Editorial Commentary

When to initiate durvalumab after concurrent chemoradiation in unresectable stage III non-small cell lung cancer?—A commentary on the phase II TORG 1937 (DATE) study

Megan Smith-Uffen[1#], Raman Sambhi[1#], Saurav Verma[2], Daniel Breadner[1,2], Jacques Raphael[1,2]

[1]Department of Medicine, University of Western Ontario, London, ON, Canada; [2]Department of Oncology, Verspeeten Family Cancer Centre, London Health Sciences Centre, London, ON, Canada

[#]These authors contributed equally to this work.

Correspondence to: Jacques Raphael, MD, MSc. Assistant Professor, Department of Oncology, Verspeeten Family Cancer Centre, London Health Sciences Centre, 800 Commissioners Rd E, London, ON N6A 5W9, Canada; Department of Medicine, University of Western Ontario, London, ON, Canada. Email: Jacques.Raphael@lhsc.on.ca.

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Introduction

We are pleased to provide our commentary on the DATE study by Nakamichi *et al.* (1). DATE was a prospective, single arm, open-label, phase II clinical trial of 47 Japanese patients which aimed to determine the optimal timing for initiating durvalumab after concurrent chemoradiation therapy (CRT) in patients with unresectable stage III non-small cell lung cancer (NSCLC). The primary endpoint was one year progression-free survival (PFS), measured from registration before the start of CRT. The trial reported that immediate initiation of durvalumab was associated with a survival benefit [1-year PFS rate of 71.5%; 95% confidence interval (CI): 54.2–83.2], albeit with considerable toxicity (78.7% rate of pneumonitis of any grade).

Lung cancer is the leading cause of cancer-related death. In 2020, 1.8 million people died of lung cancer worldwide (2), and in 2024, 125,070 and 20,700 patients are expected to die in the United States and Canada, respectively (3,4). NSCLC is the most common type of lung cancer. Of those with NSCLC, 30% present with stage III, locally advanced disease, most of whom have unresectable tumours (5). The standard treatment for stage III unresectable NSCLC is concurrent chemoradiation with a platinum-based doublet, followed by durvalumab for up to 12 months. This was established in the landmark PACIFIC trial (6,7).

PACIFIC randomized stage III unresectable NSCLC patients to receive durvalumab or placebo for up to 12 months after at least 2 cycles of platinum-based CRT. Primary outcomes included PFS and overall survival (OS), which were measured from the time from randomization (which occurred up to 6 weeks after chemoradiotherapy). The trial demonstrated an impressive survival advantage with a median PFS of 16.9 months and OS of 47.5 months. Tolerability was comparable between the two arms, however the durvalumab arm resulted in greater rates of pneumonitis (33.9% compared with 24.8%, of any grade). This regimen was further examined in PACIFIC-R (8), a real-world trial that also demonstrated survival benefit (24.1 months median PFS, median OS not reached) and tolerability profile (17.9% pneumonitis of any grade). A detailed comparison of the trials can be found in *Table 1*.

Since the publishing of PACIFIC there has been interest in the optimal timing of durvalumab start. In PACIFIC, durvalumab was initiated within 42 days of CRT, but a pre-specified subgroup analysis found a trend toward increased benefit among those who received it within 14 days,

Table 1 Comparison of patient demographics, treatment regimens, survival outcomes and toxicity profiles for the DATE, PACIFIC and PACIFIC-R studies

Characteristics	DATE (1)	PACIFIC [durvalumab arm; (7)]	PACIFIC-R (8)
Patient demographics (unresectable stage III NSCLC who did not have disease progression after CRT, who were age 18 or older and World Health Organization performance status of 0 or 1)			
Asian (%)	100 (Japanese)	25.5	Not reported
Stage of disease (%)	Stage IIIA 40.4	Stage IIIA 52.9	Stage IIIA 46.4
	Stage IIIB 44.7	Stage IIIB 44.5	Stage IIIB or IIIC 53.6
	Stage IIIC 14.9	Other 2.5	
Age (years), median [range]	65 [42–74] (excluded patients ≥75)	64 [31–84]	66 [26–88]
Active smoker (%)	51.1	16.4	26
Performance status 0 (%)	59.6	49.2	98.4 (0 or 1)
PD-L1 expression (%)	≥50%: 40.4	≥25%: 39.3	≥1%: 72.4
	1–49%: 23.4	<25%: 24.2	<1%: 18
	<1%: 21.3	Unknown: 36.6	
Treatment regimen (durvalumab, 10 mg/kg intravenously, every 2 weeks for up to 12 mo or until disease progression)			
Initiation of durvalumab	Planned for day 1–5	Planned for day 1–42	Within 42 days: 30.1%
	71.4% initiated the day after completion of concurrent chemoradiation		Within 14 days: 1.2%
			3 months or more: 14.4%
			6 months or more: 1.0%
Chemoradiotherapy	At least two cycles of CRT with a platinum-based regimen		Included both sequential CRT (14.4%; which includes 1 cycle of overlapping chemo and RT) and concurrent CRT (76.6%)
Radiotherapy	Definitive radiotherapy with the V20 at less than 35%		
Median total radiotherapy dose (Gy)	60 (excluded patients with prophylactic mediastinal radiation)	54 to 66	66
Chemotherapy	Two or more cycles of CRT with a platinum-based chemotherapy regimen which included vinca alkaloids, taxanes, or antimetabolites		
Etoposide status	Excluded etoposide	Included etoposide	Included etoposide
Survival			
mPFS (mo; 95% CI)	12.7 (12.7–NR)	16.9 (13–23.9)	24.1 (20.2–27.8) [among patients with PD-L1 expression greater than or equal to 1% *vs.* less than 1% (22.4 *vs.* 15.6 mo)]
PFS rate (%; 95% CI)	1-year: 71.5	1-year: 55.7 (51.0–60.2)	1-year: 62.2 (59.6–64.6) (2022 paper)
	2-year: not calculable as follow-up duration not adequate	2-year: 45.0 (40.1–49.8)	2-year: 50.1 (47.2–53.0)
mOS (mo; 95% CI)	Not reached	47.5 (38.1–52.9)	Not reached

Table 1 (*continued*)

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Characteristics	DATE (1)	PACIFIC [durvalumab arm; (7)]	PACIFIC-R (8)
OS rate (%; 95% CI)	1-year: 97.7 (84.6–99.7)	1-year: 83.1 (79.4–86.2)	2-year: 72.3 (69.7–74.8)
PFS by PD-L1 status	Not reported	HR (95% CI)[†]:	mPFS (95% CI):
PD-L1 ≥1%		• 0.61 (0.44–0.85)	• 22.4 mo (18.4–25.5)
PD-L1 <1%		• 1.15 (0.75–1.75)	• 15.6 mo (12.2–23.2)
Survival by timing of durvalumab start PFS	Not applicable	Not reported	mPFS (mo), (95% CI)
			• ≤42 days: 26.6 (18.4–36.2)
			• >42 days: 22.4 (19.1–26.9)
			2-year PFS (mo), (95% CI)
			• ≤42 days: 52.3 (47.3–57.1)
			• >42 days: 48.9 (45.3–52.5)
Survival by timing of durvalumab start OS	Not applicable	Unstratified HR (95% CI)	mOS (mo), (95% CI)
		<14 days: 0.54 (0.37 to 0.80)	• ≤42 days: 46.3 (44.5–NE)
		≥14 days: 0.79 (0.63 to 1.00)	• >42 days: NR (NE–NE)
			2-year OS (%), (95% CI)
			• ≤42 days: 76.9 (73.8 to 79.8)
			• >42 days: 63.0 (58.0 to 67.6)
Adverse events			
Pneumonitis of any grade (%; grade 3–4)	78.7 (4.3)	33.9 (3.4)	17.9 (11.7 moderate to life-threatening or fatal)
Leukopenia of any grade (%; grade 3–4)	89.4 (55.3)	Not reported	Not reported
Anemia of any grade (%; grade 3–4)	95.7 (8.5)	7.6 (2.9)	Not reported
Febrile neutropenia of any grade (%; grade 3–4)	4.3 (4.3)	Not reported	Not reported
Ast increased of any grade (%; grade 3–4)	42.6 (2.1)	Not reported	Not reported
Pneumonia of any grade (%; grade 3–4)	21.3 (14.9)	13.1 (4.4)	Not reported
Diarrhea of any grade (%; grade 3–4)	23.4 (4.3)	18.3 (0.6)	Not reported
Pyrexia of any grade (%; grade 3–4)	Not reported	14.7 (0.2)	Not reported

[†], post hoc analysis. CI, confidence interval; CRT, chemoradiation; HR, hazard ratio; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; NR, not reached; NE, not estimable; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RT, radiotherapy; V20, the volume of lung parenchyma that received 20 Gy or more.

although it was not significant [hazard ratio (HR): 0.97; 95% CI: 0.77–1.22]. DATE aimed to address this important clinical question. Notably, in PACIFIC-R, the median time to initiation was 52 days, but an improved survival benefit was also seen among those who received it earlier (26.6 months for those starting within 42 days compared

with 22.4 months for those who did not). Given that DATE builds off the findings of PACIFIC, it's important to thoroughly compare the two in terms of patient demographics, study design, survival and toxicity.

The patient populations of DATE and PACIFIC were distinct. DATE was comprised entirely of Japanese patients, whereas only 25.5% of PACIFIC patients were of Asian descent. DATE also included patients with stage IIIC disease (14.9%), which were excluded from PACIFIC, and had a larger proportion of current smokers (51.1% compared to 16.6% in PACIFIC). However, the performance status was comparable (59.6% with performance status 0 in DATE and 49.2% in PACIFIC). It is difficult to compare the programmed death ligand 1 (PD-L1) expression between the trials. DATE reported 40.4% with PD-L1 ≥50%, and PACIFIC reported 39.3% with PD-L1 ≥25%. However, we do not have a direct comparison of how many were ≥50% or ≥25%.

The study designs were somewhat comparable. Both started durvalumab after two or more cycles of CRT with a platinum-based chemotherapy regimen which included vinca alkaloids, taxanes, or folic acid metabolism inhibitors. However, PACIFIC included patients treated with etoposide, but DATE did not.

In DATE, the median PFS from the start of durvalumab was 12.7 months, the 1-year PFS rate was 71.5%, and median OS was not reportable. However, this survival analysis is limited by very short follow-up time—only 14 months from registration (before starting CRT).

78.7% of patients in the DATE trial experienced pneumonitis (4.3% grade 3–4), which was considerably more than the 33.9% in PACIFIC (3.4% grade 3–4). It is noteworthy that on our assessment of DATE's *Fig. S3*, it appears that 32% (15 patients) experienced grade 2 pneumonitis.

Discussion

The preclinical rational for multimodality use of chemoradiation and immunotherapy is that it causes both local damage, in which radiation increases the immunogenicity of the tumour microenvironment through genotoxic stress, cell death and the release of local neoantigens that prime a local immune response; and an abscopal effect in which the primed immune system can recognize these antigens distally, eliminating micro metastatic disease (9). Radiation can also directly upregulate expression of PD-L1 on the tumour surface, enhancing response to checkpoint inhibitors (9,10).

Indeed, studies are underway investigating the concurrent use of all three modalities, such as PACIFIC-2 (11), a phase III trial comparing concurrent durvalumab and platinum CRT with CRT alone. Interestingly, this trial did not find a significant difference in PFS (HR 0.85; 95% CI: 0.65–1.12; P=0.247) or OS (HR 1.03; 95% CI: 0.78–1.39; P=0.823). The reasons for this are unclear. Possibly, the increase in PD-L1 expression and creation of an immunogenic tumour microenvironment requires time to develop after a radiation insult. Also unexpectedly, the rate of pneumonitis was similar between the two arms (28.8% *vs.* 28.7%), which may be due to a similar pathophysiology, although this is also unclear. The full results of this study have yet to be published and require a more detailed review to explain these findings.

The preferred timing of durvalumab initiation is clearly an area of clinical interest, and the DATE trial aimed to address this important question. While the study reports a survival benefit and what is described as a reasonable toxicity profile, on deeper review of this paper we feel that the interpretation of its survival analysis is severely limited by a very short follow up time, its translatability to broader patient populations is limited by its narrow patient demographics and a treatment regimen that is somewhat inconsistent with North American standards, and its safety profile would be considered by many to have an unacceptably high risk of pneumonitis.

As noted above, DATE's survival analysis is limited by short follow-up—14 months from registration (before starting CRT). Most patients included would only have been analyzed until the time of planned durvalumab completion, and the analysis would not capture survival after completing the regimen. Further, it is difficult to interpret the 1-year PFS or median PFS of approximately 12 months, as most of the patients were censored between 9 and 12 months [*Fig. 1B*, (1)]. It is unclear why the follow up time was so short – the trial started recruitment in 2020, and published results in 2024, which should allow for a longer follow-up period. This is unfortunately not addressed in the text. For comparison, PACIFIC followed patients for a median of 34.2 months. We feel this makes DATE's data immature, difficult to interpret, and not possible to meaningfully compare to PACIFIC.

DATE's patient population was entirely comprised of Japanese patients, making it difficult to expand its findings to other patient groups. Its chemotherapy regimen did not include etoposide, which is inconsistent with North

American standards of care. Moreover, DATE included patients with EGFR and ALK mutations (6.4% and 10.6% of patients, respectively). Although these patients were included in the PACIFIC trial as well, immunotherapy has shown limited benefit for them (12) and current treatment standards recommend they receive targeted therapy instead (13,14).

The rate of pneumonitis was also far higher in DATE than PACIFIC or PACIFIC-R, with over 75% of patients developing pneumonitis and over 30% developing grade 2 disease. Certainly, pneumonitis is more common amongst patients of an Asian background and current smokers (15-17), both of which were overrepresented in DATE. Reportedly, the rate of pneumonitis in DATE was similar to the Asian cohort in PACIFIC, although we are unable to find this data through the public domain. For many oncologists and their patients, however, these high rates of pneumonitis would be considered a significant, if not unacceptable risk, particularly given the unclear efficacy as outlined above.

Immediate durvalumab initiation also comes with some practical challenges. It can be difficult to organize imaging within this time frame, and interpretation of short-term scans may be fraught, as post-radiation changes can mimic disease progression (18). Patients may require more recovery time. Indeed, PACIFIC initially intended to start durvalumab within 14 days, however, due to recruitment issues, extended this to 42 days. In PACIFIC-R, which tested the real-world application of the regimen, median time to start was actually 52 days, 10 days greater than PACIFIC allowed on trial. Close sequencing of durvalumab may also introduce uncertainty of the etiology of treatment side effects. For those who do develop pneumonitis, it would be difficult to distinguish whether it was the immunotherapy or the CRT that was the culprit. Practically speaking, this could make it difficult for clinicians to decide the best next steps in treatment.

We recognize the potential benefits to immediate durvalumab start after CRT. Standard of care therapy takes patients over 1 year to complete, and immediate start of durvalumab would reduce the total time of treatment, improving a patient's "time toxicity" and allowing them to spend this time on other pursuits (19). Further, an earlier CT scan introduces the possibility of earlier detection of progressive disease, recognizing the limitations on imaging interpretation as above.

Limitations of the DATE trial include its study design of a single-arm study, limited sample size, unique patient demographics, and short follow-up time. We also have concerns regarding the statistical design of the study. The alpha was one sided and was 20%, which is quite high. Increasing the alpha level increases the chance of rejecting the null hypothesis, but it also increases the chance of a type 1 error.

Strengths of this study include that over 70% of participants started durvalumab 1 day after CRT, allowing for a meaningful assessment of immediate durvalumab start, and the study recruited from a large number of centers across Japan, allowing its limited sample size to perhaps be translatable across a larger population of Japanese patients.

Conclusions

The DATE trial investigates whether immediate initiation of durvalumab after CRT can improve survival outcomes, with a tolerable safety profile, for patients with unresectable stage III NSCLC. We found that the interpretation of DATE's results is unfortunately limited by immature data, and its toxicity profile would be prohibitive for many. Ultimately, we feel that this study is hypothesis generating, but additional results are required with a longer follow-up time, and, once safety is established, ultimately a larger randomized trial is needed to answer this important question.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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