Transportability of Overall Survival Estimates from **US to UK** Populations Receiving First-Line Treatment for Advanced Non-Small-Cell Lung Cancer

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Background

- Health technology assessment bodies prefer local data to answer questions about the use and outcomes of therapies in routine practice but local data may not always be available or sufficient.
- Global pharmaceutical companies increasingly submit international data, especially from the US, to ex-US countries incl. European HTA bodies.
- There is substantial uncertainty in the relevance of such data to local decision-making given important differences in populations, healthcare systems, and healthcare practice between countries. This leads to variation in decision-making between and within countries.
- Empirical evidence could potentially improve our understanding of the relevance of US data to local decision making.
- In this study we **aim to explore the transportability of estimates of overall survival (OS) and time-on-treatment for patients treated in the US to UK receiving different classes of drugs for 1L treatment of advanced non-small cell lung cancer (aNSCLC)**.

Methods

- **UK data**: We used published data from a multi-centre UK study (Lester et al.) reporting overall survival for patients initiating 1L therapy by drug class (chemotherapy, targeted treatment, and immunotherapy) [1]. Patients were recruited between June 2016 and March 2018.
  - A sensitivity analysis used alternative published data based on the national cancer registry for England which reported OS for patients initiating 1L chemotherapy alone diagnosed between 2014 and 2017 (Pilleron et al) [2].
- **US data:** We emulated the UK study using the US Flatiron Health EHR-derived de-identified database, comprising patient-level structured and unstructured data, curated via technology-enabled abstraction,[3,4] originating from ~280 cancer clinics.
- **Methods:** We compared patient baseline characteristics for UK and US patients by 1L drug class and characterised treatment patterns in 2L. We compared OS estimates before and after population-adjustment between the US and UK cohorts. We used matching adjusted indirect comparison such that the US data reflected the average characteristics of the UK cohort in terms of age, sex, ECOG PS, and histology.

Results

- The UK cohort included 1,003 patients meeting inclusion criteria: 69.6% initiated chemotherapy, 17.8% immunotherapy, and 12.6% targeted therapy. After applying inclusion criteria, the US cohort included 3,819 patients initiating 1L therapy. Of these, 60.6% initiated chemotherapy, 21.9% immunotherapy, and 17.5% targeted therapy (**Table 1**).
- Median follow-up was 9.0 months in the US versus 9.2 months in the UK but this varied substantially by 1L drug class.
- A lower proportion of patients went on to receive 2L treatment in the UK compared to the US: 287 (29%) in the UK versus 1,835 (48%) in the US.
- The median OS across all therapies was 9.5 months (95% CI 8.8-10.7) in the UK compared to 10.4 months (95% CI 9.7-11.0) in the US prior to population adjustment (standardisation). After population adjustment, median OS was more similar in the US (9.6 months [95% CI 9.0-10.2]).

Was the survival similar between countries?

OS curves from US and UK cohorts exhibited a similar shape for each 1L drug class over the duration of follow-up (**Figure 1**). For 1L chemotherapy, irrespective of adjustment the OS curves overlap until about 12 months, after which OS estimates are lower in the UK versus the US. Overall survival is very similar in the 1L immunotherapy and 1L targeted therapy groups after adjustment over the entire follow-up period.

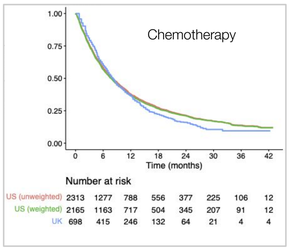
How does this compare with other studies?

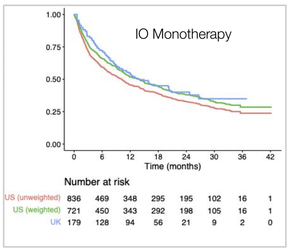
For the comparison with data from Pilleron et al. [2], median OS for patients receiving 1L chemotherapy was similar for the UK and US after standardisation for both those aged less than 75 years (7.7 months [7.5-7.9] for the UK versus 8.1 months [7.8-8.5] for the US) and those 75 years or older (7.9 months [7.5-8.2] for the UK versus 7.6 months [7.0-8.4] for the US).

Did the time of adoption matter?

A post-hoc analysis restricted the time period for US data to the period before the widespread adoption of immunotherapies and repeated the analyses for 1L chemotherapies only. In this analysis we saw overlapping OS curves after adjustment for the UK and the US cohorts.

Figure 1. Contrast of UK vs US overall survival estimates before and after population adjustment





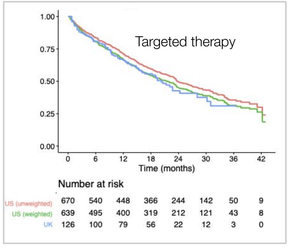


Table 1. Patient characteristics of UK and US cohorts initiating first-line therapies

	Overall		1L Chemotherapy		1L IO monotherapy		1 L Targeted Therapy	
Characteristic	**UK** (n = 1003)	**US** (n = 3819)	**UK study** (n = 698)	**US** (n = 2313)	**UK** (n = 179)	**US** (n = 836)	**UK** (n = 126)	**US** (n = 670)
Proportion of study pop., %	100	100	69.6	60.6	17.8	21.9	12.6	17.5
Median follow-up, months (range)	9.2 (0.0–42.7)	9.0 (0.0-42.9)	7.9 (0.0–42.7)	7.3 (0.0-42.9)	12.7 (0.1–37.3)	8.1 (0.0-42.3)	16.3 (0.1–37.1)	20.3 (0.2-42.9)
Median age(range), years	68 (28–93)	69 (21-81)	68 (28–88)	69(21-81)	67 (48–90)	71(38-81)	70 (32–93)	69 (25-81)
Sex, n (%)								
Male	541 (53.9)	2,013 (52.7)	395 (56.6)	1,311 (56.7)	94 (52.5)	439 (52.5)	52 (41.3)	263 (39.3)
Female	462 (46.1)	1,806 (47.3)	303 (43.4)	1,002 (43.3)	85 (47.5)	397 (47.5)	74 (58.7)	407 (60.7)
Tumor histology, n (%)								
Squamous	243 (24.2)	957 (25.1)	202 (28.9)	730 (31.6)	38 (21.2)	210 (25.1)	3 (2.4)	17 (2.5)
Non-squamous	641(63.9)	2,684 (70.3)	391 (56.0)	1,460 (63.1)	133 (74.3)	584 (69.9)	117 (92.9)	640 (95.5)
Not specified	119 (11.9)	178 (4.7)	105 (15.0)	123 (5.3)	8 (4.5)	42 (5.0)	6 (4.8)	13 (1.9)
ECOG PS score, n (%)								
0–1	759 (75.7)	2,786 (73.0)	513 (73.5)	1,714 (74.1)	157 (87.7)	556 (66.5)	89 (70.6)	516 (77.0)
2+	244 (24.3)	1,033 (27.0)	185 (26.5)	599 (25.9)	22 (12.3)	280 (33.5)	37 (29.4)	154 (23.0)

Discussion

The survival **outcomes for patients with lung cancer in the US and UK were similar** after adjusting for a small set of common demographic and clinical characteristics.

- Estimates were similar for those initiating 1L chemotherapy for the first 12 months, after which OS was higher in the US versus the UK. This was also observed using data from the national cancer registry [2]. Post-hoc analysis found some indication of a time-period effect with OS curves similar when restricting US data to the period before the widespread use of immunotherapies in the US.
- While we showed good concordance for the UK and the US in 1L treatment for aNSCLC by drug class, the generalisability of these results to other countries, indications, lines of therapy, products, subgroups, or outcomes is unclear and should be explored further. Of note, a previous study in the same indication found OS results from the US were similar to those in Canada [5], although with greater differences identified for 1L immunotherapy than for chemotherapy.

Key limitations of the study relate to the UK data source used for comparison:

- The representativeness of 9 UK sites to the general UK population was unknown. However, we found similar results for 1L chemotherapy when using data from the national cancer registry [2].
- The published UK retrospective study lacked some study design details, for instance, how combination therapies consisting of more than one drug class were classified in 1L and 2L.
- We only had aggregate data for comparison. This limited our ability to further adjust for patient characteristics or subsequent lines of therapy.
- There may be additional prognostic variables for which adjustment could improve comparability of OS between countries but were not available in the aggregate data source selected.
- Differences in the definition of time-on-treatment between the two data sources prevented appropriate comparison.

Conclusions

- **US data has potential to be used in technology evaluations to understand long-term OS where UK data is unavailable or sparse for aNSCLC patients receiving 1L treatment.**
  - This was achieved despite only having access to limited published data. While access to individual patient level data could have further improved transportability, this better reflects the context in which such studies will be used to inform decision making in practice.
  - The ability to make use of international data where local data is currently unavailable or limited could help address decision uncertainties such as real-world outcomes, long-term survival, and time-on-treatment.
- This research should be extended to consider other lines of therapy, patient subgroups, indications, HTA-relevant outcomes, and countries as well as the impacts of subsequent lines of therapy on transportability.

References

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