Lung Cancer 134 (2019) 259–267

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Immune checkpoint-inhibitors and chemoradiation in stage III unresectable non-small cell lung cancer

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ARTICLE INFO

Keywords:
Non-small cell lung cancer
Stage III
Checkpoint-inhibitors
Radiochemotherapy
Immunotherapy
Durvalumab

ABSTRACT

Lung cancer resulted in an estimated 1.8 million deaths worldwide in 2018 and approximately 20% of patients with non-small cell lung cancer (NSCLC) are diagnosed with stage III unresectable disease. Phase III data from the PACIFIC trial show significantly improved progression-free survival for the checkpoint-inhibitor durvalumab given as consolidation following definitive chemoradiotherapy (cCRT). Overall survival results from this study have now been reported, along with outcomes from other phase II trials. A thorough review of the efficacy and safety of checkpoint-inhibitors used in conjunction with cCRT for stage III unresectable NSCLC is needed.

Published and presented literature on phase II and III data was identified using the key search terms "non-small cell lung cancer" AND "checkpoint-inhibitors" (OR respective aliases).

One randomized phase III clinical trial and three phase II trials reporting outcomes of checkpoint-inhibitors in conjunction with cCRT for stage III unresectable NSCLC were identified. PACIFIC reported significantly improved overall survival for consolidation durvalumab following cCRT compared with placebo. Although discontinuation due to adverse events (AEs) was higher with durvalumab, rates of grade 3/4 pneumonitis or radiation pneumonitis were low and comparable between arms. Results from phase II trials also show promising activity for other checkpoint-inhibitors and alternative sequencing strategies, although these need to be confirmed in a randomized context. Preliminary data suggest differences in the safety profiles between PD-1 and PD-L1 inhibitors. Currently, the role of PD-L1 expression levels for patient selection in this setting remains unclear, and durvalumab should be administered on an individual basis in patients with known driver mutations.

Consolidation durvalumab following cCRT significantly improves overall survival with an acceptable safety profile in patients with stage III unresectable NSCLC, now representing a new standard of care.

1. Introduction

Lung cancer is one of the most common types of cancer, with an estimated 2.1 million new cases diagnosed resulting in an estimated 1.8 million deaths worldwide in 2018 [1]. Non-small cell cancer (NSCLC) accounts for approximately 85% of lung malignancies [2] and about 70% are diagnosed with a non-squamous histology such as adenocarcinoma or large cell carcinoma [3]. Approximately one quarter of

Abbreviations: AACR, American Association for Cancer Research; AEs, adverse events; ALK, anaplastic lymphoma kinase; ASCO, American Society of Clinical Oncology; Atez, atezolizumab; Carbo, carboplatin; cCRT, concurrent chemoradiation therapy; CD8 T-cells, cytotoxic T-lymphocytes; CI, confidence interval; CT, chemotherapy; Durv, durvalumab; ECOG, eastern cooperative oncology group; EGFR, epidermal growth factor receptor; ESMO (IO), European Society for Medical Oncology (Immuno-Oncology); FDA, United States Food and Drug Administration; Gr, grade; HR, hazard ratio; n, number of patients; n/a, not applicable; Niv, nivolumab; NR, not reported; NSCLC, non-small cell lung cancer; NYR, not yet reached; OS, overall survival; Pac, paclitaxel; Pembro, pembrolizumab; PFS, progression-free survival; PD-1, programmed cell death protein 1; PD-L1(2), programmed cell death ligand 1(2); PS, performance status; Pt, platinum chemotherapy, qXw, every X weeks; TKIs, targeted tyrosine kinase inhibitors; TMDD, time to metastatic disease or death; v, versus; WCLC, World Conference on Lung Cancer

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https://doi.org/10.1016/j.lungcan.2019.05.027
Received 15 April 2019; Received in revised form 17 May 2019; Accepted 26 May 2019

NSCLC patients are diagnosed as locally advanced, typically defined as disease involving regional lymph nodes, and the majority of these (20%) are stage III [4,5]. The expected 5-year survival is from 13% to 36% in patients with stage III unresectable NSCLC [6].

Radiotherapy is a mainstay of treatment for early stage unresectable NSCLC and hyperfractionated or accelerated radiotherapy delivered over a shorter time period improved 5-year overall survival (OS) by 2.5% compared with conventional radiotherapy alone [7]. A meta-analysis involving 1764 good performance patients with stage III unresectable NSCLC from nine clinical trials with accrual completion prior to 2000 showed that the addition of platinum-based chemotherapy given either sequentially or concurrently to radiotherapy (CRT) resulted in an absolute OS benefit of 4% at 2 years compared with radiotherapy alone (hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.81 to 0.98, p = 0.02) [8]. A subsequent meta-analysis of 1205 patients with locally advanced NSCLC from 6 trials further showed a significant 4.5% OS benefit at 5 years for concurrent compared with sequential CRT (HR 0.84, 95% CI 0.74 to 0.95, p = 0.004), and although concurrent CRT (cCRT) was associated with a significantly increased risk of grade 3/4 acute esophageal toxicity (18% vs. 4%, p < 0.001), acute pulmonary toxicities were not significantly different [9]. Guidelines recommend 60 Gy of thoracic radiation concurrently with chemotherapy as standard of care in patients with stage III unresectable NSCLC [10–13].

The majority of recurrences in Stage III NSCLC following cCRT occur at distant sites, likely due to the higher incidence of initial micrometatstases [14–16]. The addition of chemotherapy to cCRT is designed to improve overall systemic control with potential curative intent. The addition of induction chemotherapy preceding cCRT has become common practice in some jurisdictions, mainly due to logistical reasons [17], while strategies using consolidation chemotherapy alone have failed to show improved tumor control or survival benefit beyond standard of care cCRT in patients with stage III unresectable NSCLC [18,19]. New therapeutic advances are therefore needed to improve survival for these patients.

Checkpoint-inhibitors regulate T-cell activation to prevent immune-mediated damage to healthy tissues, and the activation of inhibitory checkpoints may enable tumors to evade the immune response [20]. Expression of checkpoint regulator molecules such as programmed cell death ligand 1 (PD-L1) can down-regulate cytotoxic T-lymphocytes (CD8 T-cells) in the tumor microenvironment through interactions between PD-L1 and the programmed cell death protein 1 (PD-1) [21,22]. The upregulation of PD-L1 can therefore help tumors evade the immune response, and data indicate that approximately 23% of advanced NSCLCs have a PD-L1 tumor proportional score ≥50% [23]. Monoclonal antibody checkpoint-inhibitors have been developed, however, that disrupt the PD-1 axis, re-engaging the effector and activation phases of T-cell activity and enhancing immune-mediated cytotoxic antitumor responses [22,24]. These agents evaluated for advanced NSCLC include the PD-1 inhibitors pembrolizumab and nivolumab and the PD-L1 inhibitors atezolizumab and durvalumab, which have been approved in various lines of therapy [25–29] showing favorable safety profiles compared with chemotherapy, often with durable responses [17,30–33]. Given the success of checkpoint-inhibitors in advanced NSCLC, there is great interest in their use in earlier stage disease.

The rationale for combining PD-1/L1 checkpoint inhibition with cCRT is the potential additive and possibly synergistic interaction of the combination, leading to improved outcomes by overcoming resistance to radiotherapy and more effective treatment for micrometastatic disease [34]. Substantial preclinical evidence showed that radiotherapy provoked DNA damage and cell death in tumor cells, in addition to increasing the production of tumor-associated neoantigens and other molecular signals of cellular damage [35]. This can promote the activation of cytotoxic T-cells and subsequent immune responses against untreated distant tumors through the abscopal effect [34,36], which could be potentiated through combination with PD-1/PD-L1 inhibitors [37]. Furthermore, radiotherapy has been shown to induce tumor PD-L1 levels in preclinical studies [38–41]. Radiation-induced upregulation of PD-L1 on tumor cells may therefore re-engage immune-mediated tumor cell death [42,43], potentially increasing the benefit of adding PD-1/PD-L1 inhibitors and overcoming resistance to immune checkpoint blockade in this setting [44,45]. The benefits of this approach were seen in the phase I KEYNOTE-001 clinical trial which showed that single agent pembrolizumab improved progression-free survival (PFS, 4.4 vs. 2.1 months) and OS (10.7 vs. 5.3 months) in NSCLC patients who received prior radiotherapy compared with those who did not [46]. Moreover, the first interim analysis of the phase III PACIFIC trial comparing consolidation durvalumab to placebo in patients with stage III NSCLC following cCRT showed statistically significant PFS benefits for durvalumab compared to placebo [17], leading to the approval of durvalumab as consolidation therapy in a number of jurisdictions [29,47,48]. Recently, OS data from PACIFIC have become available, along with preliminary results from phase II studies evaluating other checkpoint-inhibitors and treatment strategies including concurrent administration with cCRT [49–51]. A thorough analysis of this new data is therefore warranted to confirm the role of checkpoint-inhibitors used in conjunction with cCRT for stage III unresectable NSCLC and to consider the clinical implications.

2. Methods

PubMed (to January 28, 2019), the American Association for Cancer Research (AACR; 2016–2018), the proceedings of the American Society of Clinical Oncology (ASCO; 2016–2018), the Annual Congress of the European Society for Medical Oncology (ESMO; 2016–2018), ESMO Immuno-Oncology Congress (ESMO IO; 2016–2018), and the World Conference on Lung Cancer of the International Association for the Study of Lung Cancer (WCLC; 2016–2018) meetings were searched using the key search terms “non-small cell lung cancer” AND “checkpoint-inhibitors” (OR respective aliases) AND phase II and III trials aliases and/or filters. A supplemental bibliographic search of recent review articles and directed searches for updated reports of specific studies was also conducted.

Records were vetted at abstract and full text level as needed and phase II or phase III trials with published or presented results evaluating the efficacy and/or safety of checkpoint-inhibitor use in conjunction with cCRT for the treatment of stage III unresectable NSCLC were eligible.

3. Findings

3.1. Literature search

The literature search produced a total of 643 records representing one phase III and three phase II clinical trials that reported efficacy and/or safety data on checkpoint-inhibitors used in conjunction with chemoradiation for the treatment of stage III unresectable NSCLC (PRISMA Diagram, Fig. 1) [17,49–52].

3.2. Phase III PACIFIC

The phase III double-blind, placebo-controlled international PACIFIC trial randomized PD-L1 unselected patients with stage III, locally advanced, unresectable NSCLC that had not progressed after ≥2 cycles of cCRT 2:1 to receive up to 12 months of consolidation therapy with durvalumab (n = 476) or placebo (n = 237) starting one to 42 days following cCRT [17]. At a median follow-up of 14.5 months, a significant improvement in the co-primary endpoint of blinded independent review committee assessed PFS was observed for durvalumab versus placebo (16.8 vs. 5.6 months, HR 0.52, 95% CI 0.42 to 0.65, p < 0.001), with a 12-month PFS rate of 55.9% versus 35.3% and an 18-month PFS rate of 44.2% versus 27.0% for durvalumab versus

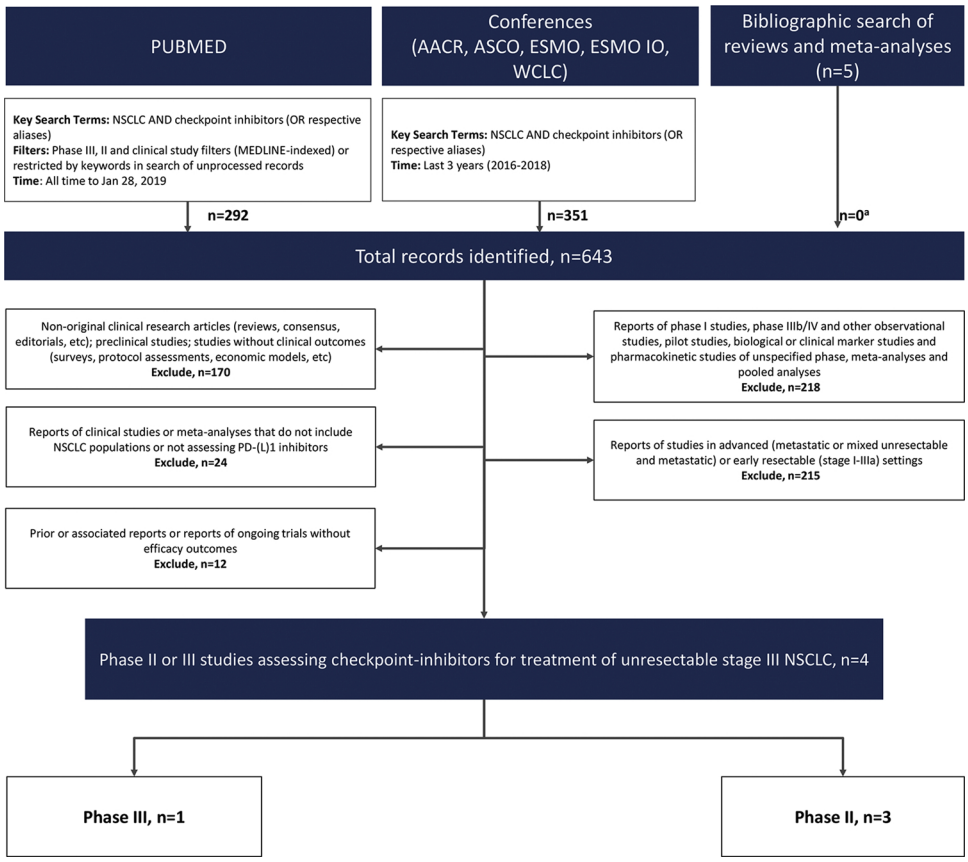

Fig. 1. PRISMA diagram of phase II and III trials evaluating checkpoint-inhibitors in conjunction with cCRT for the treatment of stage III unresectable NSCLC.[a]Primary reports of eligible studies that were not identified through database. Abbreviations: AACR, American Association for Cancer Research; ASCO, American Society of Clinical Oncology ; ESMO (IO), European Society for Medical Oncology (Immuno-Oncology) ; n, number; NSCLC, non-small cell lung cancer; PD-(L)1, programmed cell death (ligand) 1; WCLC, World Conference on Lung Cancer.

placebo, respectively (Table 1) [17]. The time to metastatic disease or death (TMDD) was also improved for durvalumab compared with placebo (median 23.2 vs. 14.6 months, HR 0.52, 95% CI 0.39 to 0.69, $p < 0.0001$). In an updated analysis at a median follow-up of 25.2 months, the PFS outcomes were similar to prior reports and a significant improvement in the co-primary endpoint of median OS was also seen for consolidation durvalumab versus placebo (not yet reached [NYR] vs. 28.7 months, HR 0.68, 95% CI 0.47–1.0, $p = 0.0025$) which was observed across all pre-specified subgroups [52]. The 12-month OS rate for durvalumab was 83.1% compared with 75.3% for placebo, and the 24-month OS rate was 66.3% versus 55.6% for consolidation durvalumab versus placebo. Discontinuation due to adverse events (AEs) occurred in 15.4% of patients on durvalumab arm and 9.8% of patients on placebo (Table 2). Rates of grade 3/4 AEs of any cause were similar for durvalumab compared with placebo (29.9% vs. 26.1%) and the most common any cause grade 3/4 AEs in the durvalumab arm were pneumonia (4.4%), pneumonitis or radiation pneumonitis (3.4%), anemia (2.9%) and dyspnea (1.5%). AE-associated deaths occurred in 4.4% versus 5.6% of patients in the durvalumab and placebo arms, respectively.

3.3. Phase II LUN 14–179

The phase II single arm LUN 14–179 study evaluated the safety and efficacy of consolidation therapy using pembrolizumab for up to 12 months in 92 patients with stage III unresectable NSCLC who did not have progressive disease 28–56 days following cCRT. A small number of patients (4.3%) had received up to 2 cycles of consolidation chemotherapy prior to enrollment. At a median follow-up of 18.6 months, the primary endpoint of median time to TMDD was 22.4 months (95% CI 17.9 to NYR) (Table 1) [49]. The 12-month TTMD rate was 74.7%, at 18-months 60.0%, and at 24-months 49.9%. Median PFS was 17.0 months (95% CI 11.9 to NYR), with 12- 18- and 24-month PFS rates of 60.2%, 49.9%, and 44.6%, respectively. Median OS was not yet reached at the time of this analysis (95% CI 22.4 to NYR), and 12- 18- and 24-month OS rates were 81.0%, 68.0%, and 61.9%. Discontinuation due to AEs occurred in 19.6% of patients, and although overall rates of grade 3/4 AEs were not reported, the most frequent grade 3/4 AEs were pneumonitis (5.4%), dyspnea (5.4%), fatigue (4.3%) and diarrhea (4.3%) (Table 2). Overall deaths due to AEs were not reported, although a pneumonitis-related death occurred in one patient.

3.4. Phase II DETERRED

The two part phase II DETERRED trial evaluated the use of atezolizumab with cCRT for locally advanced NSCLC. Part I assessed consolidation atezolizumab plus chemotherapy for 2 cycles following cCRT then continued atezolizumab for up to 12 months (n = 10) and if no concerning toxicities were observed, part II then investigated the concurrent administration of atezolizumab with cCRT then consolidation with atezolizumab plus chemotherapy for two cycles followed by further consolidation with atezolizumab for up to 12 months (n = 30). The safety of combining atezolizumab with cCRT was the primary endpoint of this study. With a median follow-up of 15.6 months and 9.0 months in parts I and 2, three patients (30% and 10%, respectively) discontinued treatment due to AEs (Table 2) [50]. AEs of grade 3 or higher occurred in 60% and 57% of patients in part I and II, respectively. Pneumonia was the most common AE of grade 3 or higher in both part I and part II (20% of patients in both), with grade 3 or higher pneumonitis or radiation pneumonitis reported in 0% and 3.3% of patients in parts I and II, respectively. One patient in part I experienced a grade five tracheoesophageal fistula, two patients in part II died due to treatment-related neutropenic sepsis and gastric hemorrhage. In part I, both the median PFS and OS was 20.1 months (one year PFS and OS rates of 60%), and the median PFS and OS was not yet reached in part II (one year PFS and OS rates of 66% and 77%, respectively) (Table 1).

Table 1
Clinical trials assessing efficacy of consolidation checkpoint-inhibitors with chemoradiation for the treatment of stage III unresectable NSCLC.

Trial Phase	PACIFIC (Antonia NEJM 2017, NEJM 2018) Phase III		LUN-14-179 (Durm ASCO 2018) Phase II	DETERRED (Lin WCLC 2018) Phase II		NICOLAS (Peters ASCO 2018) Phase II
Treatment Algorithm	cCRT then Durv consolidation	cCRT then Placebo consolidation	cCRT then Pembro consolidation	cCRT then CT plus Atez →Atez consolidation	cCRT plus concurrent Atez then CT plus Atez →Atez consolidation	CT induction then cCRT plus concurrent Niv then Niv consolidation
cCRT	Pt-based CT 54 to 66 Gy		Pt-based CT[a] 59.4 to 66.6 Gy	Carbo + Pac 60 to 66 Gy		Pt-based CT ≥60 Gy
Checkpoint-Inhibitor dose and timing	Durv 10 mg/kg q2w 1–42 days following Ccrt for up to 12 months		Pembro 200 mg q3w 28–56 days following cCRT for up to 12 months	Atez 1200 mg q3w plus CT x 2 → Atez 1200 mg q3w for up to 12 months	Atez 1200 mg q3w plus cCRT then Atez 1200 mg q3w plus CT x 2 → Atez 1200 mg q3w for up to 12 months	Niv 360 mg q3w x 2 then Niv 360-480 mg q4w for up to 12 months
n	476	237	92	10	30	62[b]
Median follow-up, months	14.5 (PFS) 25.2 (OS)		18.6	15.6	9.0	6.6
Median PFS, months	16.8	5.6	17.0	20.1	NYR	NR
HR	0.52		n/a	n/a	n/a	n/a
(95% CI)	0.42 to 0.65					
P-value	P < 0.001					
12-month PFS, % (95% CI)	55.9 (51.0 to 60.4)	35.3 (29.0 to 41.7)	60.2 (48.7 to 69.9)	60	66	NR
18-month PFS, % (95% CI)	44.2 (37.7 to 50.5)	27.0 (19.9 to 34.5)	49.9 (38.2 to 60.5)	NR	NR	NR
Median Time to Distant Metastasis or Death, months	23.2	14.6	22.4	NR	NR	NR
HR	0.52		n/a	n/a		n/a
(95% CI)	(0.39 to 0.69)					
P-value	P < 0.001					
Median OS	NYR	28.7	NYR	20.1	NYR	NR
HR	0.68		n/a	n/a		n/a
(95% CI)	(0.47 to 1.0)[c]					
P-value	P = 0.0025					
12-month OS, % (95% CI)	83.1 (79.4 to 86.2)	75.3 (69.2 to 80.4)	81.0 (71.2 to 87.7)	60	77	NR
24-month OS, % (95% CI)	66.3 (61.7 to 70.4)	55.6 (48.9 to 61.8)	61.9 (48.1 to 73.0)	NR	NR	NR
Median Time to Second Progression or Death, months	28.3	17.1	NR	NR	NR	NR
HR	0.58		NR	NR	NR	NR
(95% CI)	(0.46 to 0.73)					
P-value	P = NR					

Efficacy data from phase III and phase II trials are ordered by phase then by type of checkpoint inhibitor administration and date of presentation.
Abbreviations: Atez, atezolizumab; cCRT, concurrent chemoradiation therapy; Carbo, carboplatin; CI, confidence interval; CT, chemotherapy; Durv, durvalumab; HR, hazard ratio; n/a, not applicable; Niv, nivolumab; NR, not reported; NYR, not yet reached; OS, overall survival; Pac, paclitaxel; Pembro, pembrolizumab; PFS, progression-free survival; Pt, platinum CT, qXw, every X weeks.
[a] Patients could have received ≤ 2 cycles of consolidation chemotherapy at the physicians discretion.
[b] Accrual continues to 74 patients total to assess efficacy.
[c] 99.73% CI.

3.5. Phase II NICOLAS

The feasibility of concurrent nivolumab with cCRT was evaluated in the phase II NICOLAS trial in a total of 62 patients enrolled to date with stage III unresectable NSCLC (safety cohort, n = 58). Patients received chemotherapy for one cycle, then concurrent nivolumab plus cCRT for two cycles and consolidation with nivolumab for up to 12 months. Overall discontinuations due to AEs were not reported at a median follow-up of 6.6 months, although one patient was reported to discontinue treatment due to a serious febrile neutropenia event [51]. The most common grade 3/4 AEs reported were neutrophil count decrease (22.4%), febrile neutropenia, lymphocyte count decrease, and pneumonitis (10.3% each) (Table 2). Three patients (5.3%) died due to AEs (one oesophageal fistula and two stroke events). An efficacy analysis is planned after the accrual of 74 patients, with PFS results expected the third quarter of 2019.

4. Discussion

One phase III and three phase II studies have now reported outcomes for the use of checkpoint-inhibitors plus cCRT either as consolidation therapy following cCRT (PACIFIC phase III, LUN 14–179 and DETERRED phase II) [17,49,50,52], or concurrently with cCRT (DETERRED and NICOLAS phase II) [50,51]. To date, only PACIFIC has demonstrated significantly improved PFS and OS for consolidation durvalumab compared with placebo following cCRT in unresectable stage III NSCLC [17,52].

4.1. What is the clinical benefit for the addition of checkpoint-inhibitors to cCRT for the treatment of stage III unresectable NSCLC?

A change in clinical practice is warranted when level 1 evidence is available, meaning when an investigational therapy demonstrates a significant improvement in overall survival compared to a standard of care in a phase III trial. Of the trials reviewed [17,49–52], only the

Table 2
Safety outcomes from clinical trials assessing consolidation checkpoint-inhibitors with chemoradiation for the treatment of stage III unresectable NSCLC.

Trial Phase		PACIFIC Antonia 2017 Phase III		LUN-14-179 Durm 2018 Phase II	DETERRED Lin 2018 Phase II		NICOLAS Peters 2018 Phase II
Treatment Algorithm		cCRT then Durv consolidation	cCRT then Placebo consolidation	cCRT then Pembro consolidation	cCRT then CT plus Atez →Atez consolidation	cCRT plus concurrent Atez then CT plus Atez →Atez consolidation	CT induction then cCRT plus concurrent Niv then Niv consolidation
Safety Population (n)		475	234	93	10	30	58
Overall							
Any Cause AEs n (%)	Any Gr	460 (96.8)	222 (94.9)	NR	NR	NR	52 (89.7)
	Gr 3/4	142 (29.9)	61 (26.1)	NR	6 (60.0)	17 (56.7)	24 (41.4) [serious AE]
AEs leading to discontinuation of any treatment n (%)		73 (15.4)	23 (9.8)	18 (19.6)	3 (30)	3 (10)	NR
AE- or Treatment-associated Deaths n (%)		21 (4.4)[a]	13 (5.6)[a]	NR[b]	1 (10.0)	2 (6.7)[c]	3 (5.2)
Select AEs							
Pneumonia n (%)	Any Gr	62 (13.1)	18 (7.7)	NR	NR	NR	11 (19.0)[d]
	Gr 3/4	21 (4.4)	9 (3.8)	NR	2 (20.0)	6 (20.0)	1 (1.7)[d]
Pneumonitis or radiation pneumonitis n (%)	Any Gr	161 (33.9)	58 (24.8)	16 (17.2)[e]	3 (30.0)[c]	3 (10.0)	19 (32.8)
	Gr 3/4	16 (3.4)	6 (2.6)	6 (6.5)[b]	0 (0.0)	1 (3.3)	6 (10.3)
Anemia n (%)	Any Gr	36 (7.6)	25 (10.7)	NR	NR	NR	24 (41.4)
	Gr 3/4	14 (2.9)	8 (3.4)	NR	NR	NR	3 (5.2)
Dyspnea n (%)	Any Gr	106 (22.3)	56 (23.9)	20 (21.5)	NR	NR	12 (20.7)
	Gr 3/4	7 (1.5)	6 (2.6)	5 (5.4)	1 (10.0)[f]	NR	1 (1.7)
Diarrhea n (%)	Any Gr	87 (18.3)	44 (18.8)	14 (15.1)	NR	NR	NR
	Gr 3/4	3 (0.6)	3 (1.3)	4 (4.3)	NR	1 (3.3)[f]	NR
Asthenia n (%)	Any Gr	51 (10.7)	31 (13.2)	43 (46.2)[g]	NR	NR	NR
	Gr 3/4	3 (0.6)	1 (0.4)	4 (4.3)[g]	NR	NR	NR
Musculoskeletal pain n (%)	Any Gr	39 (8.2)	24 (10.3)	NR	NR	NR	10 (19.0)[h]
	Gr 3/4	3 (0.6)	1 (0.4)	NR	NR	NR	1 (1.7)[h]

Phase III and phase II data are ordered by phase then by type of checkpoint inhibitor administration and date of presentation. Any grade and grade 3/4 AEs were reported for those AEs with grade 3/4 AEs occurring in at least 0.5% of patients from the phase III PACIFIC trial.
Abbreviations: AEs, adverse events; Atez, atezolizumab; cCRT, concurrent chemoradiotherapy; CT, chemotherapy; Durv, durvalumab; Gr, grade; n, number of patients; Niv, nivolumab; NR, not reported; NSCLC, non-small cell lung cancer; Pembro, pembrolizumab.
[a] Grade 5 adverse events of any cause or grade 5 events deemed related to treatment.
[b] One grade 5 pneumonitis event reported.
[c] Data from abstract.
[d] Reported as lung or bronchial infection.
[e] Only grade ≥2 pneumonitis reported.
[f] Attributed to atezolizumab.
[g] Reported as fatigue.
[h] Reported as pain.

phase III PACIFIC trial evaluated the addition of checkpoint-inhibitor consolidation to the current standard of care, cCRT [17,52]. At the first analysis, this trial showed long lasting PFS benefits for durvalumab consolidation following cCRT [17]. Although the median PFS of 5.6 months reported in the placebo arm of PACIFIC [17] could be interpreted as relatively short compared with the 11.8 month median PFS seen in a comparable patient cohort from the phase III RTOG 0617 trial [53], this is likely as PFS was measured following cCRT in PACIFIC and prior to cCRT in RTOG 0617. In addition to significant PFS improvements, investigator-assessed TMDD was also prolonged in the durvalumab group compared with placebo (median 23.2 vs. 14.6 months, HR 0.52, 95% CI 0.39 to 0.69, $p < 0.001$) [17]. After a median follow-up of 25.2 months, PFS remained significantly improved and the frequency of new lesions as assessed by blinded independent review committee was 22.5% versus 33.8%. The incidence of new brain metastases was 6.3% versus 11.8% in the durvalumab and placebo groups, respectively [52]. Median OS was NYR for durvalumab versus 28.7 months for placebo (HR 0.68, 95% CI 0.47 to 0.997, $p = 0.0025$), with only a modest increase in rates of discontinuation due to AEs (15.4% vs. 9.8%) [17]. An additional post-hoc exploratory analysis also indicated that durvalumab improved PFS and OS regardless of type of chemotherapy administered, dose of radiation, or time from radiation therapy to randomization [54]. Although this 2-year data is compelling, long term data is awaited to confirm the safety and efficacy of durvalumab in this setting.

The phase II LUN 14–179 (n = 92) trial reported similar median PFS (17.0 months), TMDD (22.4 months) and 12-month OS (81.0%) for pembrolizumab consolidation following cCRT in stage III unresectable NSCLC [49]. Although outcomes for this study were comparable to those seen in PACIFIC, the use of pembrolizumab consolidation therapy following cCRT will require confirmation in a randomized context before it can be recommended for widespread use. Of note, the United States Food and Drug Administration (FDA) [28] recently approved pembrolizumab as first-line therapy in patients with unresectable stage III EGFR-/ALK- NSCLC and PD-L1 expression ≥1% who are not candidates for definitive cCRT, based on significant OS benefit seen for pembrolizumab compared to a platinum-based chemotherapy in the phase III KEYNOTE-042 trial [55]. However, this trial had a small number of stage III patients (13%) and benefit was more pronounced in patients with PD-L1 expression ≥50% (n = 599, HR 0.69, p = 0.0003) compared with the approved PD-L1 expression ≥1% population (n = 1,274, HR 0.81, p = 0.0018). Taken together, PACIFIC remains the only study to demonstrate a statistically significant improvement in survival with the addition of durvalumab consolidation following cCRT in patients with stage III unresectable NSCLC [52], and therefore is the only treatment that warrants consideration as a new standard of care in this setting at this time. Durvalumab has been approved by the FDA [29] and Health Canada [48], regardless of PD-L1 status.

4.2. Should biomarkers be used to guide checkpoint-inhibitor therapy following cCRT in stage III unresectable NSCLC?

Given the high costs associated with checkpoint-inhibitor therapy, there is a great need for biomarkers that will help select patients for these treatments, and PD-L1 is an established biomarker for single agent checkpoint-inhibitors in NSCLC [30,33]. PACIFIC allowed any level of PD-L1 expression and tumor tissue collection was not required for trial inclusion [17]. As such, only 76% of patients had tumor tissue available and 63% were evaluable for PD-L1 expression retrospectively using the Ventana SP263 immunohistochemistry assay from archived tumor tissue [52]. Furthermore, as tissue was collected prior to cCRT and cCRT may increase PD-L1 expression [38–41], the reported PD-L1 status may not have reflected the PD-L1 status at the time of consolidation therapy. Nevertheless, a post-hoc exploratory analysis for efficacy based on PD-L1 expression showed that durvalumab following cCRT improved PFS and OS compared with placebo in all patients with PD-L1 expression ≥1% [52]. In the small number of patients with known PD-L1 expression < 1% (20.8% of patients), PFS was numerically improved for patients receiving durvalumab (HR 0.73, 95% CI 0.48 to 1.11). However, the direction of benefit shifted for OS in these patients and showed numerically better survival in patients receiving placebo (HR 1.36, 95% CI 0.79 to 2.34) [52]. Based on these findings, The European Medicines Agency restricted their approval of durvalumab to patients with PD-L1 ≥ 1% tumor cell expression [47]. As the subgroup analysis was not representative, the PD-L1 < 1% cohort small and confidence intervals wide, crossing unity, the benefits of durvalumab consolidation in patients with PD-L1 expression < 1% remains unclear and these data should not be used to guide therapy at this time.

4.3. Should stage III unresectable patients with a known mutation be treated with checkpoint-inhibitors?

Many NSCLC patients have driver mutations such as epidermal growth factor receptor mutations (EGFR+, 10–50% of patients) or anaplastic lymphoma kinase gene rearrangements (ALK+, 2–5% of patients). Patients harboring EGFR mutations and/or ALK rearrangements have often been excluded from first-line checkpoint-inhibitor trials in advanced disease due to the availability of targeted therapies, so data on the benefit of checkpoint-inhibitors in these patients are scarce [32,56]. Current data from phase III trials evaluating first-line checkpoint-inhibitor combinations in advanced NSCLC showed questionable benefit in EGFR+/ALK + patients [57–59]. PACIFIC enrolled a small number of EGFR + patients (6.0%) and a subgroup analysis based on EGFR status showed numerically improved PFS for durvalumab consolidation following cCRT in patients with EGFR + disease (HR 0.76, 95% CI 0.35 to 1.64) [17]. However, confidence intervals were wide crossing unity and no OS outcomes were reported in the updated analysis so the benefit of durvalumab in these patients remains unknown. Combinations involving checkpoint-inhibitors and EGFR/ALK targeted tyrosine kinase inhibitors (TKIs) are currently under investigation [60–64], although increased toxicity may prevent the use of checkpoint-inhibitors with TKIs [65]. Results from a phase Ib study showed a higher than expected rate of lung toxicity for durvalumab given concurrently with osimertinib for advanced EGFR + lung cancer [66], and a recent retrospective analysis suggests that administration of osimertinib following a checkpoint-inhibitor may result in higher rates of grade 3 immune-related pneumonitis (10%) among patients with EGFR + NSCLC [67]. As few treatment options exist for patients with unresectable stage III NSCLC and known driver mutations, consolidation with durvalumab following cCRT may be considered on an individual basis, although further biomarker research is needed to guide treatment in this setting.

4.4. Is there a risk of pulmonary toxicities in patients with stage III unresectable NSCLC treated with checkpoint-inhibitors following cCRT?

Pulmonary toxicities are known to be associated with both checkpoint-inhibitors and radiotherapy [68,69], and concerns therefore exist regarding the potentiation of pulmonary AEs with the administration of checkpoint-inhibitors in conjunction with cCRT. Secondary analysis of the phase I KEYNOTE-001 study evaluating pembrolizumab in patients with advanced NSCLC showed that any pulmonary toxicity of any grade occurred in 63% versus 40% of patients who received previous thoracic radiotherapy compared with those who did not (p = 0.052), and that any grade pembrolizumab-related pulmonary toxicity was significantly higher in patients who received previous thoracic radiotherapy compared to patients with no previous thoracic radiotherapy (13% vs. 1%, p = 0.046) [46].

Rates of pulmonary toxicities associated with the addition of durvalumab following cCRT were evaluated in PACIFIC [17]. Any grade pneumonia occurred with greater frequency in the durvalumab arm versus chemotherapy (13.1% vs. 7.7%), although grade 3/4 pneumonia was comparable between arms (4.4% vs. 3.8%). Any grade pneumonitis or radiation pneumonitis was numerically higher in the durvalumab arm compared with placebo (33.9% vs. 24.8% respectively), although grade 3/4 events (and 3.4% vs. 2.6%, respectively) were not substantially different. An exploratory subgroup analysis showed a similar median time to pneumonitis onset from the first dose of durvalumab received (55.0 vs. 55.0 days) and from radiotherapy (73.0 vs. 76.5 days) for durvalumab and placebo, respectively [70]. Treatment exposure was also similar for all time points analyzed between patients who did or did not develop pneumonitis. While rates of grade 3/4 pulmonary toxicity were reassuringly low for the addition of durvalumab, it should be noted that the study permitted patients to be treated with doses as low as 54 Gy, which is a lower than standard dose for concurrent cCRT (60 Gy) [17]. Data detailing the number of patients receiving doses < 60 Gy and statistics regarding radiation dose metrics (e.g. percent volume of non- target lung receiving > 20 Gy) are presently unpublished. In addition, radiation plan quality has been shown to be associated with outcome in cCRT trials of patients with unresectable stage III NSCLC receiving cCRT [71,72], and this was not assessed in PACIFIC. This therefore makes it difficult to interpret the reported rates of pulmonary toxicity in comparison to other large randomized trials in this patient population.

Considerable research has been conducted on the differential risk of pulmonary toxicities for various checkpoint-inhibitors [73,74]. PD-1 inhibitors block the PD-1/PD-L2 interaction between macrophages and T-cells which could increase autoimmune AEs such as pneumonitis, whereas PD-L1 inhibitors preserve this interaction potentially reducing these toxicities [75–77]. Two recent meta-analyses evaluating PD-(L)1 inhibitors given for NSCLC (n = 5744) [74] or across tumor sites (n = 5038) [73] showed that PD-1 inhibitors such as pembrolizumab and nivolumab were associated with statistically significant higher incidence of any grade pneumonitis (4% vs. 2%, p = 0.01 and 3.6% vs. 1.3%, p = 0.001, respectively) [73,74] and grade 3/4 pneumonitis (1.1% vs. 0.4%, p = 0.02) [73] compared with PD-L1 inhibitors. Although cross study comparisons must be interpreted with caution, PACIFIC and LUN 14–179 evaluating checkpoint-inhibitor use as consolidation therapy following cCRT showed similar numerically lower rates of grade 3 or greater pneumonitis for the PD-L1 inhibitor durvalumab compared to the PD-1 inhibitor pembrolizumab (3.4% vs. 6.5%) [17,49]. Although rates of all reported pneumonitis or radiation pneumonitis were numerically higher for durvalumab compared with pembrolizumab (33.9% vs. 17.2%), this is likely explained by the selective reporting of toxicity in LUN 14–179 which was limited to grade ≥2 events [49]. A similar cross study comparison of checkpoint-inhibitors administered concurrently with cCRT and then as further consolidation therapy showed numerically higher rates of grade 3/4 pneumonitis or radiation pneumonitis for the PD-1 inhibitor nivolumab

compared with the PD-L1 inhibitor atezolizumab (10.3% vs. 3.3%) [50,51]. Taken together, findings indicate a safety signal for PD-1 inhibitors relative to PD-L1 inhibitors in this setting, although this must be confirmed in a randomized context.

4.5. What is the optimal timing for checkpoint-inhibitor administration in stage III unresectable NSCLC?

The optimal timing of checkpoint-inhibitor use relative to radiotherapy is a point of interest. Available data in NSCLC show clinical benefit when immunotherapy is given following radiotherapy [46,52,78,79]. A subgroup analysis of PACIFIC found that the PFS improvement in favor of durvalumab was more pronounced among patients who had their last radiotherapy dose < 14 days before randomization (HR 0.39, 95% CI 0.26 to 0.58) compared with those who had their last radiotherapy dose ≥14 days before randomization (HR 0.63, 95% CI 0.49 to 0.80) [54]. Although provocative, these findings should be interpreted with caution as differences in baseline variables such performance status (approximately 47% vs. 53% PS 0 patients) and age (approximately 52% vs. 62% patients < 65 years of age) in the ≥14 days versus < 14 days groups, respectively, may have confounded outcomes.

The timing of checkpoint-inhibitor therapy relative to cCRT is a topic of ongoing inquiry. Of the studies reviewed, three studies (PACIFIC, LUN 14–179 and DETERRED) assessed checkpoint-inhibitor use as consolidation therapy following cCRT [17,49,50] and two (DETERRED and NICOLAS) assessed their administration concurrently with cCRT and then as consolidation therapy following cCRT [50,51]. For checkpoint-inhibitor use in conjunction with cCRT, 12-month PFS rates ranged from 55.9% to 66% (PACIFIC 55.9%, LUN 14–179 60.2% and DETERRED part I 60%, DETERRED part II 66%) [17,49,50] and 12-month OS rates were from 60% to 83% (PACIFIC 83.1%, LUN 14–179 81.0%, DETERRED part I 60%, DETERRED part II 77%) [49,50,52]. Differences in OS across trials may be due to trial methodologies as approximately one-third of screened patients completing cCRT were ineligible for PACIFIC [17], whereas patients who did not respond well to cCRT were included in DETERRED [50]. Strategies administering checkpoint-inhibitors concurrently with cCRT [50,51] or adding chemotherapy to checkpoint-inhibitors following cCRT [50] require further investigation. At present, checkpoint-inhibitor consolidation using durvalumab alone following cCRT is the only approach supported by level 1 evidence and other sequencing options require confirmation in a randomized context.

5. Summary

Randomized phase III data from PACIFIC support the use of consolidation durvalumab monotherapy following cCRT in patients with stage III unresectable NSCLC, based on an acceptable safety profile and significantly improved OS. Although pulmonary toxicities were higher with durvalumab compared to placebo in PACIFIC, grade 3/4 toxicities were low. PD-L1 expression levels should not be used to guide therapy at this time and durvalumab may be administered on an individual basis in patients with known driver mutations. Consolidation durvalumab following cCRT should be the new standard of care for patients with stage III unresectable NSCLC.

Funding

This work was supported by unrestricted educational grants from AstraZeneca Canada Inc. and Merck Canada Inc..No discussion or viewing of review content was permitted with sponsors at any stage of review development.

Acknowledgments

We would like to thank Ilidio Martins from Kaleidoscope Strategic Inc. for his research support and AstraZeneca Canada Inc. and Merck Canada Inc. for their financial support.

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