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CLINICAL INVESTIGATION

Real-World Safety and Efficacy of Consolidation Durvalumab After Chemoradiation Therapy for Stage III Non-small Cell Lung Cancer: A Systematic Review and Meta-analysis

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Purpose: Consolidation durvalumab after chemoradiation therapy (CRT) has improved patient outcomes in stage III non-small cell lung cancer (NSCLC) since the practice-changing results of the PACIFIC trial, whereas real-world evidence regarding the PACIFIC regimen has not been systematically reviewed. This meta-analysis comprehensively investigated the real-world toxicity and efficacy of this regimen and identified differences between the real world and clinical trials.

Methods and Materials: Real-world studies (RWSs) on patients with stage III NSCLC treated with durvalumab after CRT were identified in MEDLINE, EMBASE, PubMed, and Cochrane Library databases. We summarized the differences in demographic and therapeutic characteristics between RWSs and the PACIFIC trial. A meta-analysis of short-term efficacy and adverse event rates was performed. Subgroup analyses were conducted to identify potential influencing factors.

Results: Thirteen studies involving 1885 patients were included. More elderly and poor-performance-status patients, prolonged interval from CRT completion to durvalumab exceeding 42 days, median infusions of durvalumab <20 cycles, and sequential CRT were observed in the real world. The pooled 12-month overall survival (OS) and progression-free survival (PFS) rates were 90% (95% confidence interval [CI], 83%-98%) and 62% (95% CI, 56%-68%), respectively. Subgroup analysis determined that delay in durvalumab initiation beyond 42 days did not affect 12-month OS (P = .068) or PFS (P = .989). Pooled incidences of all-grade and grade ≥3 pneumonitis were 35% (95% CI, 22%-48%) and 6% (95% CI, 3%-8%), respectively. Higher all-grade pneumonitis rates were observed in the studies of patients with a median age of >65 years (P = .008) and from Asian regions (P = .017), whereas expanded access program−related studies reported significantly lower rates (P = .024).

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Conclusions: The safety and short-term efficacy of consolidation durvalumab in real-life use aligns with the PACIFIC trial. RWSs can be helpful for understanding the true efficacy and toxicity of consolidation durvalumab given the less-restrictive eligibility criteria.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide.[1] Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all types of lung cancer, and more than 30% of NSCLC patients were initially diagnosed at a locally advanced (LA) stage.[2,3] For patients with unresectable and LA-NSCLC, definitive concurrent chemoradiation therapy (cCRT) used to be the standard-of-care (SoC) treatment. However, the long-term outcomes of cCRT remain dissatisfactory, with a 5-year survival of 15% to 30%.[4-7] The therapeutic armamentarium available to radiation oncologists for the treatment regimen of LA-NSCLC has appreciably expanded since the practice-changing results of the PACIFIC trial in 2017 were reported.[8]

This randomized, double-blinded, placebo-controlled phase 3 trial included patients with unresectable stage III NSCLC and examined consolidation durvalumab—a programmed death-ligand 1 (PD-L1) immune checkpoint inhibitor (ICI)—after cCRT with curative intent.[9] At a median follow-up of 34.2 months, recently updated survival analyses showed that the 5-year overall survival (OS) and 5-year progression-free survival (PFS) rates were 42.9% and 33.1% with consolidation durvalumab, respectively.[10] The results of the PACIFIC trial demonstrated significant and sustained survival benefits compared with CRT alone and thus further established consolidation durvalumab after CRT (the PACIFIC regimen) as the new SoC in this setting.[8-13] Currently, the consolidative use of durvalumab is not only approved by worldwide health authorities but is also widely accepted in the guidelines as the SoC.[11,14]

A growing body of evidence from clinical trials suggests that a combination of ICIs and CRT has the potential to achieve a synergistic antitumor effect and thus improve long-term survival outcomes.[15] However, some subsets of patient with cancer are usually underrepresented in randomized controlled trials (RCTs), such as elderly patients, patients with poor performance status (PS), or immunodeficient patients.[16] In other words, the safety profile and results of pivotal RCTs often lack external validity, because clinical trials with strict eligibility criteria could exclude a considerable number of patients who are actually treated in real-world oncology practice.

Real-world studies (RWSs), which are emerging in medical oncology as a useful tool to collect data from daily medical practice, might narrow this giant gap and overcome some intrinsic limits of clinical trials. According to the US Food and Drug Administration, the expanded access program (EAP), mainly supported by pharmaceutical and biotechnology companies, is intended to improve access to investigational drugs for patients with serious diseases who lack other therapeutic options and may benefit from such treatments.[17] Therefore, EAP is generally considered as a special kind of RWS, especially for those cancer patients excluded from clinical trials due to poor conditions. The term *real-world data* (RWD) refers to population-level data gathered from multiple sources, such as administrative or disease-specific databases, hospital records, existing registries, and insurance claims, in a postmarket context.[16,18] Real-world evidence (RWE) comes from the collection and analysis of RWD with less-restrictive eligibility criteria than clinical trials,[19] and thus, RWE could be more informative and helpful in understanding the true efficacy and toxicity of a new regimen. Nevertheless, feedback about the toxicity profile and efficacy of consolidation durvalumab in such real-world scenarios has not yet been formally collected and analyzed. Hence, we systematically reviewed the existing RWD and performed this meta-analysis to investigate the efficacy and toxicity of the PACIFIC regimen in oncology practice. Through this review, we sought to further identify differences between the real world and the PACIFIC trial, aiming to provide a comprehensive summary with practical implications and to propose strategies for better applying RWE.

Methods and Materials

Search strategy

This systematic review and meta-analysis of RWSs was conducted according to the Reporting Items for Systematic Reviews and Meta-Analyses systematic review guidelines.[20] We searched the MEDLINE, EMBASE, PubMed, and Cochrane Library databases for literature published from January 1, 2017, to October 1, 2021, mainly using the search terms "non-small cell lung cancer," "real-world," and "immunotherapy or durvalumab" with all relevant synonyms to avoid missing literature retrieval. For example, for the MEDLINE search, we used the following terms: exp carcinoma, non-small cell lung/ AND real world.mp. AND (exp *Immunotherapy/or durvalumab.mp.). The EMBASE search used the following structured and free-text terms: 'non-small cell lung cancer' AND (immunotherapy OR durvalumab) AND 'real world'. The PubMed search used the terms (non-small cell lung cancer) AND ((immunotherapy) OR (durvalumab)) AND (real world).

Inclusion and exclusion criteria

After removing the duplicates, we included studies that used consolidation durvalumab after curative-intent CRT for

patients with unresectable stage III NSCLC, according to the American Joint Committee on Cancer eighth edition. English-language studies published in peer-reviewed journals were primarily considered. Conference abstracts of RWSs from major conference proceedings were also included based on careful review.[21] Retrieved results described as case reports, clinical trials, reviews, meta-analyses, and letters were excluded. Studies focused on advanced NSCLC or involving early-stage NSCLC were excluded. RWSs using other interventions, including surgery, palliative therapy, tyrosine kinase inhibitors, and other consolidation ICIs instead of durvalumab, were also excluded. Two investigators (Y.W. and T.Z.) independently searched the databases, screened titles and abstracts, and assessed full-text articles. Any discrepancies between the 2 researchers were resolved by consulting senior authors.

Data extraction

The following data were collected from eligible studies: basic information, including first author's name, year of publication or presentation, study region, number of involved centers, and study type; patient characteristics, including number of patients, median age, Eastern Cooperative Oncology Group (ECOG) PS score, PD-L1 status, and other driver gene mutation status; anticancer treatment information, including cCRT or sequential CRT (sCRT), dose and fraction of radiation therapy (RT), interval from CRT completion to durvalumab initiation, and durvalumab treatment duration; and real-world efficacy, including median OS (mOS), median PFS (mPFS), 12-month OS, and 12-month PFS rates. These data were reported in a standardized data extraction spreadsheet for subsequent analysis. We also collected and analyzed the real-world toxicity profile, including pneumonitis or radiation pneumonitis (RP) of any grade and grade ≥3 (G3) and other all-grade adverse events (AEs) or immune-related AEs (irAEs). All toxicity grading was based on the Common Terminology Criteria for Adverse Events version 5.0 scoring system.

Study quality assessment and statistical analysis

We used the Methodological Index for Non-randomized Studies (MINORS) to assess the quality of these non-randomized RWSs.[22] Some degree of heterogeneity was expected, and thus, we used the DerSimonian and Laird random-effect models to analyze RWD. Statistical heterogeneity was evaluated using I^2 statistics. The inverse variance method was used to calculate the pooled incidence and its 95% confidence interval (CI). Publication bias was assessed using Egger's linear regression test. A nonparametric "trim-and-fill" method was also applied to minimize the influence of publication bias on the results. Subgroup analyses were additionally performed to identify potentially influencing factors. All analyses were performed using R language (The R Project for Statistical Computing; www.r-project.org).

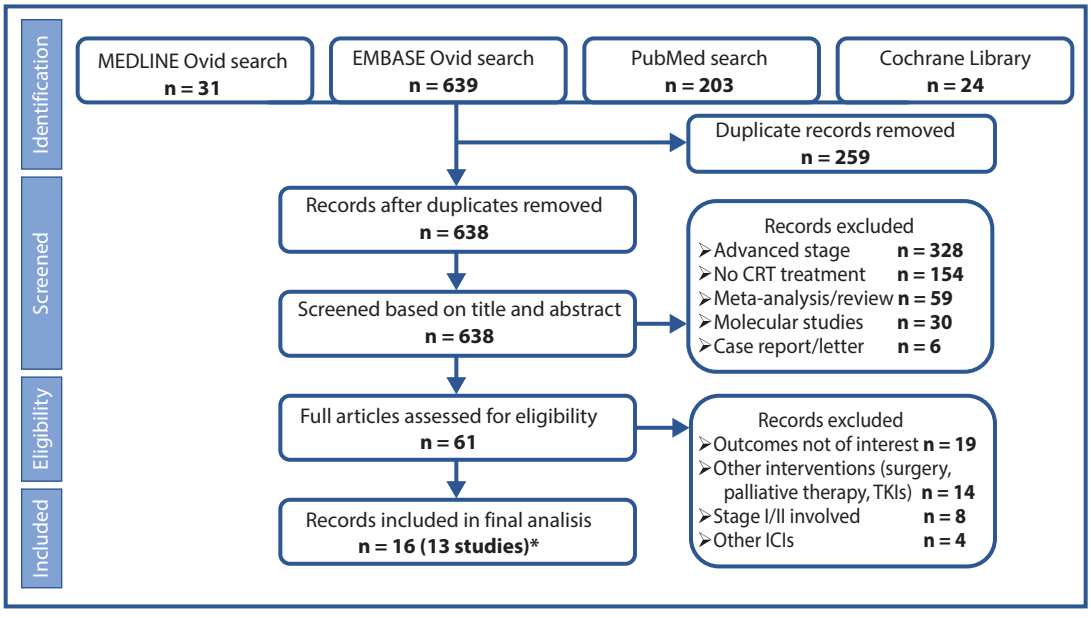

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 diagram. *Sixteen useful records were included in the final summarization and analysis, but 4 were from the same study (PACIFIC-R). *Abbreviations:* CRT = chemoradiation therapy; ICIs = immune checkpoint inhibitors; PACIFIC-R = First Real-World Data on Unresectable Stage III NSCLC Patients Treated With Durvalumab After Chemoradiotherapy; TKIs = tyrosine kinase inhibitors.

Table 1 Characteristics of included real-world studies

Author (year)	Study region	EAP or non-EAP	Center (n)	Study type	Patients (n)	Median age, y (range)	ECOG-PS score	cCRT or sCRT	Time from CRT to durvalumab, d (range)	RT	Durvalumab treatment duration (range)	PD-L1 status	Driver mt	Real-world efficacy
Miura et al[23] (2020)	Japan	Non-EAP	1	Retrospective	41	72 (51-80)	0: 58%; 1: 42%	cCRT	Median 11 (1-42) <14: 61%; 14-42: 39%	60 Gy/30 F: 98%; 54 Gy/25 F: 2%	Median 6.75 doses, 14.6% completed 1-y treatment	<1%: 29%; 1%-49%: 27%; ≥50%: 22%; unknown: 22%	EGFR mt: 12%	-
LeClair et al[24] (in press)	United States	Non-EAP	1	Retrospective	83	69.8	0: 28%; 1: 65%; 2: 7%	-	Median 57.3 (8-226)	Median 60 Gy <60 Gy: 4%; 60 Gy: 48%; >60 Gy: 16%	Median 13.9 doses (1-47)	<1%: 20%; 1%-49%: 18%; ≥50%: 29%; unknown: 33%	-	-
Tsukita et al[25] (2021)	Japan	Non-EAP	7	Retrospective	107	70 (43-86)	0: 66.4%; 1: 33.6%	cCRT	-	Median 6 0 Gy	Median 14 doses (1-26)	<1%: 20.6%; 1%-49%: 27.1%; ≥50%: 29%	EGFR mt: 10.3%; ALK fusion: 3.7%	12-mo PFS: 70.6%
Chu et al[29] (2020)	Taiwan	EAP	1	Retrospective cohort	31	64 (52-74)	0: 80.7%; 1: 16.1%; 2: 3.2%	cCRT	Median 84 (54-111)	66 Gy: 74.2%; >66 Gy: 25.8%	-	<1%: 19.3%; ≥1%: 45.2%	ALK fusion: 3.3%; EGFR mt: 12.9%	12-mo PFS: 56.4%
Desilets et al[30] (2021)	Canada and Japan	Non-EAP	8	Retrospective cohort	147	67	0: 36.1%; 1: 57.8%; 2: 4.1%	-	Median 33 <14: 15%; 14-42: 57.8%; >42: 27.2%	-	-	<1%: 21.8%; 1%-49%: 27.2%; ≥50%: 36.1%	-	12-mo OS: 92.5%
Faehling et al[31] (2020)	Germany	EAP	56	Retrospective	126	62.4 (34-82)	0: 48.7%; 1: 46%; 2: 5.3%	cCRT: 96.8%; sCRT: 3.2%	-	Median 65 Gy	Completed 1-y treatment: 42.9%	0: 28.8%; 1%-49%: 37.8%; ≥50%: 33.3%	-	12-mo PFS: 56%; 12-mo OS: 78.6%; mPFS: 20.1 mo
Jung et al[32] (2020)	Korea	Non-EAP	1	Retrospective cohort	21	65.9 (36-77)	0: 19%; 1: 81%	cCRT	-	-	-	<1%: 23.8%; 1%-9%: 23.8%; 10%-49%: 19%; ≥50%: 23.8%	EGFR mt: 9.5% -	-
Jain et al[35] (2020)	United Kingdom	EAP	Multi	Retrospective	28	66	-	cCRT: 96%; sCRT: 4%	Median 39 (28-77)	66 Gy/33 F: 60%	Median 6 cycles (1-26)	<1%/Unknown: 29%	-	mPFS: 13.8 wk
Jegannathen[36] (2020)	United Kingdom	Non-EAP	3	Retrospective	18	-	0: 72%; ≥1: 28%	cCRT: 61%; sCRT: 39%	-	66 Gy/32-33 F: 61%; 55 Gy/20 F: 39%	Median 10 infusions (2-33)	<1%: 27.8%; >1%: 72.2%	-	12-mo OS: 94%
Shaverdian et al[40] (2020)	United States	Non-EAP	1	Retrospective cohort	62	66 (49-86)	0: 53%; 1: 47%	cCRT	Median 45	54-66 Gy/27-33 F Median 60 Gy	-	≥1%: 53%; ≥50%: 29%; unknown: 17%	-	-
Taugner et al[37] (2021)	Germany	Non-EAP	1	Prospective	26	67.6	-	cCRT: 96%; sCRT: 4%	Median 25 (13-103)	60 Gy/30 F: 92%	Median 14 cycles (2-24)	≥50%: 46%	-	12-mo PFS: 62%; 12-mo OS: 100%
Offin et al[39] (2020)	United States	Non-EAP	1	Retrospective	62	66 (49-86)	0: 53%; 1: 47%	cCRT	Median 45 (9-231)	54-66 Gy/27-33 F	Median 18 doses (4-24)	<1%: 34%; 1%-49%: 30%; ≥50%: 36%	EGFR mt: 2%	12-mo PFS: 65%; 12-mo OS: 85%
Girard et al[34,38,52,53] (2021, 2020, 2021, 2019, respectively)	*	EAP	Multi	Retrospective	1155	-	-	cCRT: 77.3%; sCRT: 14.1%	Median 52 (39-89)	Median 65 Gy	Median 22 infusions	<1%: 11.9%; ≥1%: 49.7%	-	mPFS: 22.5 mo

Abbreviations: ALK = anaplastic lymphoma kinase; cCRT = concurrent chemoradiation therapy; EAP = expanded access program; ECOG-PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; F = fraction; mPFS = median progression-free survival; mt = mutation; OS = overall survival; PD-L1 = programmed death-ligand 1; RT = radiation therapy; sCRT = sequential CRT.

* United Kingdom, France, Italy, Germany, Norway, Israel, Netherlands, Belgium, Australia, and United States.

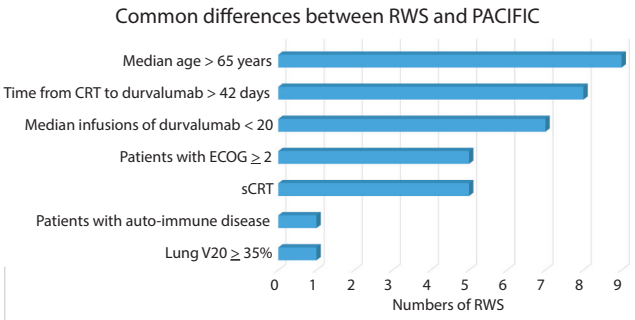

Fig. 2. Common differences in demographic and therapeutic characteristics between real-world studies and the PACIFIC trial. *Abbreviations:* CRT = chemoradiation therapy; ECOG = Eastern Cooperative Oncology Group; PACIFIC = Intensified Chemo-immuno-radiotherapy With Durvalumab for Stage III Non-Small Cell Lung Cancers; RWS = real-world study; sCRT = sequential CRT; V20 = volume at least received 20 Gy.

Results

Characteristics of eligible studies

The original database search yielded 897 records. After removal of 259 duplicates, 638 titles and abstracts were screened. After the selection process (Fig. 1), a total of 61 records underwent full-text assessment, and 16 were eligible. However, 4 of them were actually from the same study—PACIFIC-R. Therefore, 13 studies involving 1885 patients from 14 countries were finally included in the meta-analysis. The baseline characteristics of all included studies are summarized in Table 1. Nine (69%) studies were mainly conducted in Western countries, and 4 (31%) were conducted in Asia. Six (46%) of them were multicenter studies, and 7 (54%) were based on a single research center. Four (31%) studies were EAP initiated, whereas the other 9 (69%) studies were non-EAP related. More detailed information on each eligible study is presented in Table E1.

Common differences in demographic and therapeutic characteristics between RWSs and the PACIFIC trial were identified and summarized in Figure 2. Among them, 9 (69%) studies indicated that the most common difference was more elderly patients in the real world (median age >65 years). The second obvious difference was the prolonged interval from the end of CRT to initiation of durvalumab (median time >42 days) in 8 (62%) studies. The third-most frequent difference was median infusions of durvalumab of fewer than 20 cycles, observed in 7 (54%) studies. Other common differences included more patients with ECOG ≥2 (38%) and the use of sCRT instead of cCRT (38%) in the real world.

Short-term efficacy of the PACIFIC regimen in RWSs

Meta-analyses of short-term efficacy, including 12-month OS and 12-month PFS rates, were performed based on RWD. The pooled 12-month OS and 12-month PFS rates were 90% (95% CI, 83%-98%) and 62% (95% CI, 56%-68%), respectively (Fig. 3A and 3B). Egger's test indicated that there was no significant publication bias in the 12-month OS and 12-month PFS analyses (P = .481 and P = .835, respectively). Further subgroup analysis that compared the delayed initiation of durvalumab >42 days with ≤42 days determined that a prolonged interval from completion of CRT to initiation of durvalumab (median time >42 days) did not have a significant effect on 12-month OS (85%; 95% CI, 77%-94% vs. 96%; 95% CI, 89%-100%; P = .068) or on 12-month PFS (62%; 95% CI, 43%-80% vs. 62%; 95% CI, 52%-72%; P = .989) (Fig. 3C and 3D).

Pooled analysis of pneumonitis

The pooled incidence of all-grade pneumonitis from eligible RWSs was 35% (95% CI, 22%-48%) (Fig. 4A). No significant publication bias was observed using Egger's test (P = .194). The pooled rate of ≥G3 pneumonitis was 6% (95% CI, 3%-8%), without significant publication bias found using Egger's test (P = .702) (Fig. 4B).

Subgroup analysis of all-grade pneumonitis

The rate of all-grade pneumonitis from Western RWSs was significantly lower than that from Asian studies (22%; 95% CI, 17%-26% vs. 62%; 95% CI, 29%-94%; P = .017) (Fig. 5A). The comparative analysis of all-grade pneumonitis rates from multicenter RWSs versus single-center RWSs showed no significant difference (32%; 95% CI, 10%-54% vs. 37%; 95% CI, 21%-53%; P = .699) (Fig. 5B). Studies from EAP reported a significantly lower rate of all-grade pneumonitis than non-EAP studies (18%; 95% CI, 16%-20% vs. 42%; 95% CI, 21%-62%; P = .024) (Fig. 5C). Furthermore, studies with older patients (median age >65 years) reported significantly higher all-grade pneumonitis rates than those with a median age ≤65 years (44%; 95% CI, 24%-64% vs. 15%; 95% CI, 10%-21%; P = .008) (Fig. 5D).

Incidence of other all-grade AEs

The real-world incidences of other all-grade AEs of interest were additionally analyzed (Fig. E1). The pooled rates of all-grade endocrinal, cutaneous, musculoskeletal, and gastrointestinal toxicity in RWSs after consolidation durvalumab were 11% (95% CI, 6%-15%), 7% (95% CI, 3%-11%), 5% (95% CI, 2%-7%), and 3% (95% CI, 1%-5%), respectively.

Discussion

Our study summarizes and outlines the existing RWE with respect to consolidation durvalumab after definitive CRT in stage III NSCLC. To the best of our knowledge, this is the

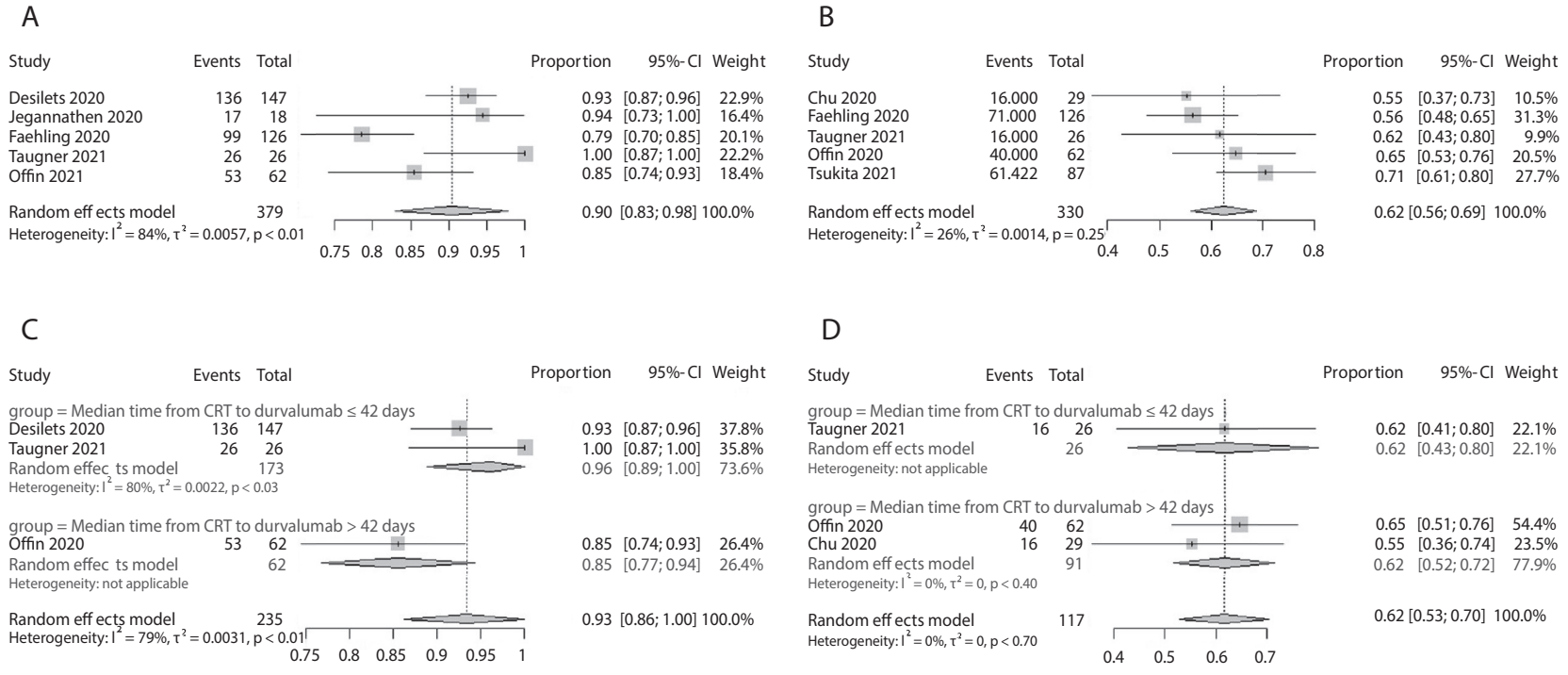

Fig. 3. Pooled analysis of short-term efficacy in the real world and subgroup analysis. (A) Pooled 12-month overall survival (OS) rate. (B) Pooled 12-month progression-free survival (PFS) rate. (C) OS rate of the median time from chemoradiation therapy (CRT) durvalumab ≤42 days versus >42 days. (D) PFS rate of the median time from CRT durvalumab ≤42 days versus >42 days. *Abbreviation:* CI = confidence interval.

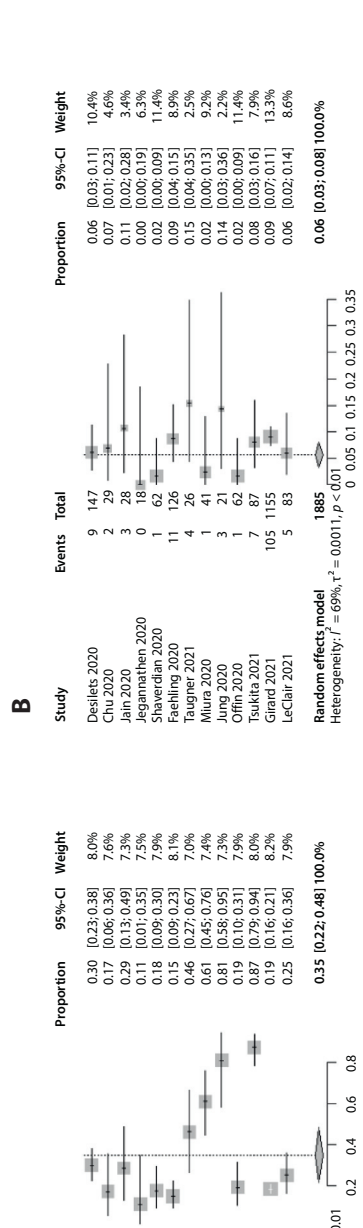

Fig. 4. Pooled analysis of pneumonitis in the real world. (A) Pooled rate of pneumonitis of any grade. (B) Pooled rate of ≥grade 3 pneumonitis.

first quantitative meta-analysis of RWD to characterize the toxicity profile and efficacy of the PACIFIC regimen in the real world. We found manageable safety and similar short-term efficacy in the real-life use of consolidation durvalumab, albeit with obvious differences between the real world and RCTs.

There are great disparities in patient characteristics and treatment strategies between RWSs and the PACIFIC trial. First, the median age of patients in the real-world setting was greater than that of patients in clinical trials, which indicated that there were more elderly patients using consolidation durvalumab than we expected. Our findings showed that the median ages from RWSs, such as those by Miura et al,[23], LeClair et al,[24] and Tsukita et al,[25] were 72, 69.8, and 70 years, respectively—older than those of patients in RCTs, including 64 in the PACIFIC trial,[8] 62 in CheckMate 017,[26] and 61 years in CheckMate 057.[27] The median age of lung cancer patients at diagnosis is 70 years,[28] yet elderly patients are underrepresented in most RCTs, which might lead to uncertainty about directly applying the results of clinical trials to medical practice. Second, patients with ECOG ≥2 were also using consolidation durvalumab after CRT in the real world,[29-32] whereas most pivotal trials of ICIs in NSCLC, such as the PACIFIC trial, limited eligibility criteria to PS 0 to 1.[33] Because many drug management organizations, including the European Medicines Agency and the Food and Drug Administration, have approved available ICIs, regardless of the PS and ECOG of cancer patients, we should pay more attention to the tolerability and safety of ECOG ≥2 patients using ICIs. Moreover, sCRT is still widely accepted and used in special populations with stage III NSCLC, such as elderly individuals or those with larger tumor volumes,[34-38] whereas the protocol of the PACIFIC trial only allowed cCRT.[8] Finally, we found the median time from CRT completion to durvalumab in RWSs often exceeded 42 days,[24,29,34,39,40] which apparently differed from the PACIFIC study design (<42 days).[8] Also, the median number of durvalumab infusions was often less than 20 cycles,[23-25,35-37,39] whereas the median number of infusions received was 20 in the PACIFIC trial.[9]

Despite such obvious differences between RWSs and the PACIFIC trial, our results suggested manageable safety and similar short-term efficacy in the real-life use of consolidation durvalumab. We found that the pooled 12-month OS (90%) and 12-month PFS (62%) in the real world were slightly higher than those reported in the PACIFIC trial (83.1% and 55.9%, respectively).[8,9] One possible explanation might be publication bias in real-world retrospective studies. To avoid this much-discussed bias (ie, an inclination to handle the reporting of positive results), more objective and unbiased analyses with respect to RWSs should be promoted, and negative findings should also be valued. Another possible reason is that Response Evaluation Criteria in Solid Tumours for tumor assessments is used heterogeneously across countries, leading to potentially overestimated efficacy. Furthermore, assessments for progression in the real world may not occur as frequently or consistently in clinical

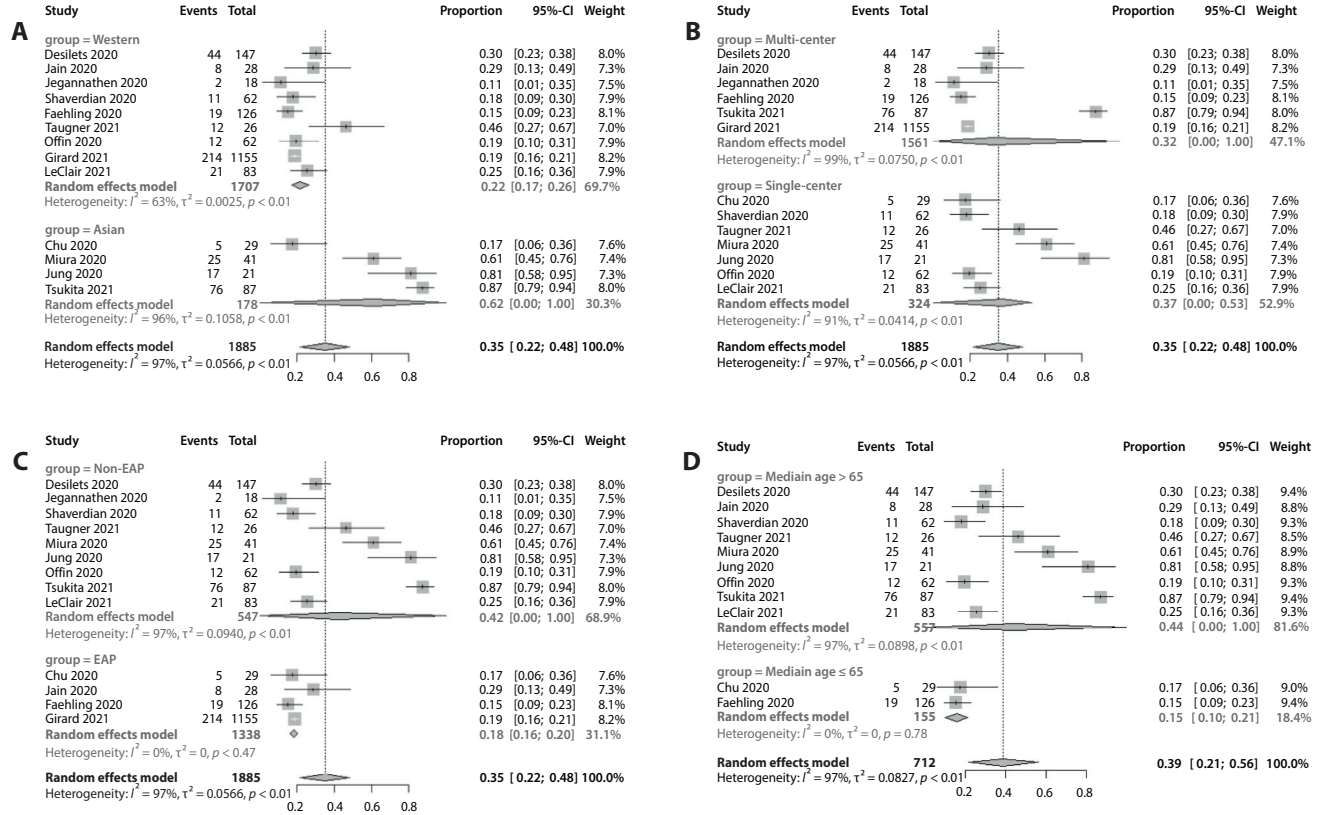

Fig. 5. Subgroup comparative analysis of all-grade pneumonitis. (A) Studies from Western countries versus Asian regions. (B) Multicenter studies versus studies from a single center. (C) Nonexpanded access program (non-EAP) versus EAP-related studies. (D) Studies with the median age of all patients >65 versus ≤65 years.

trials, especially when the ongoing COVID-19 pandemic could result in fewer hospital visits; thus, the real-world PFS may be higher than expected.

Further analyses determined that the delayed initiation of durvalumab did not significantly affect the 12-month OS or PFS of RWD, although diminished survival benefits of an interval >14 days were reported by the PACIFIC trial.[9] Of note, selection bias in the PACIFIC trial should be taken into account. If patients after cCRT were in good condition without immediate severe AEs, they could start consolidation durvalumab earlier, probably within 14 days. However, if researchers initiated durvalumab later, they could have a better chance to screen out patients who are predisposed to progression. Either possibility could have resulted in biases, to some extent, when researchers attempted to analyze whether the time interval between CRT and durvalumab caused different outcomes in the PACIFIC trial. More importantly, from our results, whether the interval between CRT and durvalumab should be limited to less than 42 days warrants further investigation, because more elderly and frail patients probably require a longer time to recover from AEs after CRT.

The pooled incidence of all-grade pneumonitis or RP from RWSs was 35%, and ≥G3 pneumonitis was 6%, which was slightly higher than the results of the PACIFIC trial (pneumonitis of any grade occurred in 33.9%, and ≥G3 pneumonitis occurred in 4.2%).[8] The rates of other real-world toxicity, such as endocrinal, cutaneous, and musculoskeletal AEs (11%, 7%, and 5%, respectively), were close to those reported in the PACIFIC trial (11.6%, 12.2%, and 8.2%, respectively).[8] The subgroup analyses further suggested that different real-world settings could have considerable effects on the results of RWSs. A significantly higher rate of all-grade pneumonitis was observed in Asian RWSs than in Western countries, which might be explained by population differences in tolerance of toxicities, as well as in the sensitivity to consolidation ICIs. Genetic disparities could result in different individual susceptibility. For example, more common epidermal growth factor receptor−sensitizing mutations in Asian patients (~40%-50%) with NSCLC than in non-Asian patients (~10%-15%) lead to a more potent response to tyrosine kinase inhibitors.[41] In addition, single nucleotide polymorphism at rs1982073: T869C of the TGFβ1 gene was demonstrated to be associated with a significantly lower risk of RP in the United States,[42] whereas this polymorphism was not detected in Asian patients.[43] Currently, many RCTs open Asian-subset studies to investigate effectiveness and safety in relation to ethnic disparities,[44,45] including an ongoing multicenter phase 3 RCT PACIFIC-5 (ClinicalTrials.gov:

NCT03706690), evaluating the efficacy and toxicity of consolidation durvalumab after cCRT or sCRT.[46] In addition, we found that elderly patients older than aged 65 had a higher risk of pneumonitis after the PACIFIC regimen in RWSs. Older and frail patients, who represent the majority of NSCLC cases worldwide, were often excluded from registration studies. It has been reported that the median age of patients enrolled in clinical trials is 10 years younger than what is seen in the clinic.[47] Therefore, the suggestion of increased pneumonitis in elderly patients and those in Asian regions warrants further investigation. On the contrary, studies supported by EAP were found to have reported significantly lower rates of all-grade pneumonitis compared with non-EAP-related studies, which was lower than the pooled rate from all included studies. This observation probably implies that EAP could have an influence on the results of RWSs. Therefore, we recommend drawing a clear distinction between EAP-related and investigator-initiated studies in future real-world evaluations.

RWE of newly approved drugs and therapies is being increasingly requested by funding bodies in countries with publicly funded health care systems, especially when a large number of patients with poorer PS, older age, or other comorbidities are excluded by clinical trials but are treated in daily practice. Herein lies the discrepancy and uncertainty between the real-world setting and highly controlled RCTs. It is clear that data obtained from health records, cancer registries, and other RWE sources can produce valuable insights into new treatments and their true efficacy, as well as toxicity, in real-world oncology practice.[18]

The advent of immunotherapy has led to a paradigm shift in the treatment of lung cancer. Notably, the impressive results from the PACIFIC trial have demonstrated for the first time that ICI benefit is not limited to advanced disease and that they are the first practice-changing results in stage III LA-NSCLC in recent decades.[48] Based on recently updated analyses, an estimated 42.9% of patients randomized to durvalumab remain alive after 5 years, and approximately one-third remain both alive and free of disease progression.[10] In terms of side effects, the PACIFIC regimen was associated with a manageable safety profile and did not detrimentally affect patient-reported outcomes compared with placebo.[33] However, only 2% of adult patients with cancer actually participate in clinical trials,[49] representing a population that is motivated, has access to clinical trials, and manages to meet increasingly numerous and restrictive eligibility criteria.[50] These individuals are often younger and healthier than the broader oncology patient population and are therefore more likely to tolerate treatment toxicity and derive clinical benefits. Broader and more inclusive eligibility criteria in clinical trials might be a possible effective solution.[51] From our perspective, the cooperation of formidable expertise from clinical practitioner groups (eg, the Medical Oncology Group of Australia) and clinical research groups (eg, the Australasian Lung Cancer Trials Group), along with optimized real-world research design and setting, such as appropriate subsets of patients and investigator-initiated and larger population-based studies, is likely to better fill the gap between oncology practice and clinical trials.

Our study has several limitations. First, this is a systemic review and meta-analysis based on observational RWSs, most of which have retrospective designs. Therefore, selection bias could not be excluded owing to its retrospective design. Second, several analyses are based on studies with high heterogeneity, as evidenced by the large I^2 values, probably because of inherent flaws in RWSs. Another limitation is that most of the included RWSs were small-to-moderate case series with relatively short follow-up. Additionally, the reduced number of studies used in some AE incidence analyses, due to the lack of data from original literature, has to be taken into consideration when interpreting the overall results. However, while we were preparing this article, the interim analysis results (51.8% of events) of PACIFIC-R (NCT03798535), a large international observational study (N = 1155), were recently reported at the 2021 European Society for Medical Oncology meeting.[52] An mPFS of 22.5 months (95% CI, 19.7-25.5) and a rate of any-grade pneumonitis of 18.5% were reported, which were similar to our pooled results. The magnitudes of survival benefits observed in the PACIFIC trial, individual RWS, and the current pooled data from RWSs are large enough to allow us to comfortably conclude that these benefits should be robust.

Conclusions

Our study demonstrated that the manageable toxicity and potentially favorable efficacy of consolidation durvalumab in real-life use align with the results of the PACIFIC trial, albeit with obvious differences between RWSs and RCTs. RWSs can be helpful in understanding the true efficacy and toxicity given the less-restrictive eligibility criteria.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin* 2021;71:7–33.
2. Govindan R, Bogart J, Vokes EE. Locally advanced non-small cell lung cancer: The past, present, and future. *J Thorac Oncol* 2008;3:917–928.
3. Gridelli C, Rossi A, Carbone DP, et al. Non-small-cell lung cancer. *Nat Rev Dis Primers* 2015;1:15009.
4. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:2181–2190.
5. Yamamoto N, Nakagawa K, Nishimura Y, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. *J Clin Oncol* 2010;28:3739–3745.
6. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–2699.

7. Bradley JD, Hu C, Komaki RR, et al. Long-term results of NRG Oncology RTOG 0617: Standard- versus high-dose chemoradiotherapy with or without cetuximab for unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 2020;38:706–714.
8. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017;377:1919–1929.
9. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med* 2018;379:2342–2350.
10. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes with durvalumab after chemoradiotherapy in unresectable stage III NSCLC: An update from the PACIFIC trial. *J Clin Oncol* 2021;39 (15):8511. suppl.
11. Ettinger DS, Wood DE, Aggarwal C, et al. NCCN guidelines insights: Non-small cell lung cancer, version 1.2020. *J Natl Compr Canc Netw* 2019;17:1464–1472.
12. Faivre-Finn C, Vicente D, Kurata T, et al. Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC—an update from the PACIFIC trial. *J Thorac Oncol* 2021;16:860–867.
13. Gray JE, Villegas A, Daniel D, et al. Three-year overall survival with durvalumab after chemoradiotherapy in stage III NSCLC—update from PACIFIC. *J Thorac Oncol* 2020;15:288–293.
14. Ettinger DS, Wood DE, Aisner DL, et al. NCCN guidelines insights: Non-small cell lung cancer, version 2.2021. *J Natl Compr Canc Netw* 2021;19:254–266.
15. Käsmann L, Eze C, Taugner J, et al. Chemoradioimmunotherapy of inoperable stage III non-small cell lung cancer: Immunological rationale and current clinical trials establishing a novel multimodal strategy. *Radiat Oncol* 2020;15:167.
16. Pasello G, Pavan A, Attili I, et al. Real world data in the era of immune checkpoint inhibitors (ICIs): Increasing evidence and future applications in lung cancer. *Cancer Treat Rev* 2020;87 102031.
17. Food and Drug Administration; HHS. Expanded access to investigational drugs for treatment use. Final rule. *Fed Regist* 2009;74:40900–40945.
18. Di Maio M, Perrone F, Conte P. Real-world evidence in oncology: Opportunities and limitations. *Oncologist* 2020;25:e746–e752.
19. Hall PS. Real-world data for efficient health technology assessment. *Eur J Cancer* 2017;79:235–237.
20. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
21. Scherer RW, Saldanha IJ. How should systematic reviewers handle conference abstracts? A view from the trenches. *Syst Rev* 2019;8:264.
22. Wells G, Shea B, O'Connell J, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital Research Institute. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed July 2, 2021.
23. Miura Y, Mouri A, Kaira K, et al. Chemoradiotherapy followed by durvalumab in patients with unresectable advanced non-small cell lung cancer: Management of adverse events. *Thorac Cancer* 2020;11:1280–1287.
24. LeClair JN, Merl MY, Cohenuram M, Luon D. Real-world incidence of pneumonitis in patients receiving durvalumab. [e-pub ahead of print] *Clin Lung Cancer* 2020. https://doi.org/10.1016/j.cllc.2021.08.006. Accessed October 4, 2021.
25. Tsukita Y, Yamamoto T, Mayahara H, et al. Intensity-modulated radiation therapy with concurrent chemotherapy followed by durvalumab for stage III non-small cell lung cancer: A multi-center retrospective study. *Radiother Oncol* 2021;160:266–272.
26. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373:1627–1639.
27. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015;373:123–135.
28. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
29. Chu CH, Chiu TH, Wang CC, et al. Consolidation treatment of durvalumab after chemoradiation in real-world patients with stage III unresectable non-small cell lung cancer. *Thorac Cancer* 2020;11:1541–1549.
30. Desilets A, Blanc-Durand F, Lau S, et al. Durvalumab therapy following chemoradiation compared with a historical cohort treated with chemoradiation alone in patients with stage III non-small cell lung cancer: A real-world multicentre study. *Eur J Cancer* 2021;142:83–91.
31. Faehling M, Schumann C, Christopoulos P, et al. Durvalumab after definitive chemoradiotherapy in locally advanced unresectable non-small cell lung cancer (NSCLC): Real-world data on survival and safety from the German expanded-access program (EAP). *Lung Cancer* 2020;150:114–122.
32. Jung HA, Noh JM, Sun JM, et al. Real world data of durvalumab consolidation after chemoradiotherapy in stage III non-small-cell lung cancer. *Lung Cancer* 2020;146:23–29.
33. Hui R, Ozguroglu M, Villegas A, et al. Patient-Reported Outcomes with Durvalumab After Chemoradiotherapy in Stage III, Unresectable Non-small Cell Lung Cancer (PACIFIC): A randomised, controlled, phase 3 study. *Lancet Oncol* 2019;20:1670–1680.
34. McDonald F, Mornex F, Garassino MC, et al. 79mo PACIFIC-R: Real-world characteristics of unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy. *J Thorac Oncol* 2021;16: S738–S739.
35. Jain P, Murray P, Clarke K, et al. Early experience of maintenance durvalumab post chemoradiation (CRT) in stage III non-small cell lung cancer (NSCLC) across West Yorkshire network: From expanded access programme (EAP) to routine clinical use. *Lung Cancer* 2020;139:S46.
36. Jegannathen A. Real-world data of using durvalumab in stage III non-small cell lung cancer (NSCLC): West Midlands experience. *Lung Cancer (Amerstam, Netherlands)*. 2020;139:S51.
37. Taugner J, Käsmann L, Eze C, et al. Real-world prospective analysis of treatment patterns in durvalumab maintenance after chemoradiotherapy in unresectable, locally advanced NSCLC patients. *Invest New Drugs* 2021;39:1189–1196.
38. Girard N, Fietkau R, Garassino M, et al. 1242P Characteristics of the first 615 patients enrolled in PACIFIC R: A study of the first real-world data on unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy. *Ann Oncol* 2020;31:S805–S806.
39. Offin M, Shaverdian N, Rimner A, et al. Clinical outcomes, local-regional control and the role for metastasis-directed therapies in stage III non-small cell lung cancers treated with chemoradiation and durvalumab. *Radiother Oncol* 2020;149:205–211.
40. Shaverdian N, Thor M, Shepherd AF, et al. Radiation pneumonitis in lung cancer patients treated with chemoradiation plus durvalumab. *Cancer Med* 2020;9:4622–4631.
41. Zhang YL, Yuan JQ, Wang KF, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: A systematic review and meta-analysis. *Oncotarget* 2016;7:78985–78993.
42. Yuan X, Liao Z, Liu Z, et al. Single nucleotide polymorphism at rs1982073:T869c of the TGFβ1 gene is associated with the risk of radiation pneumonitis in patients with non−small-cell lung cancer treated with definitive radiotherapy. *J Clin Oncol* 2015;27:3370–3378.
43. Wang L, Bi N. TGF-beta1 gene polymorphisms for anticipating radiation-induced pneumonitis in non-small-cell lung cancer: Different ethnic association. *J Clin Oncol* 2010;28:e621.
44. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): An open-label. randomised phase 3 trial. *Lancet Oncol* 2014;15:213–222.
45. Cho BC, Chewaskulyong B, Lee KH, et al. Osimertinib versus standard of care EGFR TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA Asian subset. *J Thorac Oncol* 2019;14:99–106.

46. A study of durvalumab as consolidation therapy in non-small cell lung cancer patients (PACIFIC-5). Available at: https://clinicaltrials.gov/ct2/show/NCT03706690?term=pacific-5&draw=2&rank=1. Accessed July 17, 2021.
47. Califano R, Gomes F, Ackermann CJ, Rafee S, Tsakonas G, Ekman S. Immune checkpoint blockade for non−small cell lung cancer: What is the role in the special populations? *Eur J Cancer* 2020;125:1–11.
48. Botticella A, Mezquita L, Le Pechoux C, et al. Durvalumab for stage III non-small-cell lung cancer patients: Clinical evidence and real-world experience. *Ther Adv Respir Dis* 2019;13 1753466619885530.
49. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: Race-, sex-, and age-based disparities. *JAMA* 2004;291:2720–2726.
50. Rashdan S, Gerber DE. Immunotherapy for non-small cell lung cancer: From clinical trials to real-world practice. *Transl Lung Cancer Res* 2019;8:202–207.
51. Unger JM, Barlow WE, Martin DP, et al. Comparison of survival outcomes among cancer patients treated in and out of clinical trials. *J Natl Cancer Inst* 2014;106:dju002.
52. Girard N, Smit HJM, Sibille A, et al. 1171MO − PACIFIC-R real-world study: Treatment duration and interim analysis of progression-free survival in unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy. *Ann Oncol* 2021;32:S939–S940.
53. Girard N, Mornex F, Christoph DC, et al. PACIFIC-R: First real-world study of patients with unresectable, stage III NSCLC treated with durvalumab after chemoradiotherapy. *Ann Oncol* 2019;30:ii37.