Cost-effectiveness modelling based on a clinical trial reanalysis using multimodal artificial intelligence methodology: Predicting which patients may benefit most from the addition of tremelimumab to durvalumab plus chemotherapy in 1st line metastatic non-small-cell lung cancer

MSR63

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Objective

- To develop an economic analysis based on a multimodal predictive model, integrating clinical, genomic, and imaging data, to identify patients with 1L metastatic NSCLC who may receive greater OS benefit from the addition of tremelimumab to durvalumab and chemotherapy (versus the overall population) in the global, phase 3, randomised POSEIDON clinical trial (NCT03164616).
- Assess whether such approaches may enhance precision in tailoring therapies for individual patients, and thus improve healthcare system efficiency

Conclusions

- A model yielded genetic signatures identifying patients with non-squamous metastatic NSCLC who may derive higher OS benefit from the addition of tremelimumab to durvalumab plus chemotherapy in 1L setting.
  - *EGFR* wild-type, *FGFR3* wild-type, *CDKN2A* wild-type, *KRAS* mutation, and *STK11* mutation signature drives higher benefit.
- An economic analysis demonstrated an additional 2.59 life years gained in patients designated “high-benefiter”, of which 0.6 came in the pre-progressed and 2.0 in the progressed disease state

Plain language summary

Why did we perform this research?

- In a large clinical trial called POSEIDON in patients with non-small cell lung cancer (NSCLC) that had spread outside of the lung (metastatic NSCLC), patients who received two types of immunotherapy (called tremelimumab and durvalumab) and chemotherapy had a better chance of living longer, and of living longer before their disease got worse, than patients who received chemotherapy alone.
- The aim of this study was to assess whether TRIDENT results could be extrapolated for use in economic analyses and thus inform decision making in healthcare.

How did we perform this research?

- Using survival projections deemed a good fit for the study results, we ran an economic model comparing tremelimumab + durvalumab + chemotherapy (T+D+Ctx) with durvalumab + chemotherapy (D+Ctx), estimating life-years gained and how time is spent before and after disease progression.

What were the findings of this research?

- In the economic projections, high-benefit patients receiving T+D+Ctx gained an estimated 2.59 additional life-years versus D+Ctx. Gains were demonstrated in both pre-progression and progressed health states.

What are the implications of this research?

- Multi-modal AI may identify the patients most likely to benefit from adding tremelimumab, enabling more precise, value-based use of immunotherapy in advanced NSCLC.
- Better patient selection and robust survival modelling may shorten evidence-generation timelines, support faster health-technology assessments, and help clinicians match treatments to those who will benefit most.

Introduction

- In the phase 3, global, randomised, open-label POSEIDON clinical trial, PFS and OS were significantly improved in patients with 1L metastatic NSCLC who received tremelimumab plus durvalumab and chemotherapy compared with chemotherapy alone;[1] based on these data, tremelimumab plus durvalumab and chemotherapy received global approvals in this indication.
  - Durvalumab plus chemotherapy significantly improved PFS vs chemotherapy, with a positive trend for OS.
  - Further, exploratory analyses suggested patients with non-squamous NSCLC and mutations in *STK11*, *KEAP1*, and/or *KRAS* had clinically meaningful and numerically longer OS with tremelimumab plus durvalumab and chemotherapy vs chemotherapy alone.
- In the TRIDENT analysis, an artificial intelligence driven multimodal predictive model identified patient subgroups from POSEIDON who may receive greater OS benefit from the addition of tremelimumab to durvalumab and chemotherapy (D+T+Ctx vs. D+Ctx).
- In this analysis, we created an economic model to (1) estimate life-years (LYs) gained in high-benefiter patients receiving T+D+Ctx compared with D+Ctx;(2) evaluate the feasibility and challenges of applying economic modelling to AI-derived evidence.

Methods

TRIDENT analysis overview

- The TRIDENT analysis used data modalities of clinical (also including laboratory and radiology report), genomic, and radiomics from the POSEIDON trial (data cut-off 12 March 2021).
- To derive the radiomics modality, thoracic tumours were automatically segmented from injected CT scans using a deep-learnng algorithm and radiomics features were extracted according to the IBSI standards.
- Multivariable machine learning models were trained using a counterfactual approach to estimate hypothetical patient outcomes on two different treatments.
- A CATE (conditional average treatment effect) score was calculated per patient as their estimated overall survival outcome on tremelimumab and durvalumab plus chemotherapy vs outcome on durvalumab plus chemotherapy.
- The 50% of patients with actual and predicted best response to addition of tremelimumab (D+T+Ctx vs. D+Ctx) were identified based on their CATE scored, and classified as “high-benefit”
- A nested cross-validation procedure was used to estimate the model performance.

Economic modelling

- Population - Patients in the POSEIDON PhIII trial are defined as untreated adults with a histologically or cytologically documented metastatic NSCLC, with tumours that lack activating EGFR mutations and ALK fusions. A subset of these patients are defined as deriving higher-benefit of tremelimumab treatment based on the TRIDENT artificial intelligence outcome prediction methodology. Specifically in the non-squamous sub-population, *EGFR* wild-type, *FGFR3* wild-type, *CDKN2A* wild-type, *KRAS* mutation, and *STK11* mutation signature drive higher OS benefit in the model.
- Intervention & Comparator - The TRIDENT analysis investigated the use of durvalumab, tremelimumab and chemotherapy (T+D+Ctx) vs. durvalumab and chemotherapy (D+Ctx) to treat first-line patients with metastatic non-squamous NSCLC. The full TRIDENT dataset included squamous patients, however this analysis was limited to the non-squamous patient population.
- Outcomes - The primary outcome in the model is life-years gained, based on overall survival outcomes and extrapolations. Outcomes were discounted at a rate of 3.5%.
- Model Structure - A partitioned-survival structure with the three health states of 'Pre-Progression', 'Progressed disease' and 'Dead’ was used to assess T+D+SoC versus D+SoC . The proportion of the cohort in each health state is tracked over a maximum of lifetime horizon (30 years) using a weekly cycle length. For the time on treatment, the model applies time to treatment discontinuation (TTD) data to both arms.

Results and interpretation

Multimodal AI model performance and patient stratification

Table 1. Summary of dataset for analysis

Dataset descriptions and baseline characteristics	Non-squamous 1LNSCLC
Dataset modalities	Non-squamous with clinical and genomic data
Number of patients	345
Median age (range)	64.0 (32–87)
Sex, n (%)	Male: 249 (72.2) Female: 96 (27.8)
PD-L1 status, n (%)	<1%: 124 (35.9) ≥1%: 219 (63.5) Missing: 2 (0.6)

- The TRIDENT AI model successfully identified *high-benefiter* NSCLC patients—those with conditional-average treatment effect (CATE) scores above the median.
- In the non-squamous NSCLC (NSCC) “high-benefiter” patients:
  - T+D+Ctx improved overall survival (OS) versus D+Ctx:
    - *HR = 0.56 (95% CI 0.33–0.97; n = 172)*
  - For the broader TRIDENT NSCC population (“high-benefiter” and non-“high-benefiter” patients):
    - *HR = 0.88 (95% CI 0.60–1.11; n = 345)*
- Genomic correlates of high benefit included EGFR, FGFR3, CDKN2A wild-type status, KRAS and STK11 mutations.
- Baseline characteristics which are known to have an impact on outcome is NSCLC for “high-benefiter” and non-“high-benefiter” patients can be found in table 2, with no meaningful difference apparent between groups.

Table 2. Summary of baseline characteristic for “high-benefiters” and non-high-benefiters

Variable	“high-benefiters”	Non- “high-benefiters”
Age >65	81 (47%)	93 (54%)
No Brain Metastases	154 (90%)	154 (89%)
Disease Stage IVA	76 (44%)	77 (45%)
Normal ECOG activity	45 (26%)	58 (34%)
Female	42 (24%)	54 (31%)
PD-L1 <1%	60 (35%)	65 (38%)
Asian	71 (41%)	71 (41%)
Current Smoker	34 (20%)	29 (17%)

T+D+Ctx: Tremelimumab + Durvalumab + Chemotherapy; D+Ctx: Durvalumab + Chemotherapy;OS: Overall survival; PFS: Progression Free Survival, TTD: Time to Treatment Discontinuation; AIC: Akaike Information Criterion

Figure 1: OS Kaplan-Meier extrapolation curve of “high benefit” patients

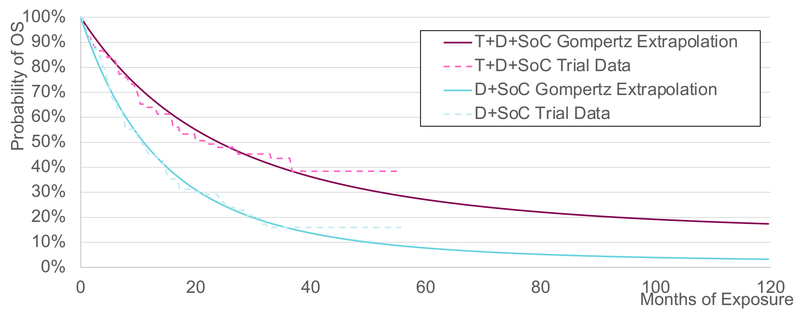
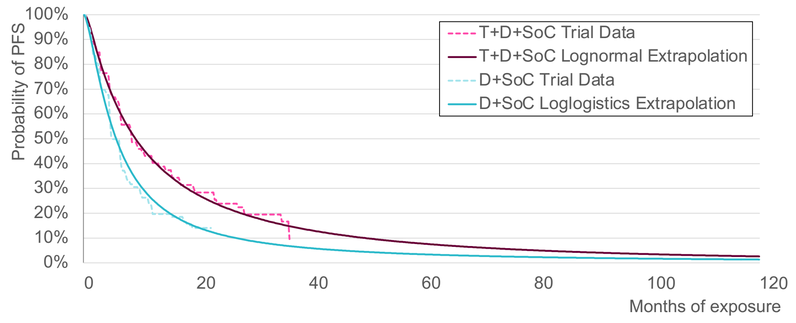
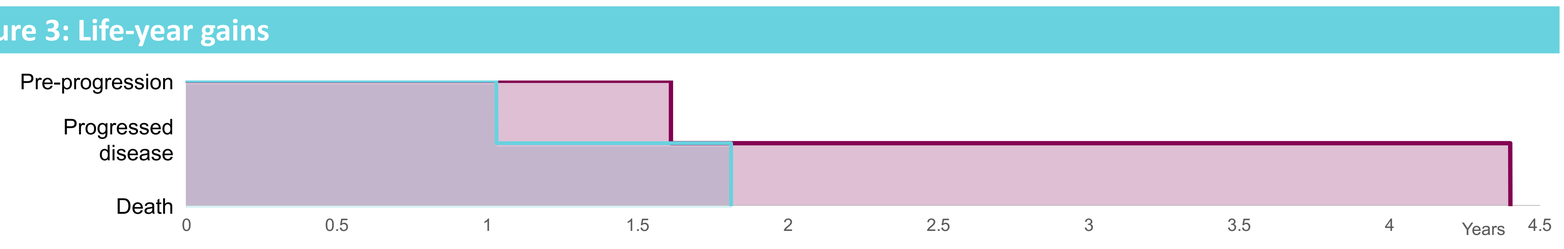


Figure 2: PFS Kaplan-Meier extrapolation curve of “high benefit” patients



OS, PFS and TTD extrapolations were selected based on the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Standard parametric and spline extrapolations were considered for each outcome. For OS, a joint-fitiing Gompertz extrapolation was selected, for PFS, independently fitting curves were selected, with lognormal for the T+D+Ctx arm, and loglogistic for the D+Ctx arm. For TTD, Independent fitted 3 knot odds spline was selected.

Figure 3: Life-year gains



Regimen	Years pre-progression	Years in progressed disease	Total Life Years	Life Years Gained
T + D + SoC	1.61	2.78	4.40	
D + SoC	1.03	0.78	1.81	2.59

The model demonstrates an increase of 2.59 life-years in patients designated “high-benefit”, treated with tremelimumab in addition to durvalumab plus chemotherapy (versus durvalumab plus chemotherapy). The increase in life-years is driven by increased time spent in both the pre-progression (+0.58 life years) the progressed state (+2.0 life years).

Discussion

In this analysis we demonstrate the ability to conduct economic modelling based on patient populations determined using multi-modal artificial intelligence. Escalating investment and risks-taken when developing new targeted drugs and immunotherapies makes oncology one of the fastest growing cost lines for health systems worldwide. This paper presents an example of how multi-modal trial reanalysis could mitigate this pressure by improving the fit between patient and therapy, informing clinical decision making and generating evidence that payers can use to demonstrate value and implement value-based contracts[2].

References

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