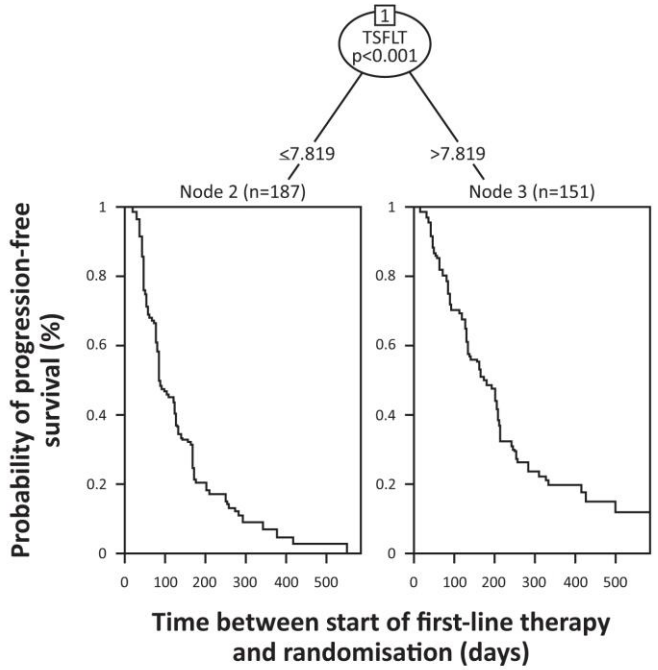
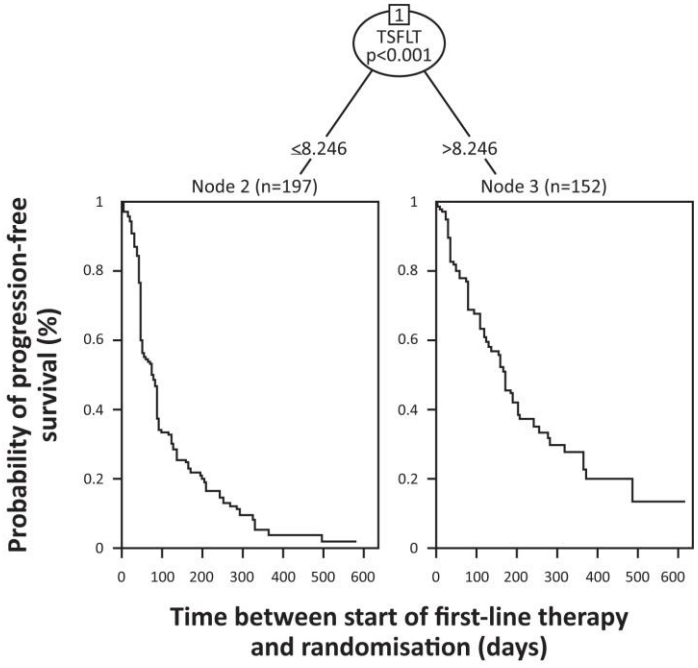
SUPPLEMENTARY MATERIAL

Supplementary Figure 1. Recursive partitioning using PFS data in patients with advanced NSCLC with non-squamous histology treated in the placebo–pemetrexed arm of LUME-Lung 2. (A) Investigator-assessed PFS[a] and (B) centrally assessed PFS.[b]

(A)



(B)

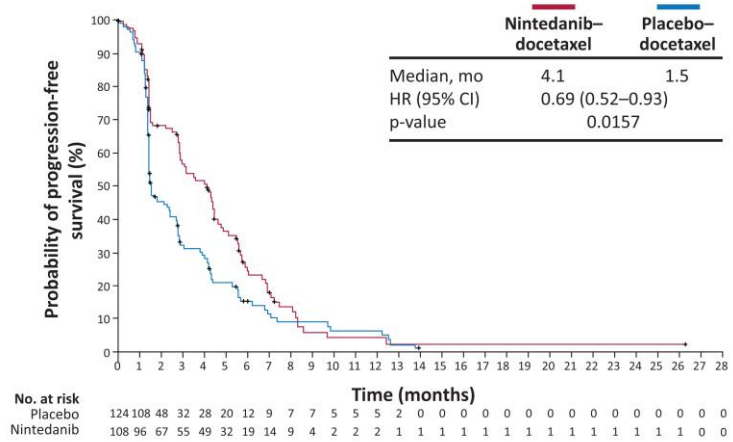


NSCLC, non-small cell lung cancer; PFS, progression-free survival; TSFLT, time since start of first-line therapy.
[a]Futility follow-up (cut-off: 14 June 2011).
[b]Primary analysis (9 July 2012; cut-off: 18 June 2011).

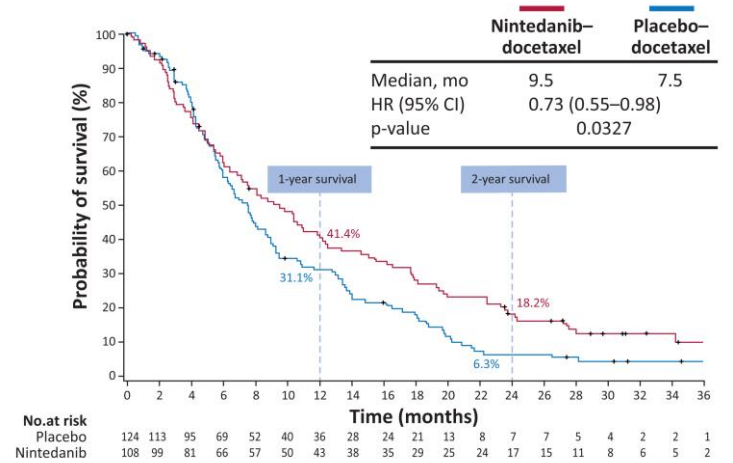
Supplementary Figure 2.

Kaplan–Meier analysis of patients with advanced NSCLC of adenocarcinoma histology treated in LUME-Lung 1. (A) PFS and (B) OS in patients with time since start of first-line therapy <6 months, and (C) OS in patients with disease progression as best response to first-line therapy.

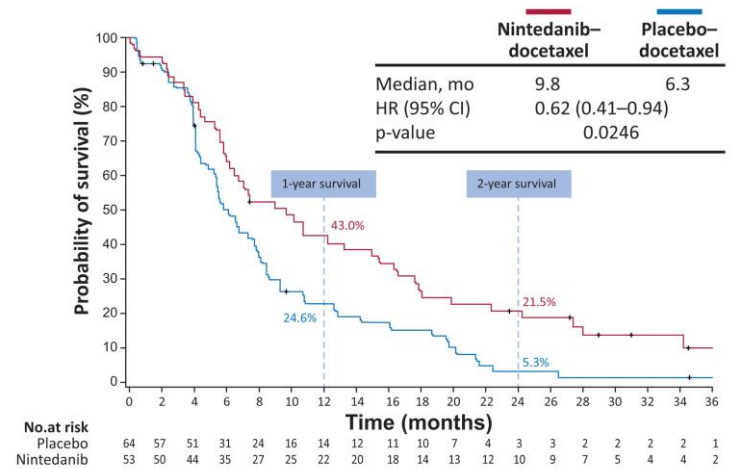
(A)



(B)



(C)



CI, confidence interval; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

Supplementary Appendix

Methods for Identification of prognostic variables

Recursive partitioning tree approach

Recursive partitioning is a nonparametric multivariable regression analysis. During this step-by-step process, a decision tree is built by splitting (or not splitting) a node into daughter nodes, based on prespecified criteria. The optimal binary split point is reached when the best fit to these prespecified criteria is achieved. The recursive partitioning algorithm used in this analysis simultaneously tested all the potentially prognostic variables against the global null hypothesis of independence between input variables (i.e. the potentially prognostic variables) and outcome (i.e. progression-free survival). The stop criterion was based on a multiplicity-adjusted p-value (Bonferroni test) in the first step of the algorithm. Recursive partitioning identified the optimal binary split when the multiplicity-adjusted significance level was <0.05. The minimum number of observations per node was ≥ 150 in order to prevent splits into subgroups that were too small in size to support valid conclusions.

The recursive partitioning approach developed by Hothorn et al., which is implemented in the R package 'party', was used to search for and characterise prognostic variables (Hothorn et al. 2006, Hothorn et al. 2012). The partitioning algorithm (implemented in the tree of the package 'party') works as follows:

- In step 1 of the algorithm, the global null hypothesis of independence between any of the input covariates and the outcome variable is tested. The algorithm is stopped if this hypothesis cannot be rejected at a prespecified alpha level. Otherwise, the input covariate with the strongest association with the outcome variable is selected
- In step 2 of the algorithm, the optimal binary split in the selected covariate is determined
- Steps 1 and 2 are then recursively repeated.

The implementation of both steps utilises a unified framework for conditional inference, or permutation tests, as developed by Strasser and Weber (1999).

References

Hothorn T, Hornik K, Zeileis A. Unbiased recursive partitioning: a conditional inference framework. *J Comput Graph Stat* 2006;15:651–74.

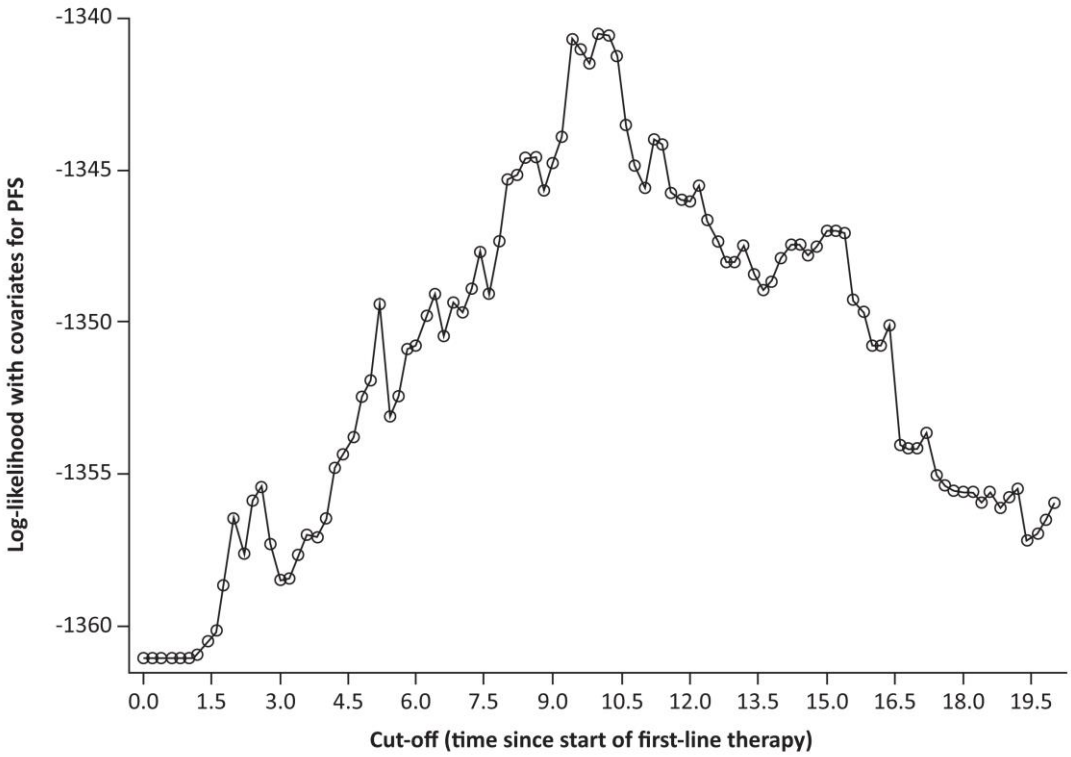
Hothorn T, Hornik K, Strobl C, Zeileis A. Package 'party': a laboratory for recursive partytioning (April 26, 2012, version: 1.0-2). Available at: https://cran.r-project.org/src/contrib/Archive/party.

Confirmation of cut-off point for time since start of first-line therapy

To perform confirmatory analysis of the cut-off point for time since start of first-line therapy identified from the recursive partitioning approach and interaction hazard ratio analysis, the cut-point method (Center for Devices and Radiological Health, 2012 and Jiang et al 2007) was applied to primary endpoint progression-free survival (PFS; central review) data from LUME-Lung 1.

The partial log likelihood as a function of cut-offs for time since start of first-line therapy for the primary endpoint PFS by central review in patients with adenocarcinoma in LUME-Lung 1 reached a maximum at approximately 9 months (see figure).

FIGURE A1. Results of the cut-point model for PFS (central review) for the patients with adenocarcinoma in LUME-Lung 1.



PFS, progression-free survival.

References

Center for Devices and Radiological Health, U.S. Department of Health and Human Services FaDA, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for industry: enrichment strategies for clinical trials to support approval of human drugs and biological products (Draft guidance – This guidance document is being distributed for comment purposes only), December 2012. Available at: http://wwwfdagov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181pdf.

Jiang W, Freidlin B, Simon R. Marker-adaptive threshold design: a procedure for evaluating treatment with possible marker-defined subset effect. J Natl Cancer Inst 2007;99:1036–43.