Poster #3703 / MSR147

Evaluating imaging artificial intelligence (AI) that matches real-world digital twins (rwDT) into an external control arm (ECA) for MYSTIC, a global phase 3 trial for treatment of metastatic non-small-cell lung cancer (mNSCLC).

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Objective

To evaluate whether external control arms (ECAs) generated from real-world digital twins (rwDTs) of clinical trial treatment arm subjects would produce similar survival curves to the control arm in a phase III randomized controlled trial (with success defined as achieving an ECA survival curve hazard ratio (HR) of ~1.0 compared to the actual control arm).

Conclusions

rwDTs matched using AI-derived spatial imaging biomarkers (SIBs) from baseline CT scans generated ECAs successfully emulating the control arm of the MYSTIC trial and the observed OS treatment effect. Future analyses will evaluate potential impacts of ECA use on sample size and statistical power calculations.

Plain-language summary

Why did we perform this research?

- In clinical trials, control arms are needed to compare effectiveness of a study treatment with the established standard of care. However, this means many patients enrolled in a trial do not receive the experimental therapy.
- External control arms (ECAs) may reduce the number of patients required to be enrolled onto the control arm of a clinical trial, allowing more patients to receive the treatment being studied.
- This project evaluated whether artificial-intelligence derived assessment of imaging tests (CT scans) could be used to create ECAs matching clinical trial patients to real-world patients.

How did we perform this research?

- We used an AI model to analyze CT scans collected from a completed lung cancer trial (MYSTIC). For each subject in MYSTIC, we identified a real-world patient with the most similar imaging features.
- We compared the survival outcomes of the MYSTIC trial patients to the outcomes for the matched real-world subjects.

What were the findings of this research?

- The real-world patients had similar survival outcomes to the patients enrolled into the control arm of the MYSTIC trial. Differences in survival between the experimental and the control groups were similar when comparing to the real-world patients.

What are the implications of this research?

- AI applied to imaging data can be used to identify ECAs for clinical trials. This approach may help with clinical trial design, potentially reducing the number of patients needed to be enrolled onto the control arm in a trial.

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Introduction

- Historical claims data and electronic medical records (EMRs) have been used to create ECAs that can help estimate treatment effect size seen in clinical trials[1].
- However, propensity score matching based on claims and EMR data can be limited by heterogenous patient populations, missing data, and selection bias[2].
- Prognostic, AI-derived spatial imaging biomarkers (SIBs) from 3D computed tomography (CT) imaging may enable improved matching of rwDTs to clinical trial subjects when generating ECAs.
- IPRO is a fully automated segmentation deep learning model trained on serial imaging data and survival outcomes from real-world aNSCLC patients[3], extracting and comparing over 5,000 SIBs from CT scan data (Figure 1).

Methods

- Eligibility criteria from MYSTIC (NCT02453282) were applied to a real-world imaging, clinical and outcomes (rwICO) database (Figure 2) to identify eligible patients receiving first-line chemotherapy (standard of care (SOC) used in the MYSTIC control arm).
- IPRO was used to generate SIBs from each MYSTIC baseline (BL) CT scan and used to identify rwDTs in the rwICO database via cosine similarity.
- Kaplan-Meier analyses and hazard ratios (HR) were used to compare overall survival (OS) across six arms: SOC, Durvalumab-only (D), Durvalumab and Tremelimumab (DT), SOC-matched ECA (ECA-SOC), D-matched ECA (ECA-D), and DT-matched ECA (ECA-DT).

Figure 1. Organ and lesion segmentation.

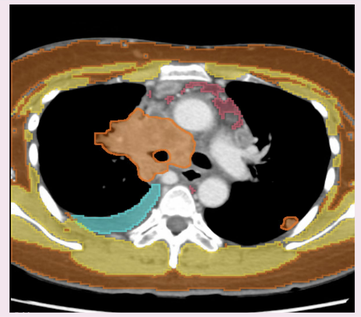


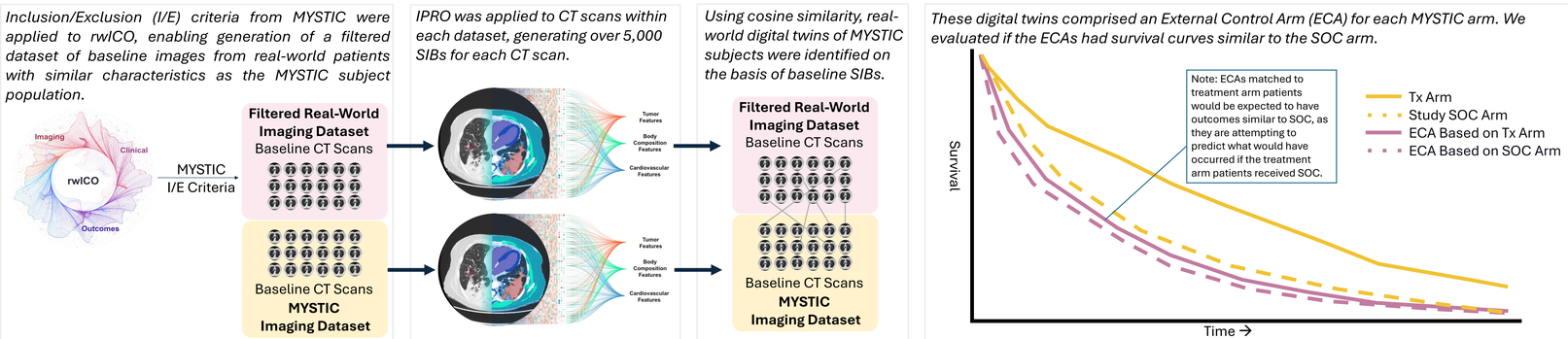
Figure 2. rwDT Methodology

Inclusion/Exclusion (I/E) criteria from MYSTIC were applied to rwICO, enabling generation of a filtered dataset of baseline images from real-world patients with similar characteristics as the MYSTIC subject population.

IPRO was applied to CT scans within each dataset, generating over 5,000 SIBs for each CT scan.

Using cosine similarity, real-world digital twins of MYSTIC subjects were identified on the basis of baseline SIBs.

These digital twins comprised an External Control Arm (ECA) for each MYSTIC arm. We evaluated if the ECAs had survival curves similar to the SOC arm.



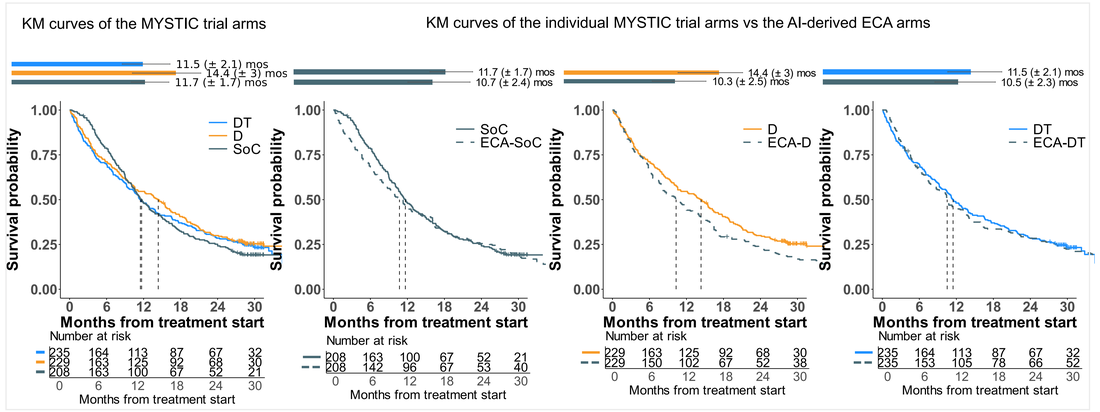
Results and Interpretation

- 672 MYSTIC patients with available BL CT scans and consent to this research were included to match rwDTs.
- The HR between SOC and ECA-SOC was 0.92, near the desired HR of 1.0.
- Comparing D vs. SOC (HR 0.89, 95%CI 0.79 – 1.11) and DT vs. SOC (HR 0.97, 95%CI 0.79 – 1.20), substituting the rwDT ECA for the SOC resulted in similar estimations of treatment effect (D vs. ECA-D HR 0.79, 95%CI 0.64 – 0.97; DT vs. ECA-DT HR 0.98, 95%CI 0.80 – 1.20).
- Comparisons across different arms are listed in Table 1.

Table 1. Analysis of mOS and HRs across observed trial arms and ECAs for MYSTIC.

Trial Arm	N	mOS (months)	HR (95% CI)
SOC	208	11.7	-
D	229	14.4	-
DT	235	11.5	-
ECA-SOC	208	10.7	-
ECA-D	229	10.3	-
ECA-DT	235	10.5	-
Comparisons			
SOC vs. ECA-SOC	-	11.7 vs. 10.7	0.92 (0.75, 1.14)
D vs. SOC	-	14.4 vs. 11.7	0.89 (0.79, 1.11)
DT vs. SOC	-	11.5 vs. 11.7	0.97 (0.79, 1.20)
D vs. ECA-D	-	14.4 vs. 10.3	0.79 (0.64, 0.97)
DT vs. ECA-DT	-	11.5 vs. 10.5	0.98 (0.80, 1.20)

Figure 3. Comparison of Kaplan-Meier survival curves for MYSTIC trial arms vs. the actual trial SOC arm and the AI-derived ECA arms.



Conclusions

- AI-derived SIB-based rwDTs generated ECAs with outcomes similar to the SOC arm of the MYSTIC clinical trial, highlighting the ability of IPRO to create ECAs that can be used as a 'matched' control in propensity score analysis.

Acknowledgments

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Disclosures

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