Abstract 6796

Comparison of Outcomes Between Responders and Nonresponders to First-Line *nab*-Paclitaxel/Carboplatin and Paclitaxel/Carboplatin Doublet Chemotherapy in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC)

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INTRODUCTION

- NSCLC is the leading cause of cancer deaths worldwide, and 70% of patients present at an advanced stage at the time of diagnosis[1]
- Platinum-based doublet chemotherapy, ie, carboplatin or cisplatin in combination with a third-generation cytotoxic such as paclitaxel, docetaxel, *nab*-paclitaxel, gemcitabine, vinorelbine, or pemetrexed is recommended as first-line therapy for advanced NSCLC[2,3]
- A phase III, multicenter, double-blind, randomized clinical trial has shown that albumin-bound paclitaxel plus carboplatin (*nab*-PC) significantly improved the objective overall response (ie, confirmed complete and/or partial response based on blinded, centralized, independent radiologic analysis[4]) rate (ORR) vs solvent-based paclitaxel plus carboplatin (sb-PC; 33% vs 25%; $P = 0.005$) as first-line therapy in locally advanced or metastatic NSCLC[4]
- Previous studies have reported mixed results of associations between treatment response and toxicity or health-related quality of life in NSCLC[5-8] The extent to which treatment response translates into quality-adjusted survival time remains unclear
- The quality-adjusted time without symptoms or toxicity (Q-TWiST) method has been used in oncology to comprehensively assess the risk and benefit of cancer treatment by incorporating toxicity, disease-free progression (PFS), and overall survival (OS) into a single measurement (ie, quality-adjusted survival)[9]

OBJECTIVE

- To understand the impact of achieving response on quality-adjusted survival in the context of the aforementioned phase III clinical trial

METHODS

Data Source

- Data from the clinical trial were used[4]:
  - Patients were randomly assigned (1:1) to:
    - ***nab*-PC**: weekly *nab*-paclitaxel 100 mg/m^2 plus every-3-week carboplatin at area under the curve (AUC) 6
    - **sb-PC**: sb-paclitaxel 200 mg/m^2 plus carboplatin AUC 6 both given every 3 weeks
  - Eligibility: had Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 1, a life expectancy of > 12 weeks, no radiotherapy within 4 weeks, and no preexisting grade ≥ 2 peripheral neuropathy at baseline
  - Tumor response was confirmed based on blinded, centralized, independent radiologic analysis. Adverse events were graded 1 through 5 per National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 3.0

Statistical Analyses

- Patients with and without complete/partial response were compared using the Q-TWiST method[9]
  - OS up to 24 months of follow-up was partitioned into time periods of 3 distinct health states: with grade ≥ 3 toxicity (TOX), without symptoms of progression or toxicity (TWiST), and relapse time (REL)
  - Using Kaplan-Meier method, the mean duration of TWiST can be calculated as the difference in area under PFS and TOX curves, and the mean duration of REL as the difference in area under OS and PFS curves
  - Mean Q-TWiST was calculated by taking the sum of the product of the time spent in each state by its respective utility

    $$\text{Q-TWiST} = U_{\text{TWiST}} \times \text{TWiST} + U_{\text{TOX}} \times \text{TOX} + U_{\text{REL}} \times \text{REL}$$
  - Major assumptions:
    - Progression from TOX/TWiST to REL then death, allowing for skipping state
    - Utility associated with each health state does not vary over time
    - Same U_{TWiST} regardless of type/severity of grade ≥ 3 adverse events (AEs)
    - AE duration was truncated when disease progressed
    - All TOX time was grouped and modeled together at the beginning of therapy
  - Nonparametric bootstrap 95% CIs were also derived
  - In the base case, the utilities were: $U_{\text{TWiST}} = 1$, $U_{\text{TOX}} = 0.5$, $U_{\text{REL}} = 0.5$
  - In sensitivity/threshold analyses, U_{TOX} and U_{REL} varied from 0 to 1
- Stratified analyses were conducted to determine the impact of potential confounders

RESULTS

- 1052 patients (intent-to-treat population, ITT) staged IIIB to IV were included in the analysis, with a median age of 60 years (Table 1)
- Comparing the baseline characteristics of responder (n = 302) vs nonresponders (n = 750), regardless of study treatment (Table 1):
  - Responder status was not significantly associated with demographics, smoking status, or baseline performance status
  - However, responders were more likely to be of squamous cell histology ($P = 0.01$) and stage IIIB NSCLC at baseline ($P = 0.006$)
- In both *nab*-PC and sb-PC arms, responders received 30% - 40% more chemotherapy cycles and higher accumulated doses, but with lower paclitaxel and carboplatin dosage intensity ($P < 0.05$)

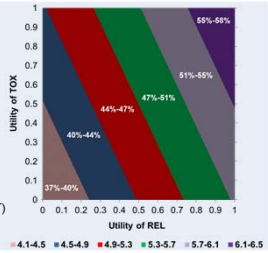
Table 1. Demographic and clinical characteristics in responders vs nonresponders

Characteristics	Responders (n = 302)	Nonresponders (n = 750)	*P* Value[a]
Age, mean ± SD, years	60.4 ± 8.4	59.3 ± 9.7	0.07
Male	225 (74.5)	564 (75.2)	0.81
Race, n (%)			0.70
Caucasian	239 (28.2)	610 (71.9)	
Asian	50 (16.6)	109 (14.5)	
Other	13 (4.3)	31 (4.1)	
Smoking status, n (%)[b]			0.49
Never smoked	87 (28.8)	194 (26.1)	
Smoked and quit smoking	84 (27.8)	232 (31.2)	
Smoked and currently smokes	131 (43.4)	317 (42.7)	
ECOG performance status, n (%)			0.10[c]
0 (Fully active)	81 (26.8)	165 (22.0)	
1 (Restrictive but ambulatory)	221 (73.2)	580 (77.3)	
2 (Ambulatory but unable to work)	0	5 (0.7)	
Stage at randomization, n (%)			**0.006**
IIIb	79 (26.2)	139 (18.5)	
IV	223 (73.8)	611 (81.5)	
Histology of primary diagnosis, n (%)			**0.010**
Squamous cell carcinoma	148 (49.0)	302 (40.3)	
Nonsquamous cell carcinoma	154 (51.0)	448 (59.7)	

[a]Based on *t* tests (for continuous variables) and chi-square or Fisher exact tests (for categorical variables).
[b]Few missing values. [c]Using Fisher exact test.

- **Compared with nonresponders, responders experienced significantly:**
  - **Better OS (median 19.8 vs 9.2 months, $P < 0.001$)**
  - **Better PFS (median 9.6 vs 4.4 months, $P < 0.001$)**
  - **Longer Q-TWiST (mean 13.8 vs 8.5 months; 95% CI of difference: 4.4 - 6.1)**
  - **Longer TWiST (mean 9.8 vs 5.7 months; 95% CI of difference: 3.1 - 5.1)**
  - **Longer REL (mean 6.6 vs 5.0 months; 95% CI of difference: 0.5 - 2.8)**
  - **Longer TOX (mean 1.3 vs 0.5 months; 95% CI of difference: 0.5 - 1.0)**

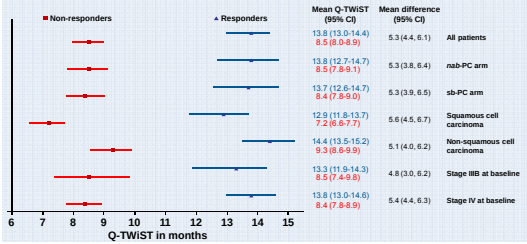
Figure 1. Threshold utility analysis: absolute and relative differences in Q-TWiST between responders and nonresponders across the range of U_{TOX} and U_{REL}



Note:
The percentage in the panel is the relative gain of Q-TWiST in responder vs nonresponders, which was calculated as (difference in Q-TWiST) /(mean OS of nonresponders)

- The longer Q-TWiST experienced by responders ranged from 4.1 - 6.5 months (relative gain in Q-TWiST, 37% - 58%) in threshold utility analysis and this benefit remained statistically significant across all TOX and REL utilities combinations (Fig 1)
- Similar and pronounced benefits in responders were observed in patients stratified by treatment arms, histology, and disease stage at baseline, with Q-TWiST gain ranging from 4.8 - 5.6 months (Fig 2)

Figure 2. Q-TWiST in responders and nonresponders, ITT and subgroups



CONCLUSIONS

- In this trial, *nab*-PC significantly improved the ORR vs sb-PC (33% vs 25%; $P = 0.005$) as first-line therapy in locally advanced or metastatic NSCLC
- Response was associated with statistically significantly more cycles and higher accumulated doses but lower dosage intensity
- Response was also significantly associated with better survival (PFS and OS) and Q-TWIST outcomes (longer Q-TWiST, TWiST, and REL) but longer TOX
- The Q-TWiST provides a comprehensive assessment of the benefit of response into quality-adjusted survival. Therefore, treatment response can be considered an important surrogate for the assessment of treatment outcomes in patients with NSCLC

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