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Surrogate endpoints for overall survival in lung cancer patients treated with PD-1/PD-L1 blockade

Anti PD-1/PD-L1 antibodies are becoming key therapies in the treatment for advanced non-small-cell lung cancer (NSCLC). Surrogate endpoints for overall survival (OS) such as tumor response and progression-free survival (PFS) are useful to detect drug efficacy earlier, but they have not been fully investigated in advanced NSCLC patients treated with anti PD-1/PD-L1 antibodies. We are reporting results from the following: (A) a systematic review of the reported prospective clinical trials and, (B) a retrospective analysis of data at the Ohio State University.

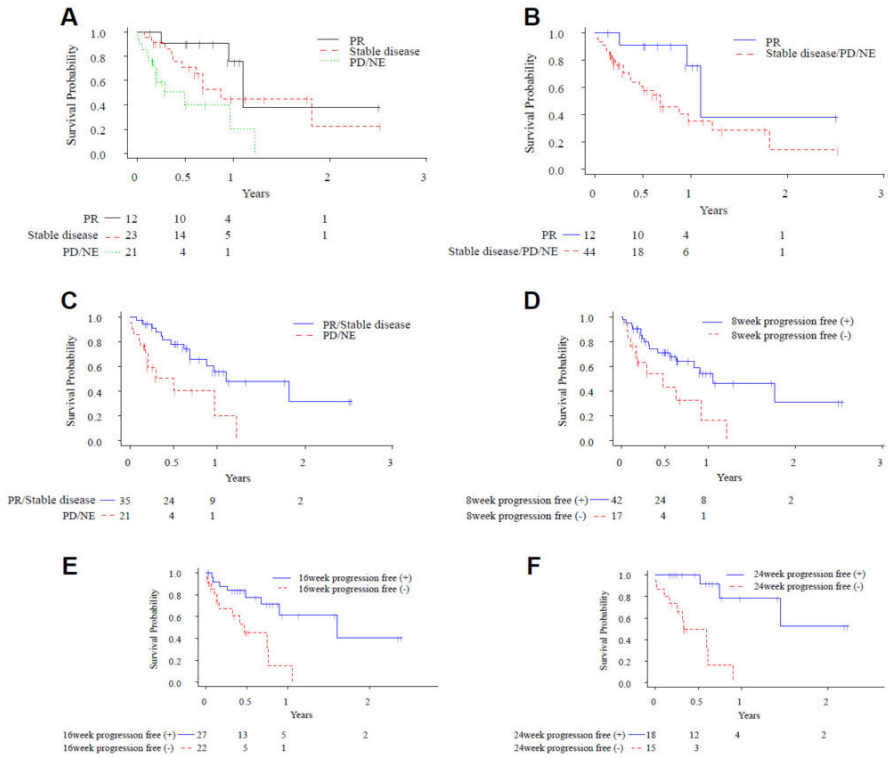

Fig. 1. (A)–(C) Kaplan–Meier curves of overall survival according to tumor response. (D) Kaplan-Meier curves of overall survival in patients who achieved and did not achieve 8-week progression-free status. (E) Kaplan–Meier curves of overall survival in patients who did and did not achieve 16-week progression-free status. (F) Kaplan–Meier curves of overall survival in patients who achieved and did not achieve 24-week progression-free status.

(A) Data for response rate (RR), PFS and OS were extracted from 12 arms in 10 reported anti PD-1/PD-L1 antibody clinical trials and the correlation among them was investigated. The disease control rate (DCR) could not be extracted in most of these studies. (B) OS was compared according to tumor response on 5- to 9-week computed tomography scans and status of being progression-free at 8, 16, and 24 weeks by landmark analysis in patients with advanced NSCLC treated with anti–PD-1/PD-L1 antibodies by log-rank test and

cox proportional hazard model. Data was available for 71 advanced NSCLC patients treated with anti PD-1/PD-L1 antibodies (nivolumab, atezolizumab and durvalumab) between 2013 and 2015.

(A) Moderate correlations between median OS and median PFS (p= 0.120, r= 0.473) and between median OS and response rate (p= 0.141, r= 0.452) were identified using the Spearman correlation coefficient, although these correlations were not statistically significant. (B) Patients had median age 65 years (39–86); male/female 54%/46%; PS 0-1/2- 85%/15%; Current/former smoker 89%; Histology ad/sq/others 49%/41%/10%; Stage IIIA/IIIB/IV 1%/4%/94%; Prior chemotherapy 0/1/2- 27%/35%/38%. Responses included 19 partial response (PR), 19 stable disease (SD), 25 progressive disease (PD) and 8 not evaluable (NE). The median follow-up time was 301 days. The median PFS and the median OS were 55 days and 277.5 days, respectively. While response (PR versus SD/PD/NE) didn't significantly predict OS (Cox proportional hazards model, PR versus SD/PD/NE, p=0.060, HR=2.84), disease control (PR/SD versus PD/NE), and progression-free status at 8, 16, and 24 weeks significantly predicted OS (Cox proportional hazards model, PR/SD versus PD/NE, p=0.010, HR=3.04; 8-week progression-free yes versus no, p=0.018, HR=2.68; 16-week progression-free yes versus no, p =0.004, HR=4.01; and 24-week progression-free yes versus no, p<0.001, HR=12.73).

Variable	*p* Value	Hazard Ratio	95% CI
Tumor response at 5-9 wk CT scan			
PR vs. stable disease/PD/NE	0.060	2.84	0.96-12.11
Tumor response at 5-9 wk CT scan			
PR/stable disease vs. PD/NE	0.010	3.04	1.31-6.97
8-wk progression-free			
yes vs. no	0.018	2.68	1.19-5.84
16-wk progression-free			
yes vs. no	0.004	4.01	1.57-11.04
24-wk progression-free			
yes vs. no	<0.001	12.73	3.05-88.36

CI, confidence interval; CT, computed tomography; PR, partial response; PD, progressive disease; NE, not evaluable.

Fig. 2. Results of Multivariate Landmark Analyses.

Both disease control (PR+SD) and landmark progression-free survival were correlated with OS, with the longer interval landmark PFS being the best predictor of survival in patients with NSCLC treated with anti–PD-1/PD-L1 antibodies.

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