BRIEF REPORT

Role of Consolidation Durvalumab in Patients With *EGFR*- and *HER2*-Mutant Unresectable Stage III NSCLC

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ABSTRACT

Introduction: Despite the recent advance of consolidation durvalumab in the treatment of unresectable stage III NSCLC, not every patient benefits from durvalumab and the predictive markers of response have been difficult to identify.

Methods: We performed a retrospective analysis of patients with unresectable stage III NSCLC treated with consolidation durvalumab after definitive chemoradiation from January 2018 to March 2020.

Results: A total of 36 patients with unresectable stage III NSCLC were treated with consolidation durvalumab. Of these patients, 14 had tumor mutations in the ERBB family including 11 *EGFR* and 3 *ERBB2*. The *ERBB2/EGFR* tumor mutation cohort was more likely to be nonsmokers; otherwise, the two groups were similar in age, sex, programmed death-ligand 1 expression, and type of previous chemotherapy regimen. Patients in the *ERBB2/EGFR* cohort had a significantly shorter disease-free survival compared with the *EGFR* or *ERBB2* wild-type cohort (7.5 mo versus not reached, $p = 0.04$).

Conclusions: Consolidation durvalumab seems to be less efficacious in patients with *ERBB2/EGFR*-mutant tumors. Future work should seek to evaluate this in the prospective setting and provide insight into the optimal treatment of *ERBB2/EGFR*-mutant stage III NSCLC.

Keywords: ERBB2; *EGFR*; Stage III; PACIFIC; Durvalumab

Introduction

Despite the aggressive upfront treatment with definitive chemoradiation for patients with stage III NSCLC, the outcomes have historically been poor with high rates of recurrent disease and estimates of median overall survival of 17 to 29 months in several studies.[1,2] The PACIFIC trial, published in 2018, realized considerable improvements in both progression-free survival and overall survival for patients with unresectable stage III disease, with the addition of up to 12 months of consolidation durvalumab after chemoradiation.[3] Despite the subsequent paradigm shift in the treatment

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of stage III NSCLC, it is evident from clinical practice that not all patients benefit from this regimen.

Driver mutations can serve as biomarkers of response and are often used in the metastatic setting to personalize treatment. The ERBB class of tyrosine kinase receptors (TKRs), which are critical to cell growth and survival,[4] is frequently mutated in NSCLC and has significant treatment and prognostic implications.[5] This family of TKR includes the EGFR (also known as ERBB1/HER1) and ERBB2/HER2, both of which are important drivers in NSCLC. Moreover, these TKRs seem to act collectively to drive tumor growth and modulate response to therapy.[5]

In the stage IV setting, there are compelling data that many patients with *EGFR* tumor mutations have suboptimal response to immunotherapy[6] and the backbones of treatment have historically been targeted therapy and cytotoxic chemotherapy. *ERBB2* tumor mutations are much less common in NSCLC (approximately 4% of NSCLC), but similarly treatment is focused primarily on cytotoxic chemotherapy and targeted agents such as HER2 monoclonal antibodies or tyrosine kinase inhibitors (TKIs).[7,8] The patients with *EGFR* tumor mutations comprised a small subset (6%) of patients treated in the PACIFIC trial (*ERBB2* mutations were not specifically delineated), and although the small numbers have limited a robust statistical analysis, the number of patients with *EGFR*-mutant tumors in the durvalumab group who died (24 of 43, 55.8%) at the 4-year follow-up has raised questions on the efficacy of durvalumab in this population.[9] In this study, we sought to describe our institution's experience with *EGFR* or *ERBB2*-mutant stage III NSCLC treated with concurrent chemoradiation followed by consolidation durvalumab.

Materials and Methods

Patients who were evaluated at the Stanford Cancer Institute and who received concurrent chemoradiation followed by consolidation durvalumab between January 1, 2018, and March 1, 2020, were identified. Clinical, demographic, and molecular data were abstracted from each patient's medical record. Patients had their tumor specimens analyzed using the Stanford Solid Tumor Actionable Mutation Panel,[8] FoundationOne, or an abbreviated panel with their local institution. Programmed death-ligand 1 (PD-L1) expression was evaluated using the PD-L1 antibody SP263 (Roche, Basel, Switzerland) on the Ventana Ultra platform (Roche) and validated against the PharmDx 22C3 PD-L1 assay (Agilent, Santa Clara, CA). The study was conducted in accordance with the ethical principles set forward in the Declaration of Helsinki and under the consent of a molecular analysis study approved by the Stanford University Institutional Review Board.

Results

A total of 36 patients with locally advanced NSCLC met the inclusion criteria for the study. There were 11 patients with pathogenic *EGFR* mutations (N = 4 exon 19 deletion, N = 1 exon 20 insertion, N = 6 L858R) and three patients with *ERBB2* exon 20 insertion mutations (Supplementary Fig. 1). The two groups were similar in terms of key tumor and clinical characteristics with the exception of smoking status (Table 1). The average length of follow-up was 14.5 months.

Disease-free survival (DFS) was compared between the two groups. Patients with tumor mutations in *ERBB2/EGFR* had significantly shorter DFS on durvalumab compared with those with *ERBB2/EGFR* wild-type tumors (median DFS = 7.5 mo versus not reached [NR], hazard ratio = 2.8, 95% confidence interval: 1.02–7.67, $p = 0.04$) (Fig. 1). At the time of analysis, the overall survival data were not mature.

Table 1. Patient and Tumor Characteristics

Characteristics	*ERBB2/EGFR* Mutations (N = 14) (%)	*ERBB2/EGFR* Wild Type (N = 22) (%)
Age (average, y)	64	66
Sex, female	8 (57)	12 (55)
Race		
White	6 (43)	16 (73)
Asian	8 (57)	6 (27)
Smoking		
Never	13 (93)	6 (27)
Former	1 (7)	16 (73)
Pathologic diagnosis		
Adenocarcinoma	12 (86)	17 (77)
Squamous	0 (0)	4 (18)
Adenosquamous	2 (14)	0 (0)
Neuroendocrine	0 (0)	1 (5)
Stage		
IIIA	4 (29)	12 (55)
IIIB	7 (50)	8 (36)
IIIC	3 (21)	2 (9)
PD-L1 status		
>25%	7 (50)	8 (36)
1%-25%	2 (14)	6 (27)
<1%	5 (36)	6 (27)
Not available	0 (0)	2 (10)
Chemotherapy regimen		
Cisplatin/pemetrexed	5 (36)	8 (36)
Carboplatin/pemetrexed	5 (36)	3 (14)
Carboplatin/gemcitabine	0 (0) 2 (14)	1 (2) 7 (32)
Carboplatin/taxol	2 (14)	3 (14)
Cisplatin/etoposide	0 (0)	1 (2)
Carboplatin/etoposide		
Time from completion of CRT to start of durvalumab, d	32	21

CRT, chemoradiotherapy; PD-L1, programmed death-ligand 1.

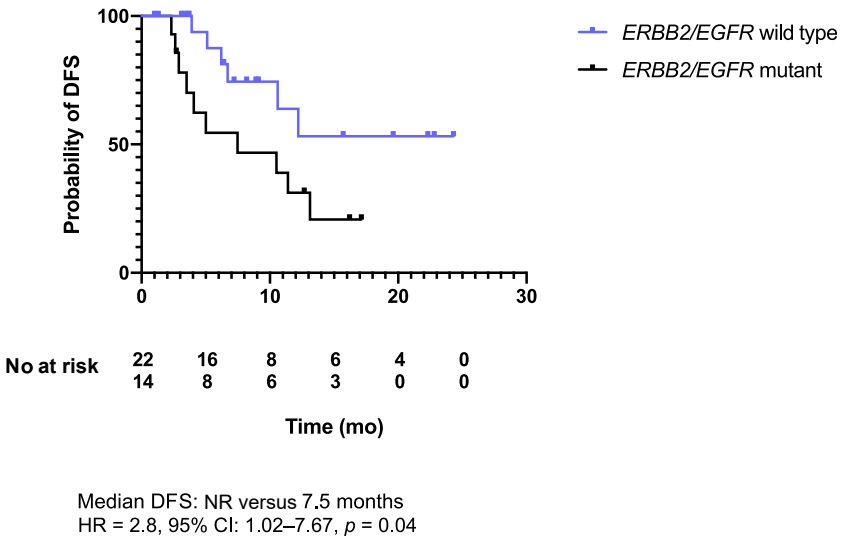

Figure 1. DFS by *ERBB2/EGFR* mutation status. CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NR, not reached.

Next, the impact of PD-L1 status on the treatment outcome was evaluated. Two patients in the *ERBB2/EGFR* wild-type cohort did not have available PD-L1 testing and were excluded from the analysis. Patients were evaluated on the basis of PD-L1 cutoffs of 1% and 25% as was done in the exploratory analysis of the PACIFIC trial[10] (Supplementary Table 1). There was a lower DFS in the patients with PD-L1 less than 1% compared with those with PD-L1 greater than 1% (6.2 mo versus NR, $p = 0.006$) (Supplementary Fig. 2*A* and *B*). When separated by mutation status, this remained significant in the *ERBB2/EGFR* wild-type cohort with median DFS of 6.5 months for the patients with PD-L1 less than 1% versus NR for those with PD-L1 greater than 1%. However, there did not seem to be a difference in DFS between PD-L1 less than 1% and greater than 1% in the *ERBB2/EGFR* arm (Fig. 2*A* and *B*).

Finally, the tolerability of consolidation durvalumab was evaluated. A total of 13 of 22 patients (59%) in the *ERBB2/EGFR* wild-type arm and 6 of 14 patients (43%) in the *ERBB2/EGFR*-mutant arm experienced immune-related adverse events while on durvalumab. Immune-related adverse events led to treatment discontinuation in six patients in the *ERBB2/EGFR* wild-type arm and in four patients in the *ERBB2/EGFR*-mutant arm.

Discussion

In our retrospective, single-institution series, patients with mutations in the ERBB family had an inferior response to treatment with consolidation durvalumab compared with those without these key driver mutations. Furthermore, although the two studies cannot be directly compared, DFS in the *EGFR* or *ERBB2*-mutant cohort in our study (7.5 mo) was more numerically similar to that in the placebo arm of the PACIFIC study (5.6 mo) compared with the durvalumab group (16.8 mo).[3] Moreover, although the field of thoracic oncology in the United States has moved to prescribe consolidation durvalumab for immunotherapy-eligible patients with stage III NSCLC, these data suggest that not all patients benefit equally from this approach.

This study adds to the growing body of evidence, largely from trials in the metastatic setting,[6] that patients with tumor mutations in the ERBB family of TKRs on average achieve less benefit from immunotherapy compared with those with *ERBB2/EGFR* wild type. For example, in CheckMate-057, patients with advanced *EGFR*-mutant tumors (N = 44) had shorter progression-free survival on nivolumab compared with docetaxel.[11] Similarly, in KEYNOTE-010, pembrolizumab failed to have a benefit over docetaxel in the small subset of patients with *EGFR*-mutant tumors.[12] Although there are less data on the use of immune checkpoint inhibitors (ICIs) in patients with *ERBB2*-mutant tumors, there are case reports of similarly poor response to single-agent ICIs.[8]

The reason for the suboptimal response to immunotherapy in *EGFR*-mutant tumors and likely other similar driver mutation subsets such as *ERBB2* remains unknown. Similar to previous work,[13] we found high rates of PD-L1 expression in the *EGFR* cohort, but this did not translate to improved response to ICIs. One theory is that tumors with up-regulation of the growth receptor pathway develop tumor-immune evasion that is independent of the programmed cell death protein-1/PD-L1 mechanism, and therefore, these tumors have less reliance on the pathway that is exploited by ICIs targeting this axis.[6] Other studies have suggested that *EGFR*-

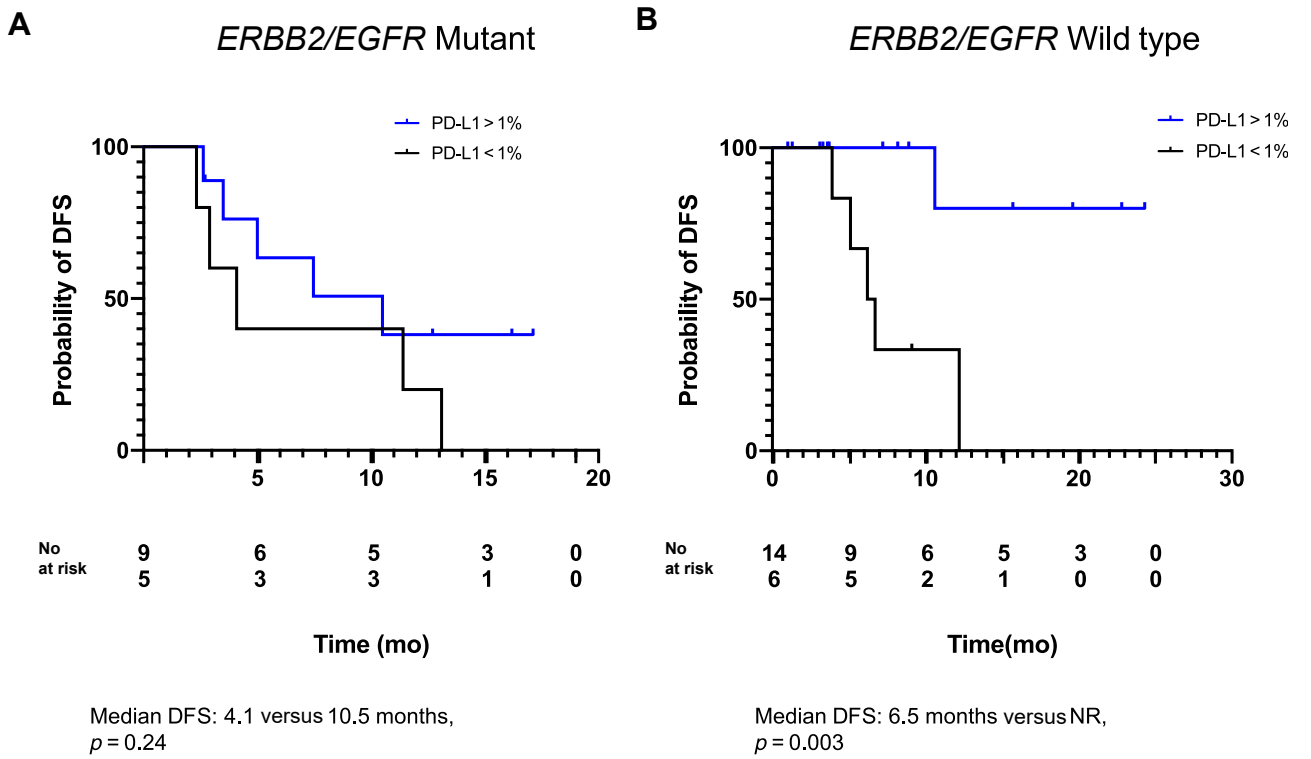

Figure 2. DFS of (*A*) *ERBB2/EGFR*-mutant cohort by PD-L1 less than 1% versus PD-L1 greater than 1% and (*B*) *ERBB2/EGFR* wild-type cohort by PD-L1 less than 1% versus PD-L1 greater than 1%. DFS, disease-free survival; NR, not reached; PD-L1, programmed death-ligand 1.

mutant tumors are a type of "immune desert" given the low prevalence of tumor-infiltrating lymphocytes and mutation burden, which makes them uniquely immune to ICIs.[14]

Although immune checkpoint inhibition may not be the optimal approach to achieve cure in patients with *ERBB2/EGFR*-mutated, unresectable stage III NSCLC, the ideal treatment regimen remains less clear. Previous trials on the role of consolidation chemotherapy after definitive chemoradiation in an unselected population failed to reveal an overall survival benefit,[15] but this has not been evaluated specifically in *ERBB2/EGFR*-mutant tumors and may be a potential approach. In the adjuvant setting, there are ongoing studies evaluating the role of TKIs either alone or after adjuvant chemotherapy for patients with early-stage, resectable *EGFR*-mutant NSCLC. To date, these studies have revealed an improvement in DFS,[16] but this has not yet translated to an overall survival benefit. Whether TKI therapy after definitive chemoradiation provides benefit to patients with *ERBB2/EGFR*-mutant tumors remains to be seen.

Limitations of this study include its retrospective nature and small sample size. In addition, consolidation durvalumab is a new adoption in the standard-of-care treatment for stage III NSCLC, and as a result, length of follow-up is relatively short. Although these limitations make it difficult to draw definitive conclusions from the data, this study nevertheless is critical in that it provides a framework for future investigation.

Although these data suggest that consolidation durvalumab after definitive chemoradiation may not be as efficacious in patients with *ERBB2/EGFR*-mutant tumors, future work in the prospective setting is needed to validate these findings. Furthermore, additional studies are needed to provide guidance on whether an alternative treatment regimen, such as consolidation chemotherapy or TKI, may be more effective in patients with unresectable *ERBB2/EGFR*-mutant, stage III NSCLC.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at XXX.

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