RWD51

Demonstrating internal and external validity in real-world datasets: A case study in *MET* exon 14 (*MET*ex14) skipping non-small cell lung cancer (NSCLC)

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CONCLUSIONS

Pooling of data allows for better estimation of outcomes despite small sample sizes in individual datasets, though with concerns regarding heterogeneity across studies

Outcomes seen with treatments within the pooled datasets were consistent across included studies, and compared with published outcomes

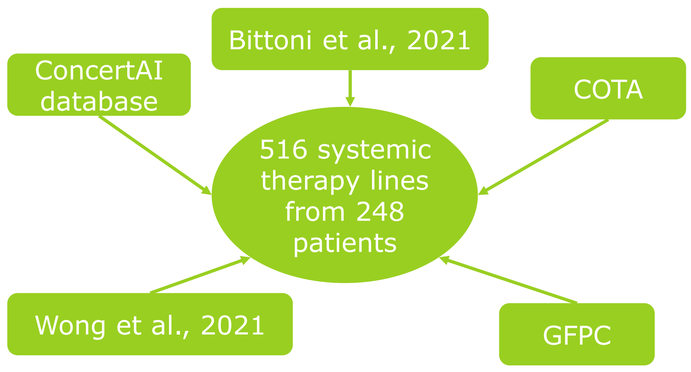
Where typical measures of heterogeneity (such as I^2) are unavailable due to low study numbers, alternative approaches can be used to demonstrate the consistency of estimates

Internal consistency can be demonstrated by methods such as 'leave one out' analysis. Reweighting to other datasets demonstrates external validity

The use of multiple approaches increases confidence in the results seen

INTRODUCTION

- Five real-world datasets (RWD) were pooled (516 total systemic therapy lines received by 248 patients) and used to provide data for immunotherapy, chemotherapy, and the tyrosine kinase inhibitor crizotinib* (an unspecific inhibitor of MET)



*Not approved for treatment of patients with *MET*ex14 skipping NSCLC.

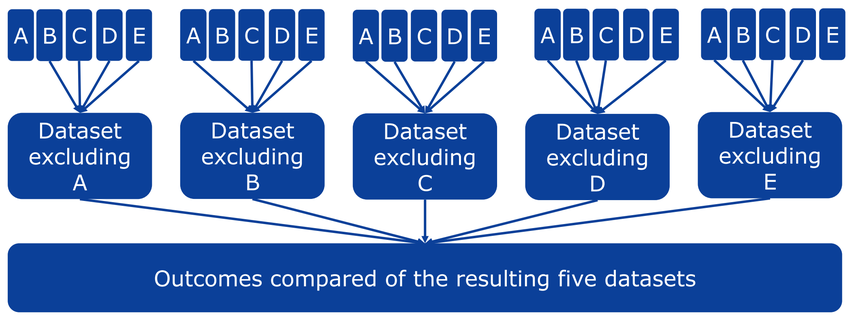
OBJECTIVES

- Create a pooled dataset allowing estimation of comparative effectiveness in *MET*ex14 skipping NSCLC, with different treatment modalities
- Ensure that the data within the pooled dataset is consistent – across included datasets, and relative to other published studies

METHODS

- Following dataset pooling, the analyses were evaluated for internal and external validity
- As there were relatively few patients (range: 21–91) in each study, a 'leave-one-out' analysis was performed to assess internal validity, where one study was omitted from the pooled dataset in successive runs, and survival outcomes compared (**Figure 1**). Any aberrant influential study would be visible when outcomes were compared
- To assess external validity, matching-adjusted indirect comparisons (MAICs) were conducted, reweighting RWD to estimates from published studies (Guisier et al., 2020; Sabari et al., 2018; Awad et al., 2019) in patients with *MET*ex14 skipping NSCLC, and comparing time-to-event outcomes for consistency

Figure 1. Conceptual diagram of leave–one-out analysis



RESULTS

- The 'leave-one-out' internal validation resulted in similar estimates of PFS and OS in all cases, including point estimates of survival at key timepoints and the shape of Kaplan–Meier curves (**Figure 2**)

  This finding was seen across all comparators:
  - Median PFS: 2.7–3.6 months for immunotherapy
  - 4.1–6.4 months for chemotherapy
  - 8.1–10.0 months for MET inhibitors
- The external validation by reweighting RWD using MAICs (Signorovitch et al., 2012) to match published data, again validated the findings of dataset pooling (**Figure 3**) in giving similar outcomes for therapies
- Two papers were available for immunotherapy:
  - Reweighting to match Guisier et al., 2020, gave a median PFS of 3.3 months compared with the published estimate of 4.7 months (HR 1.14; 95% CI: 0.70, 1.86)
  - Reweighting to match Sabari et al., 2018, led to a worse fit (median PFS 3.9 months vs published 1.9 months, HR 0.39; 95% CI: 0.25, 0.59; OS HR 0.90; 95% CI: 0.53, 1.53). It should be noted 25% of the patients in Sabari et al., 2018, had ECOG PS 2; patients who would have been excluded from the RWD
- Comparing outcomes in patients receiving crizotinib to those receiving any MET inhibitor (24/31 of whom received crizotinib) from Awad et al., 2019, only OS was reported, which again remained a good fit (median OS 12.0 vs 8.0 months, HR 0.76; 95% CI: 0.45, 1.29)

Figure 2. 'Leave–one-out' analysis

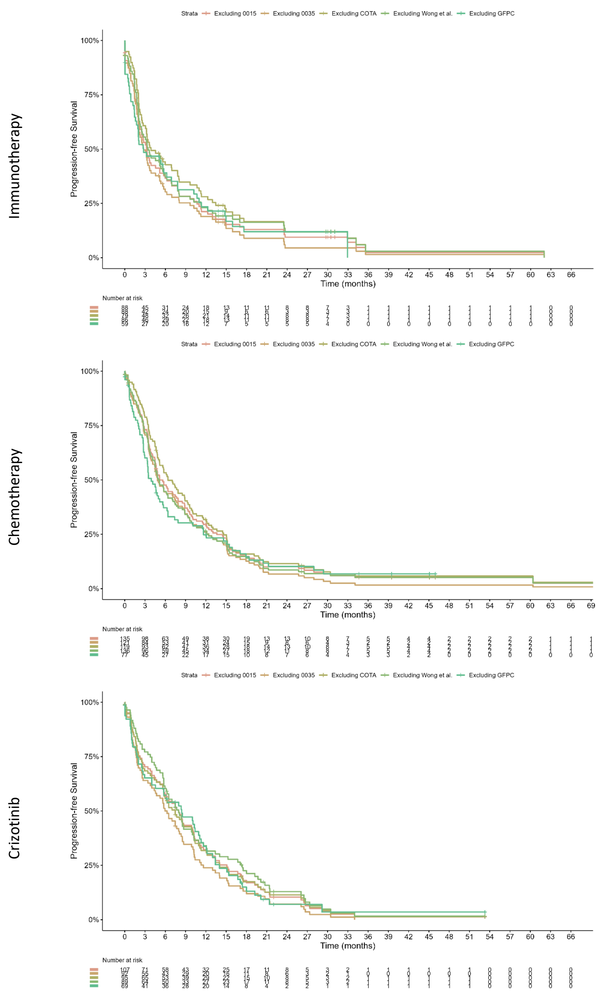
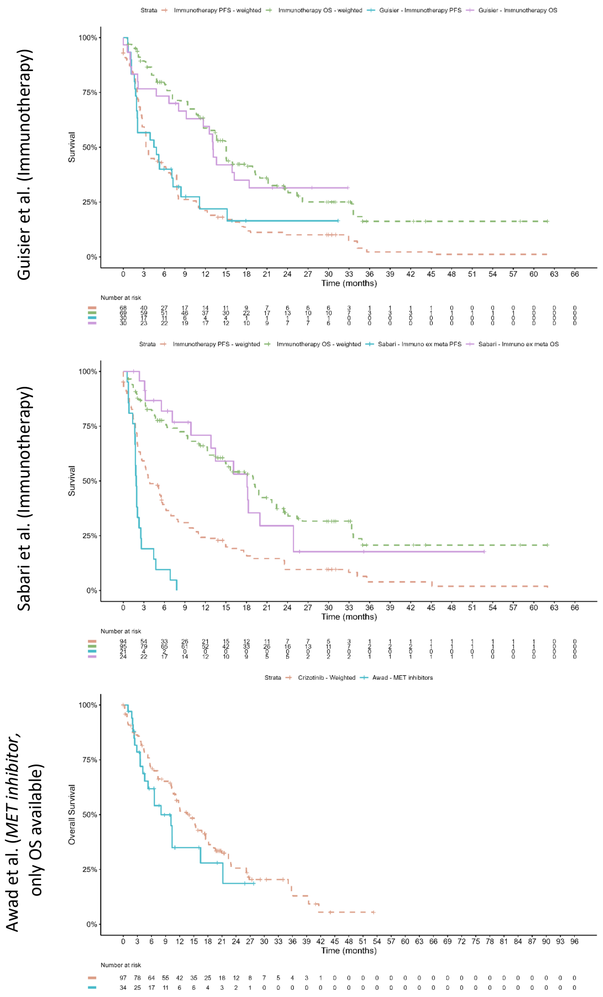


Figure 3. Reweighting to published data



Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

References: Awad MM, et al. *Lung Cancer.* 2019;133:96–102; **B**ittoni M, et al. *Lung Cancer.* 2021;159:96–106; Guisier F, et al. *J Thorac Oncol.* 2020;15(4):628–636; Sabari JK, et al. *Ann Oncol.* 2018;29(10):2085–2091; Signorovitch JE, et al. *Value Health.* 2012;15(6):940–947; Wong SK, et al. *Lung Cancer.* 2021;154:142–145.

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