programmed death-ligand 1, IO: Immunotherapy, NIV: Nivolumab, ATE: Atezolizumab, PEM: Pembrolizumab, DUR: Durvalumab, BSC: Best supportive care, CI: Confidence interval.

28.0%, respectively. These data are consistent with the findings reported in a pooled analysis of the two pivotal phase 3 clinical trials, CheckMate 017 and CheckMate 057, where the respective 1-year and 2-year OS rates for patients with squamous and non-squamous histology combined were 48.0% and 27.0% [48], indicating that the survival benefits of nivolumab treatment can be seen in previously treated patients with locally advanced or metastatic NSCLC in the real-world setting. While only two studies reported a 3-year survival rate associated with nivolumab treatment in the overall studied population [18,27], the reported rate of 17.0% aligns with that reported from a pooled population of the two CheckMate trials in patients with squamous/non-squamous histology [48]. Future real-world studies with longer follow up would be able to provide more robust evidence on OS beyond two years.

When looking specifically at outcomes by histology, the findings from the pooled estimate of RWE studies indicated a 1-year OS rate of 41.8% associated with nivolumab treatment in patients with squamous histology. This aligns with clinical trial data that recorded a 1-year OS rate of 42.0% in previously treated patients with advanced squamous NSCLC [2]. In pre-treated patients with non-squamous histology treated with nivolumab, the pooled 1-year OS rate from the RWE studies was 46.6% which is slightly lower than that reported in an RCT (51.0%) [3]. However, the 2-year OS rates for patients with non-squamous histology from the pooled estimate of RWE and that in the trial were quite similar at 32.2.% and 29.0%, respectively [3].

Patients with tumours expressing PD-L1 have been shown to have better survival outcomes associated with IO compared to PD-L1 negative patients in histologically mixed trial populations. For example, a pooled analysis of trial data has indicated respective 1-year OS rate of 45.0% and 52.0% for PD-L1 negative and PD-L1 positive patients across histologies treated with nivolumab [49]. Similarly, the respective 2-year survival rate was 24.0% and 32.0% for PD-L1 negative and positive patients across histologies treated with nivolumab [49]. Additionally, trial data also reported a 2-year OS rate of 22.0% and 25.0% in patients with squamous and non-squamous histology, respectively, with PD-L1 expression $< 1\%$ [50]. However, only one study in the present SLR reported on 2-year survival rate for PD-L1 negative patients with non-

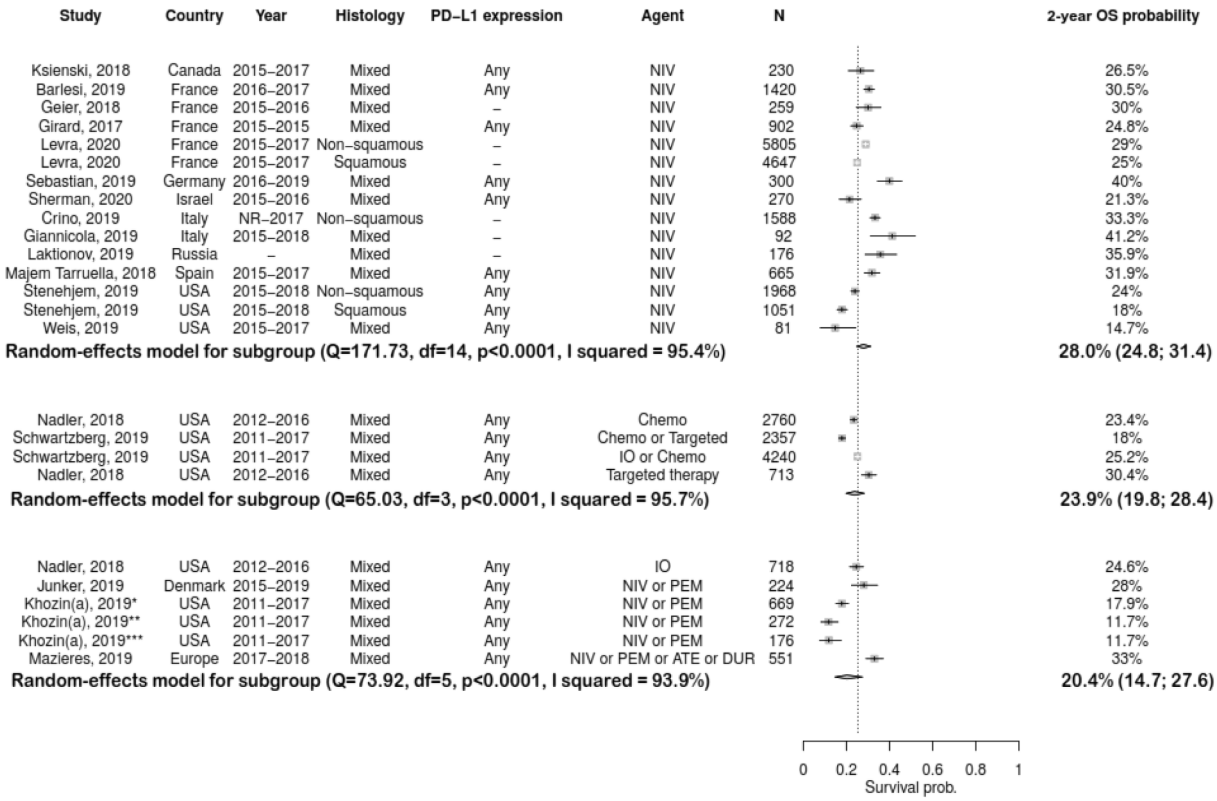

Fig. 4. Summary of meta-analysis for 2-year OS probability. The dotted vertical line represents the average 2-year survival rate across the three treatment groups. The square boxes denote the estimate and the solid horizontal lines denote the 95% CI. The size of the square boxes correspond to the weight of the study and are proportional to the precision of estimates. Abbreviations – OS: Overall survival, PD-L1: Programmed death-ligand 1, IO: Immunotherapy, NIV: Nivolumab, ATE: Atezolizumab, PEM: Pembrolizumab, DUR: Durvalumab, BSC: Best supportive care, CI: Confidence interval.

squamous histology, which was 14.0%, and somewhat lower than what had been observed in prior RCTs [32]. However, this study of 3,019 patients reported by Stenehjem et al (2019) included more elderly patients (28%) and those with poor PS (20.5%), which were underrepresented in clinical trials. The 2-year OS rate for PD-L1 negative squamous subpopulation was not reached. The 2-year OS rate in PD-L1 positive patients (≥1%) was 23.0% and 26.0% for patients with non-squamous and squamous histology, respectively, from this study reporting on outcomes by PD-L1 expression and histology in the SLR [32]. While the estimate was somewhat lower than trial data on PD-L1 positive patients with non-squamous histology, it was more closely aligned for PD-L1 positive patients with squamous histology [50]. Longer follow-up on existing studies as well as any additional studies are needed to confirm the impact of nivolumab treatment on long-term survival within subgroups defined by both PD-L1 expression and histology, in the real-world setting.

The results from the present SLR and *meta*-analysis indicate favourable survival outcomes in both elderly and non-elderly populations, that were aligned with that reported in the clinical trial study population for nivolumab, where elderly patients comprised < 10% of the treated study population [2,3]. However, in those with poor PS (defined as ECOG PS ≥ 2), the results of the SLR did find a lower 1-year OS rate compared to that observed in the clinical trial study populations treated with nivolumab (which excluded those with ECOG PS ≥ 2). It is noteworthy that previous studies [51,52] have demonstrated PS to be a stronger predictor of survival outcomes in advanced NSCLC compared to age, with better PS associated with more favourable outcomes regardless of age. Moreover, this SLR also identified studies that reported on survival outcomes specific to those with CNS metastases, where the 1-year OS rate was similar between those with and without CNS metastases, and also consistent with what was reported in the clinical trial data associated with nivolumab treatment (for patients without CNS metastases). While the pivotal trials included patients with treated, stable brain metastases, no survival outcomes were reported in the present review for these patients specifically. OS outcomes were observed to be better for patients without liver metastases than with liver metastases. However, there were only three studies reporting on 1-year OS rate in patients with liver metastases treated with nivolumab, which ranged from 14.0 to 39.1% [23,40]. While Vokes et al. (2018) reported outcomes from pooled study populations from the pivotal trials (Checkmate 017 and 057), and described the 3-year survival rate of 8.0% for patients with liver metastases treated with nivolumab [48], this information could not be confirmed in the available RWE literature. Therefore, more research is needed to assess whether nivolumab can have positive effects on survival for real-world patients with liver metastases.

Strengths of this review include the systematic approach to comprehensively review the literature, including those from recent conference proceedings. In addition, the present study allowed for the generation of pooled estimates for the overall study population as well as by key subgroups of interest. These *meta*-analyses provide a summary estimate in the real-world to be compared to clinical trial data, when available. Some limitations of the review are that these are real-world studies, with inherent limitations. Although the review specified interest in examining IO treatment in pre-treated advanced NSCLC patients, there was a lot of variation in terms of the line of treatment in which IO was actually given within studies, and this may also contribute to the variation in survival outcomes observed in these studies. The level of heterogeneity in the *meta*-analyses conducted was large, as expected, given the wide variation in the study populations and methodologies across the included studies. Another limitation is the lack of available consistent data across IOs. However, the findings are valuable and provide needed insight into the effectiveness of IOs in the real-world

setting. Finally, although patients with autoimmune diseases are underrepresented in clinical trials, they were not analysed in this SLR as a population of interest,.

5. Conclusion

Overall, this systematic review captured a comprehensive set of observational studies and was conducted according to good practice guidance. These results provide evidence complementary to RCT-based findings on the survival benefits of immunotherapy in pre-treated advanced NSCLC patients. While further research is needed for particular subgroups (e.g., those with liver metastases and autoimmune diseases), the findings can be used by oncologists and patients to inform therapeutic decision-making.

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CRediT authorship contribution statement

Ariadna Juarez-Garcia: Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. **Ruchika Sharma:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Matthias Hunger:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing – review & editing, Visualization. **Sheena Kayaniyil:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **John R. Penrod:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. **Christos Chouaïd:** Validation, Writing – review & editing.

Declaration of competing Interest

Ariadna Juarez-Garcia and John R. Penrod are employees of Bristol Myers Squibb and report stock ownership in Bristol Myers Squibb. Ruchika Sharma and Matthias Hunger are employed by ICON plc, a contract research organization conducting research on behalf of pharmaceutical companies. Sheena Kayaniyil was at the time of the research, employed by ICON plc. Christos Chouaïd reports consultancy fees from Astra Zeneca, Boehringer Ingelheim, MSD, Pierre Fabre Oncology, Lilly, Roche, Bristol Myers Squibb, and Novartis.

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Appendix

A Search Strategy in EMBASE (Embase 1974 to 2019 August 27).

	Searches	Results
1	exp lung tumor/	343200
2	(lung* adj3 canc*).mp.	454564
3	(lung* adj3 carcinoma*).mp.	104992
4	(lung* adj3 tumo?r*).mp.	107088
5	(lung* adj3 neoplasm*).mp.	219822
6	exp non small cell lung cancer/	131908
7	(“non small cell” or “nonsmall cell” or NSCLC).tiab.	169745
8	7 and (or/1–5)	165093
9	8 or 6	207259
10	*cancer immunotherapy/	25807
11	((checkpoint adj2 inhibit$) or immunotherap$ or immuno-oncology).ti,ab.	205327
12	*nivolumab/	4715
13	(nivolumab or opdivo or ONO-4538 or ONO4538 or ONO 4538 or BMS-936558 or BMS936558 or BMS 936,558 or mdx1106 or mdx 1106).ti,ab.	10698
14	*pembrolizumab/	3114
15	(pembrolizumab or Keytruda or MK3475 or MK 3475 or MK-3475 or lambrolizumab).ti,ab.	8099
16	*atezolizumab/	738
17	(atezolizumab or tecentriq or tecntriq or rg7446 or rg-7446 or rg 7446 or mpdl3280a or mpdl-3280a or mpdl 3280a).ti,ab.	2094
18	or/10–17	222847
19	9 and 18	12716
20	clinical study/	157869
21	case control study/	414469
22	family study/	26097
23	Longitudinal study/	255498
24	Retrospective study/	1582694
25	prospective study/	1057806
26	Randomized controlled trials/	293392
27	25 not 26	1046800
28	Cohort analysis/	746690
29	(Cohort adj (study or studies)).mp.	635033
30	(Case control adj (study or studies)).tw.	223815
31	(follow up adj (study or studies)).tw.	108272
32	(observational adj (study or studies)).tw.	246190
33	(epidemiologic$ adj (study or studies)).tw.	182331
34	(cross sectional adj (study or studies)).tw.	342389
35	(real world adj (data or evidence)).tw.	11072
36	electronic medical record$.tw.	44940

(*continued on next page*)

(*continued*)

	Searches	Results
37	(clinical adj regist$).tw.	3551
38	or/20–24,27–37	4567740
39	19 and 38	2244
40	conference.so.	488479
41	conference abstract.pt.	3546551
42	animal/ not (animal/ and human/)	5624721
43	Case report.tw.	684602
44	Abstract report/ or letter/	2159579
45	Case study/	2104816
46	or/40–45	13489173
47	39 not 46	897
48	limit 47 to yr="2015 -Current"	851

Appendix B

Search strategy in MEDLINE

(Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to August 27, 2019).

	Searches	Results
1	exp lung neoplasms/	565314
2	(lung* adj3 canc*).mp.	454564
3	(lung* adj3 carcinoma*).mp.	104992
4	(lung* adj3 tumo?r*).mp.	107088
5	(lung* adj3 neoplasm*).mp.	219822
6	exp Carcinoma, Non-Small-Cell Lung/	131,908
7	("non small cell" or "nonsmall cell" or NSCLC).ti,ab.	169745
8	7 and (or/1–6)	165170
9	8 or 6	207280
10	*Immunotherapy/	51989
11	((checkpoint adj inhibit$) or immunotherap$ or immuno-oncology).ti,ab.	204393
12	*nivolumab/	4715
13	(nivolumab or opdivo or ONO-4538 or ONO4538 or ONO 4538 or BMS-936558 or BMS936558 or BMS 936558 or mdx1106 or mdx 1106).ti,ab.	10698
14	(pembrolizumab or Keytruda or MK3475 or MK 3475 or MK-3475 or lambrolizumab).ti,ab.	8099
15	(atezolizumab or tecentriq or tecntriq or rg7446 or rg-7446 or rg 7446 or mpdl3280a or mpdl-3280a or mpdl 3280a).ti,ab.	2094
16	or/10–15	228585
17	9 and 16	12584
18	Epidemiologic studies/	212763
19	exp case control studies/	1177295
20	exp cohort studies/	2392352
21	Case control.tw.	271530
22	(cohort adj (study or studies)).tw.	450698
23	Cohort analy$.tw.	18761
24	(Follow up adj (study or studies)).tw.	108272
25	(observational adj (study or studies)).tw.	246190
26	Longitudinal.tw.	531769
27	Retrospective.tw.	1287291
28	Cross sectional.tw.	738510
29	Cross-sectional studies/	488033
30	(real world adj (data or evidence)).tw.	11072
31	electronic medical record$.tw.	44940
32	(clinical adj regist$).tw.	3551
33	or/18–32	5240420
34	animal/ not (animal/ and human/)	5624721
35	Case report.tw.	684602
36	Abstract report/ or letter/	2159579
37	Case study/	2104816
38	or/34–37	10034477
39	17 and 33	1862
40	39 not 38	1807
41	limit 40 to yr="2015 -Current"	1741

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2022.03.008.

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