TRIDENT

SOPHiA GENETICS™

Multimodal machine learning reanalysis of the POSEIDON trial reveals metastatic NSCLC patients most likely to benefit from adding tremelimumab to durvalumab and chemotherapy

Skoulidis F, et al. Clin Cancer Res. 2026. doi: 10.1158/1078-0432.CCR-25-3729

KEY OUTCOMES

A multimodal machine learning (ML) model combining clinical, genomic, and radiomics data from the POSEIDON phase III randomized controlled trial (RCT) identified a subset of patients with metastatic non-small cell lung cancer (mNSCLC) who derive significantly greater overall survival (OS) benefit from adding tremelimumab (T) to first-line (1L) durvalumab (D) and chemotherapy (CT).

A genomic signature (*EGFR, FGFR3, CDKN2A, KRAS, STK11* mutation status) identified patients with non-squamous NSCLC most likely to achieve greater OS benefit.

BACKGROUND

Immunotherapy has transformed care for NSCLC patients, but not all patients benefit equally

Phase 3 POSEIDON trial showed T + D + CT significantly improved OS vs. CT alone in 1L mNSCLC

A post-hoc analysis suggested OS benefit of T addition to D + CT in non-squamous disease with *STK11*, *KEAP1*, and *KRAS* mutations

OBJECTIVE

Develop a ML multimodal predictive model to identify patients who may receive greater OS benefit from the addition of T to D and CT.

METHODS & APPROACH

Retrospective analysis of the POSEIDON trial data

Data Selection

DATASET

1'013 patients randomly assigned in POSEIDON (Data cut-off: 12 March 2021) → 974 patients studied in TRIDENT

T + D + CT arm: 323 assigned to T + D + CT → 323 clinical data available (NSQ n=206; SQ n=117) → 308 radiomics data available (NSQ n=196; SQ n=112); 266 genomic data available (NSQ n=169; SQ n=97) → 254 clinical, genomic and radiomics data available (NSQ n=161; SQ n=93)

D + CT arm: 329 assigned to D + CT → 329 clinical data available (NSQ n=204; SQ n=125) → 308 radiomics data available (NSQ n=191; SQ n=117); 291 genomic data available (NSQ n=176; SQ n=115) → 272 clinical, genomic and radiomics data available (NSQ n=165; SQ n=107)

CT arm: 322 assigned to CT

Statistical Analysis

DATA PRE-PROCESSING & MODELS DEVELOPMENT

Patient multimodal data
T + D + CT and D + CT arms
Clinical · Radiomics · Genomic

→ ML "Super T-learner"± development

→ CATE score* for each patient

MODEL LEARNING & EVALUATION

Bayesian hyperparameter optimization → Stratified nested cross-validation (NCV)

±Super T-Learner is a new learner architecture, developed by the study team, that extends the T-learner approach to further optimize the treatment benefit estimation and uses an optimization metric adapted for treatment benefit purpose. The Super T-Learner predicts for each patient its expected number of life-months gained when adding T to 1L D + CT, based on its multimodal characteristics, therefore providing the individual CATE score for each patient.

*CATE (Conditional Average Treatment Effect) is defined as the difference between restricted mean survival times (RMSTs) at 24 months after randomization.

FINDINGS

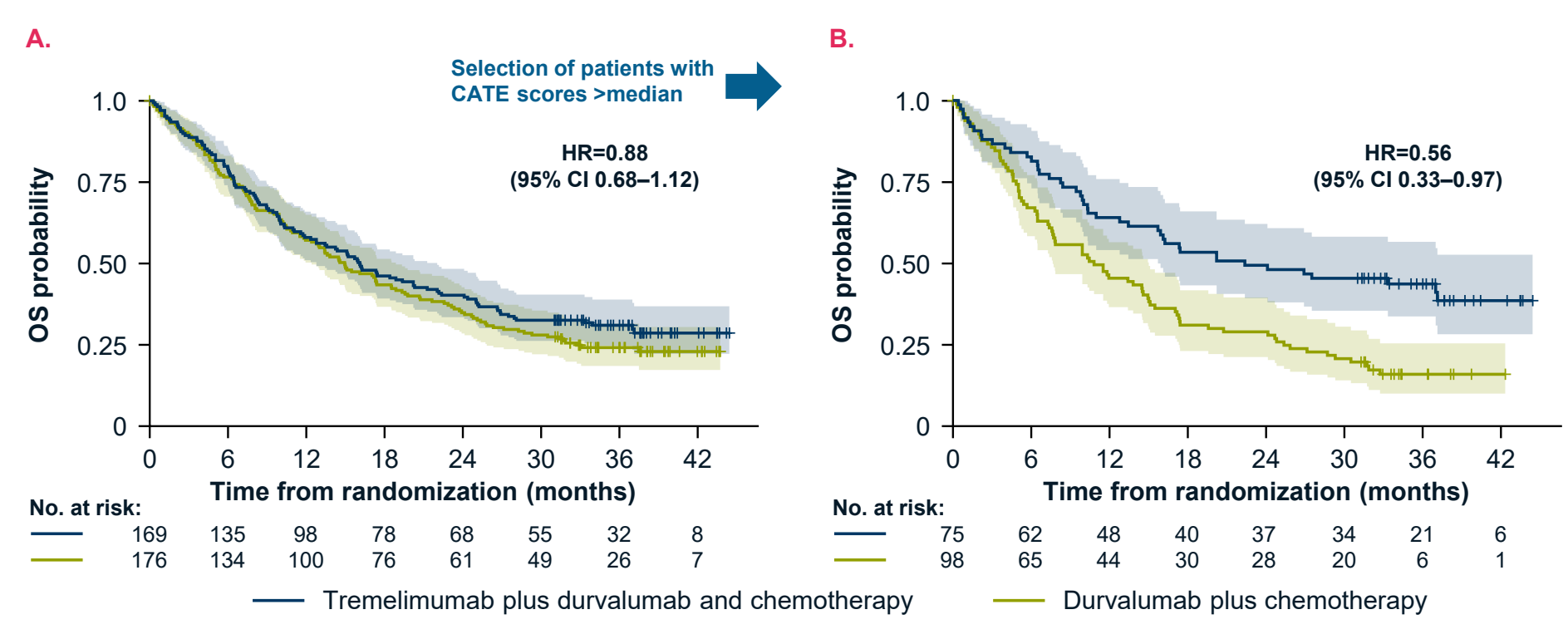
Several ML models were developed and trained, testing different combinations of data and histology types.

The best subgroup discrimination was achieved by **Model 19, combining clinical and genomics data in patients with non-squamous NSCLC.**

Model	Population	HR for all patients	HR for top 50%*	HR for top 30%*
4 (green, orange)	All histologies	0.88 [0.73; 1.05]	0.75 [0.58; 0.98]	0.75 [0.55; 1.02]
7 (green, blue)	All histologies	0.78 [0.18; 1.37]	0.75 [0.57; 0.97]	0.63 [0.44; 0.91]
19 (green, blue)	Non-squamous	0.88 [0.68; 1.12]	**0.56 [0.33; 0.97]**	**0.48 [0.24; 0.95]**

*HR for top 50% or 30% refers to the estimated hazard ratio for the 50% or 30% of patients with the highest predicted benefit from the addition of T to D and CT.
Coloured circle indicates the data modalities included in the model (green: clinical data; blue: genomic data; orange: radiomics data). Values in brackets indicate the 95% confidence interval (CI).

This model was able to identify the 50% and 30% of patients with the highest predicted benefit from adding T to 1L D and CT.



Results from model 19: T+D+CT vs D+CT in A) with all patients in the dataset (before selection) and B) with selected patients with the top 50% CATE scores.

The **five features with the highest contribution in the non-squamous model** were:

- *EGFR* wild-type
- *FGFR3* wild-type
- *CDKN2A* wild-type
- *KRAS* mutation
- *STK11* mutation

CONCLUSION AND CLINICAL IMPACT

By combining patients' clinical, genomic, and radiomics data, the developed ML **model yielded genetic signatures identifying patients with non-squamous mNSCLC who may derive greater OS benefit** from the addition of T to D and CT in the 1L setting.

The findings of this study **support a shift toward multimodal, precision medicine approaches in immuno-oncology**, with potential future applications:

Enhance precision in tailoring 1L therapies for individual patients

Improve patient selection and stratification

Inform clinical trial design
TRITON trial (NCT06008093)

AstraZeneca

This project was executed by SOPHiA GENETICS in collaboration with **AstraZeneca**, using data from the POSEIDON trial (NCT03164616).