The POSEIDON Trial

editorials

The POSEIDON Trial: Will Secondary End Points Change Our Clinical Practice?

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Over the past decade, the bleak therapeutic landscape for treatment-naive patients with advanced non–small-cell lung cancer (NSCLC) without targetable genomic alterations has been reinvigorated by the approval of immune checkpoint inhibitors (ICIs) according to different strategies: either with programmed cell death (ligand) protein 1 (PD-(L)1) inhibition monotherapy for selected patients or combined with platinum-based chemotherapy (CT) with or without CTLA-4 inhibition. Furthermore, dual-immunotherapy strategy (anti–PD-1 and anti-CTLA4) without CT has also been approved as a potential treatment approach in PD-L1 ≥ 1% tumors.[1] However, not all the phase III clinical trials testing a dual-immunotherapy strategy reported a clear benefit in overall survival (OS) from the beginning compared with CT.[2,3] Indeed, in several trials, the ICI strategy (PD-[L]1 with or without CTLA4 inhibition) underperformed compared with the CT alone during the first weeks of treatment, suggesting that a proportion of patients progress rapidly and die without obtaining any meaningful benefit from the ICI strategy. The addition of CT has been proposed as a potential strategy to overcome this scenario. Although it is still unknown whether the effect of CT combined with ICI is additive[4] or synergistic,[5] CT-ICI combinations have become the standard of care in the first-line setting regardless of histological subtype and PD-L1 expression.[1] However, the real benefit of adding dual immunotherapy instead of monotherapy ICI to CT remains unknown. Indeed, questions about selection of the right patient population for dual ICI, the optimal number of CT cycles when combined with ICI, as well as the optimal duration of the ICI strategy need to be answered to balance the potential clinical benefit of prolonged treatment with the downside of a risk of increased toxicity.

In the article that accompanies this editorial, Johnson et al[6] presented the results of the phase III POSEIDON trial, in which 1,013 patients with advanced *EGFR/ALK*-negative NSCLC were randomly assigned to tremelimumab (T, anti-CTLA4) plus durvalumab (D, an anti–PD-L1) and platinum-based CT every 3 weeks for up to four cycles, followed by D (every 4 weeks) until progression and one additional T dose; D plus CT every 3 weeks for up to four cycles, followed by D every 4 weeks until progression or CT every 3 weeks for up to six cycles. Pemetrexed maintenance was allowed for nonsquamous histology in all investigational arms. The primary end points were progression-free survival (PFS) and OS for D plus CT versus CT. Positivity for either primary end point enabled for the key secondary PFS and OS end points (T plus D plus CT *v* CT). Stratification criteria included PD-L1 expression (≥ 50% *v* < 50%), stage (IVA *v* IVB), and histology (squamous *v* nonsquamous). The trial achieved the coprimary PFS benefit with D plus CT versus CT (hazard ratio [HR], 0.74; $P = .0009$; with 1-year PFS rate of 24.4% *v* 13.1%) with a nonsignificant positive trend for improved OS (median OS: 13.3 *v* 11.7 months; HR, 0.86; $P = .076$; with a 2-year OS rate of 29.6% *v* 22.1%). On the basis of the PFS benefit, the secondary end points were formally evaluated. T plus D plus CT compared with CT significantly improved the PFS (HR, 0.72; $P = .0003$; with 1-year PFS rate of 26.6% *v* 13.1%) and the OS (median OS: 14 *v* 11.7 months; HR, 0.77; $P = .003$; with a 2-year OS rate of 33% *v* 22.1%. Fig 1). Benefit was seen across all PD-L1 subgroups, mainly in tumors with PD-L1 ≥ 50%. Treatment-related adverse events (TRAEs) were grade 3-4 in 51.8%, 44.6%, and 44.4% of patients receiving T plus D plus CT, D plus CT, and CT; 15.5%, 14.1%, and 9.9% discontinued at least one study drug because of TRAEs.

Although the PFS coprimary end point of D plus CT versus CT was statistically significant in the POSEIDON trial, the PFS benefit was less robust on the basis of a clinical perspective with only a median gain of 0.7 months compared with CT, and this came with lack of an OS benefit. The lack of OS benefit of D plus CT cannot be explained by a high percentage of patients receiving ICI in a later line of treatment in the CT control arm. Cross-over was not allowed in POSEIDON, and only one third of patients in the CT arm received a subsequent ICI at progression, despite the fact that at least four large randomized clinical trials[7-10] had already reported at the time of POSEIDON enrollment a survival benefit with second-line ICIs. In contrast, other first-line CT-ICI versus CT trials reported statistically significant and clinically meaningful OS benefits for CT-ICI, despite up to 50% of patients in the CT arm had an effective crossover rate to ICI at the time of progression.[11-13] Despite these limitations, T plus D plus CT versus CT was formally tested. However, in the unbridled and rapid approval of ICI in NSCLC,

ASSOCIATED CONTENT

See accompanying article doi: 10.1200/JCO.22.00975

Author affiliations and support information (if applicable) appear at the end of this article.

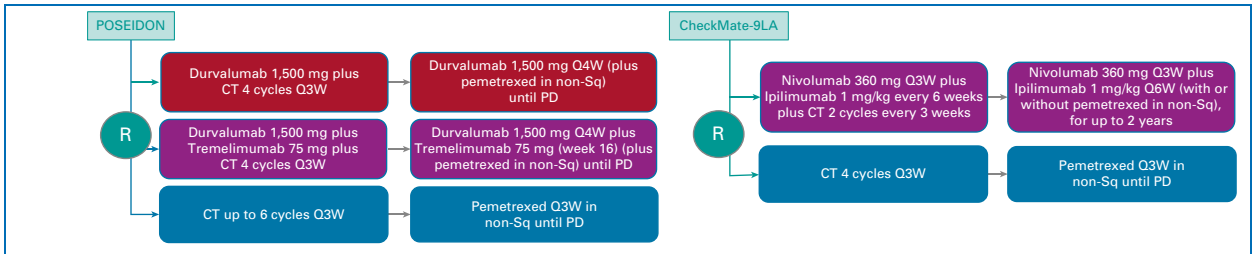
Accepted on August 25, 2022 and published at ascopubs.org/journal/jco on November 3, 2022: DOI https://doi.org/10.1200/JCO.22.01737

THE TAKEAWAY

In the article that accompanies this editorial,[6] the POSEIDON trial demonstrated that dual immunotherapy with durvalumab plus tremelimumab and chemotherapy significantly improved the outcome compared with chemotherapy alone as first-line treatment strategy in advanced non–small-cell lung cancer. POSEIDON could be considered a potential new *me too* strategy in this setting but should not change practice. However, it reinforces that the addition of anticytotoxic T-cell lymphocyte (CTLA)4 extends clinical benefit to programmed death-ligand 1 (PD-L1) < 1% tumors, a hard-to-treat population.

redundant development plans may erode the resources available for innovation. Innovation is one of the motivations for patients to participate in clinical trials and is the only way to explore how to enlarge the number of patients who may obtain benefit of ICI in daily clinical practice.[14] Therefore, will these positive secondary outcomes from POSEIDON actually change our current treatment paradigms, and do we have a meaningful new treatment option available?

As we remain conscious of the limitation of the exercise of cross-trial comparisons, the 1-year PFS rate of 26.6% and the 2-year OS rate of 33% reported in the T plus D plus CT arm from the POSEIDON trial do not seem superior to survival rates achieved with other already available CT plus ICI regimens (1-year PFS rate of approximately 35%, and 2-year OS rate of approximately 40%) with longer follow-up.[11-13] Furthermore, does adding more drugs indeed mean that we treat patients better? Similar to other phase III studies,[15] in the POSEIDON trial, the two experimental arms were not formally compared. However, the 1-year PFS rate (24% *v* 26.6%) and the 2-year OS rate (29.6% *v* 33%) of D plus CT versus T plus D plus CT look similar, but with a higher risk of immune related-AEs with T plus D plus CT (overall 33.6% *v* 19.2%, grade 3-4 in 10.0% *v* 6.9%). Unfortunately, the POSEIDON data do not shed light on the question which subset of patients with advanced NSCLC would really benefit from a more intensive immune strategy in the first-line setting when combined with CT. Currently, only PD-L1 expression and clinical parameters such as histology are accepted tools to select patients for a certain treatment regimen. One third of advanced NSCLC do not harbor PD-L1 expression (PD-L1 < 1%). In this situation, treatment strategies should try to bring T cells into the tumor before blocking PD-L1. In this regard, CTLA4 blockade has



End Point	PFS by BICR (Durvalumab plus CT *v* CT) and OS (Durvalumab plus CT *v* CT)			PFS by BICR and OS	
Arm	**CT**	**Durvalumab plus CT**	**Durvalumab plus Tremelimumab plus CT**	**Nivolumab plus Ipilimumab plus CT**	**CT**
No.	337	338	338	361	358
RR, %	24.4	41.5	38.8	38.0	25-0
DoR, mo	5.1	7.0	9.5	12.4	5.6
PFS, mo	4.8	5.5 (HR, 0.74; *P* = .0009)	6.2 (HR, 0.72; *P* = .0003)	6.4 (HR, 0.70; 95% CI, 0.59 to 0.83)	5.3
1-y PFS, %	13.1	24.4	26.6	32.0	19.0
OS, mo	11.7	13.3 (HR, 0.86; *P* = .0760)	14.0 (HR, 0.77; *P* = .0030)	15.8 (HR, 0.74; 95% CI, 0.62 to 0.87)	11.0
2-y OS, %	22.1	29.6	32.9	38.0	26.0
G3-4 TRAEs	44.4	44.6	51.8	48.0	38.0

FIG 1. Summary of the design and results of phase III POSEIDON and CheckMate9LA trials. BICR, by independent review committee; CT, platinum-based chemotherapy according to histological subtype; DoR, duration of response; G3-4 TRAEs, percentage of grade 3-4 treatment-related adverse events; HR, hazard ratio; Non-Sq, non-squamous; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, once every 3 weeks; Q4W, once every 4 weeks; Q6W, once every 6 weeks; RR, response rate (confirmed).

been shown to induce frequent increases in T-cell infiltration irrespective of tumor responses.[16] In the POSEIDON trial, the addition of anti-CTLA4 to D plus CT extended the clinical benefit to patients with PD-L1–negative tumors (HR for PFS, 0.78 *v* 0.97; and HR for OS, 0.77 *v* 0.99, D plus T plus CT *v* D plus CT in PD-L1–negative, respectively). These findings confirm the use of anti-CTLA4 in PD-L1–negative tumors, as already reported in another phase III trials such as CheckMate 227 (nivolumab-ipilimumab arm) and CheckMate9LA (nivolumab plus ipilimumab plus two cycles of CT) reporting similar long-term survival regardless of the PD-L1 status (5-year OS in PD-L1 $\geq$ 1% *v* $<$ 1%; 24% *v* 19%, for CheckMate 227; and 3-year OS: 28% *v* 25%, respectively, for CheckMate9LA).[2,12] However, in the KEYNOTE407 trial testing pembrolizumab plus CT in squamous NSCLC, the survival benefit of this strategy disappeared in PD-L1 $<$ 1% tumors (HR, 0.79; 95% CI, 0.56 to 1.11).[11]

Regarding the histology, in the CheckMate9LA trial, the magnitude of PFS and OS benefit with the treatment was also similar regardless of the histologic subtype.[12] In contrast, in the POSEIDON trial the PFS and OS benefit of T plus D plus CT appeared more prominent in the subgroup of nonsquamous than squamous. Whether some CT regimens in squamous NSCLC are superior to others in engaging the immune response in combination with immunotherapies is an important area for clinical research as these combinations become established standards of care in NSCLC. Finally, in the POSEIDON trial, with a median follow-up of 35 months for OS, the outcome in the T plus D plus CT arm mirrors the data reported in the phase III CheckMate9LA trial (1-year PFS: 26.6% *v* 32%, and 2-year OS: 33% *v* 38%, respectively. Fig 1).[12] In the POSEIDON trial, 80% of patients received the four cycles of planned induction CT compared with a compliance rate of 93% of two cycles of CT in the CheckMate9LA, suggesting that a shorter treatment duration may improve the compliance rate of CT, without negatively affecting in the outcome and minimizing the side-effects associated with a full course of CT. Both studies reported similar ICI treatment duration; however, dual ICI exposition was more prolonged in the CheckMate9LA trial as only 66% of patients in the T plus D plus CT in POSEIDON received the five doses of T per protocol. It is unclear on the basis of these two trials the optimal duration of dual immunotherapy when combined with CT. It is clinically relevant to ensure equitable access to this strategy as the economic burden of these regiments should not be neglected.

Regardless of the treatment regimen, the majority of patients will not obtain long-term disease control, and predictive biomarkers are urgently needed. The predictive role of blood or tissue tumor mutational burden for dual ICI remains controversial with some trials supporting the predictive value[3] and others not[17-20] while blood tumor mutational burden data for POSEIDON is still awaited. Therefore, other biomarkers to select patients for a certain ICI strategy are urgently needed. Although prospective validation is still needed, radiologic markers[21] and dynamic markers on the basis of circulating tumor DNA regarding the tumor burden,[22] as well as markers on the basis of artificial intelligence[23] may help to individualize the immune oncology strategy in the coming future. This is of relevance both for patients, to reduce the number of patients exposed to dual ICI with a resulting potential risk of increased percentage of TRAEs and for the community to reduce the increased financial toxicity that comes with adding another ICI to a CT-ICI treatment regimen.[24]

In conclusion, the POSEIDON trial endorses that dual ICI plus CT is safe and feasible in the first-line setting for patients with advanced NSCLC without a targetable oncogenic driver and suggests that the addition of anti-CTLA4 extends clinical benefit to PD-L1 $<$ 1% tumors, a hard-to-treat population. Nevertheless, the role of dual immunotherapy versus monotherapy when combined with CT or the optimal population for a more intensive regimen again is not answered in this trial. Today, we have probably reached a plateau with CT plus ICI regimens, and just adding new drugs in the current available strategies in an unselected population may not be the most promising avenue to pursue (eg, CANOPY-1 trial, ClinicalTrials.gov identifier: NCT03631199). Despite progress made since the introduction of immunotherapy to the clinic, given the current redundancy of ICI strategies in advanced NSCLC, we strongly need innovation in the coming clinical trials. The development of treatment guiding markers should not be part of retrospective, explorative, and frequently noninformative analyses. It should be the first obligatory step to identify populations who might benefit from customized combinations. Besides a careful use of economic resources, this also would be beneficial for patients in terms of avoiding unnecessary treatment burden and toxicities. This innovation must aim to answer relevant clinical questions and to keep patients' confidence in clinical trials. This is the only way to again shift the prognosis for these patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.01737.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No other potential conflicts of interest were reported.