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Evaluating transportability of overall survival estimates from US to UK populations receiving first-line treatment for advanced non-small cell lung cancer: a retrospective cohort study

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ABSTRACT

Objectives The objective of this study is to explore how the UK versus the USA compare in patient characteristics, treatment patterns and overall survival (OS) of patients with advanced non-small cell lung cancer (aNSCLC) initiating first-line (1L) treatment.

Design Retrospective cohort study.

Setting Oncology treatment centres in the USA and UK.

Participants People in the USA and UK diagnosed with aNSCLC and treated in the 1L setting between 2016 and 2018. The US cohort was obtained from a nationwide electronic health record-derived deidentified database. The UK cohort information was derived from a published study exploring the patient characteristics, treatments and outcomes of people with aNSCLC in the UK.

Interventions 1L chemotherapy, immunotherapy monotherapy or targeted therapy.

Primary outcome measure The primary outcome was OS—defined as the time from treatment initiation to death from any cause.

Results There were 1003 patients in the UK and 3819 in the US cohorts receiving 1L therapy for aNSCLC. After standardising the US cohort to the UK cohort, median OS in the USA and UK was similar across 1L drug classes: chemotherapies (7.7 (95% CI 7.1 to 8.3) vs 8.1 (95% CI 7.4 to 8.9) months), immunotherapies (13.9 (95% CI 11.0 to 17.1) vs 14.0 (95% CI 10.7 to 20.6)) and targeted therapies (21.6 (95% CI 18.5 to 23.7) vs 20.2 (95% CI 16.0 to 30.5)). OS curves for 1L immunotherapy and targeted therapy were almost overlapping after standardisation. OS after around 12 months was higher in US patients compared with UK patients receiving 1L chemotherapy regimens. Of those receiving 1L chemotherapy, the proportion receiving any second-line therapy appeared higher for patients in the USA versus UK.

Conclusions The results suggest that in aNSCLC patients receiving 1L treatment, US data have the potential to be used in technology evaluations to understand long-term OS where UK data are unavailable or sparse.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study assessed the comparability of overall survival among people with advanced non-small cell lung cancer in the UK versus the USA after standardising the US population to the UK population.
⇒ The study exemplifies the simple methodology that can be employed to generate empirical evidence that can help health technology assessment bodies in assessing the applicability of international evidence to local decision-making.
⇒ Limitations include that the patient-level data were not available in the UK, as a result, we used summary statistics from a recent publication in the UK, which restricted the methods available for adjusting patient characteristics between the countries.
⇒ The population adjustment was limited to patient demographic and clinical characteristics and did not include other factors that can influence transportability—for example, differences in healthcare systems across countries.

INTRODUCTION

Health technology assessment (HTA) bodies require evidence on a wide and varied number of questions to inform pricing and reimbursement decisions. Common evidence types include the characteristics of the target population, natural history of disease, diagnostic and treatment patterns, the use of medicines including time on treatment, long-term outcomes such as overall survival (OS) and event rates, resource use and costs, quality of life and the causal effects of treatment. For questions other than causal effects of treatments, real-world data are the preferred source of evidence.[1] Because the evidence must be relevant to patients treated in a given healthcare system, HTA bodies typically indicate a preference for local data.[1–3] Unfortunately, local data may not always be available or sufficient to answer all questions of interest. This is especially true where the

target population is small, such as in patients expressing a rare biomarker or tumour type, where sharing of evidence across countries may be necessary to achieve sufficient statistical power.

Given that the availability of data varies across countries, it is important to understand when and how evidence from one country can be utilised to fill evidence gaps in another. Manufacturers are increasingly submitting international data to HTA bodies as part of their evidence dossiers. The most common use case beyond comparative effectiveness has been to provide data on long-term outcomes, usually OS but also progression-free survival and time on treatment, for the local standard of care to inform extrapolation and costs in economic models. Assumptions about long-term outcomes and time on treatment are recognised to be key drivers of cost-effectiveness but are usually subject to substantial uncertainty based on trial data alone due to limited follow-up and questions about the relevance of the trial population to the decision.[4]

Where international data have been presented, there has been variation in its acceptance across HTA bodies but also across evaluations within HTA bodies.[5] Decision-making committees are uncertain about how to value international data given the differences between countries in terms of populations, healthcare systems and access and clinical practice. This is expected to be a greater challenge for absolute outcomes than for comparative outcomes such as relative treatment effects.[6] While informative general frameworks for considering transportability—that is, extending evidence beyond the population used in evidence generation—have been developed,[7] they are limited in their ability to guide specific decisions. For this, empirical studies on the transportability of evidence across countries are valuable; however, few such studies are currently available. One recent study found OS to be similar in patients receiving first-line (1L) chemotherapy or immunotherapies for advanced non-small cell lung cancer (aNSCLC) in the USA and Alberta, Canada after adjusting for baseline patient demographic and clinical characteristics.[8]

In this study, we aim to explore the transportability from the USA to the UK of estimates of OS and time on treatment for patients receiving different classes of drugs for 1L treatment of aNSCLC.

METHODS

Data sources

In the absence of available individual patient-level data from the UK, we performed a pragmatic literature review to identify studies reporting outcomes for patients with aNSCLC in the UK (online supplemental table 1). We prioritised studies that had broad population coverage, reflected current treatment practices (since the emergence of immunotherapies) and reported OS or time on treatment by treatment class. We identified three candidate studies[9–11] and selected Lester *et al* for our primary analysis because it was a multicentre study reporting detailed outcomes data by 1L drug class.[9] We used Pilleron *et al* for sensitivity analysis.[10] Pilleron *et al* presented population-level data from the national UK Systemic Anti-Cancer Treatment (SACT) registry but only for patients receiving 1L chemotherapy regimens. We excluded Snee *et al* because the study did not describe the patient characteristics of patients with advanced disease and outcomes were reported from diagnosis rather than initiation of treatment.[11]

Data for patients treated in the USA came from the nationwide electronic health record (EHR)-derived, deidentified Flatiron Health database—a longitudinal database comprising structured and unstructured data curated using technology-enabled human abstraction.[12] At the time of this study, deidentified patient-level data were derived from ~280 US cancer clinics (~800 sites of care) and rule-based lines of therapy were defined by expert oncology clinicians. The data processing and quality assurance procedures for Flatiron Health data are described in detail elsewhere.[13]

Study population

The UK patient population was based on a retrospective real-world study that identified patients from nine UK centres who initiated 1L systemic anticancer therapy between 1 June 2016 and 31 March 2018 and had a median follow-up of 9.2 months.[9] Patients were included if they were 18 years of age or older, were diagnosed with metastatic disease, were not enrolled in a clinical trial during the study period and were not missing relevant data (date of diagnosis, age, sex, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), histology, and response). We applied comparable inclusion criteria to the US data to match the population included in the UK study. We restricted the analysis to patients with a lung cancer diagnosis (International Classification of Diseases [ICD]-9 162.x or ICD-10 C34x or C39.9); at least two documented clinical visits; pathology consistent with aNSCLC that was confirmed using unstructured data; stage IV disease (confirmed using unstructured data); aged 18 years or older at diagnosis; treatment-naive; were exposed to relevant therapies in 1L; were not enrolled in clinical trials during the study period; had no gaps between diagnosis and EHR activity exceeding 90 days to ensure more complete treatment information and had ECOG PS recorded within 30 days of the index date. The UK EHR study did not report how they categorised combination therapies comprising more than one drug class, although such combinations are expected to be rare. We excluded patients with such combination therapies from the US cohort when categorising 1L treatment. Patients were selected for the US cohort over the same time period as the UK study.

Outcomes

The study outcomes of interest were OS and time-to-treatment discontinuation (TTD). OS was defined in

both cohorts as the time from initiation of 1L treatment to the date of death from any cause. Both studies have reported high sensitivity and specificity for mortality.[14 15] For the US cohort, TTD was defined as the time from initiation of 1L therapy to the last drug episode for the specific drug of interest in the 1L, which is consistent with standard definitions in HTA. For the UK cohort, TTD was defined as the time from initiation of 1L therapy to the start of the last cycle of therapy (which will tend to underestimate true TTD). Since TTD was defined differently between these studies, we present US TTD outcomes for completeness but do not compare them with UK TTD. UK patients were censored at the earliest of the end of the study period or the date of the last assessment; US patients were censored at the earliest of the end of the study period or at the last activity recorded in the EHR.

Analysis

We compared baseline characteristics for all variables available for the UK cohort plus additional variables for the US cohort, noting differences in definitions where present, for all 1L aNSCLC treatment and by drug class (chemotherapy, immunotherapy or targeted therapies). We also presented differences in use of second-line (2L) therapies after 1L. Comparison of 2L therapies is limited by uncertainty as to how combination therapies consisting of more than one drug class were categorised in the UK cohort study.

We used the matching-adjustment indirect comparison (MAIC) approach to standardise the characteristics of US patients to those of UK patients represented in Lester *et al*. We selected MAIC because it enabled us to standardise individual patient data from the USA using summary/published data from the UK. MAIC estimated weights to ensure that the average characteristics of the US study population matched those of the UK study population. Specifically, we standardised the US study population to match the average characteristics (age, sex, ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell and unknown) of patients in the UK, overall and by 1L drug class.[16] We compared OS between UK and US patients before and after standardisation, and Kaplan-Meier survival curves (KM), median survival, and restricted mean survival time (RMST) at 12 and 24 months from the index date of 1L treatment initiation. Published KM figures from the UK study were digitised and reproduced here following the algorithm from Guyot *et al*.[17] Our comparison is purely descriptive—we do not perform hypothesis tests of transportability because there is no established threshold for when results can be considered transportable; this will depend on the use case and decision context including the amount of decision uncertainty. To explore whether we were unable to account for important prognostic variables in our standardisation model, we modelled OS in the US cohort using Cox proportional hazards model regression conditional on 1L drug class (for the overall model only), age, sex, ECOG PS score, histology, race, year, time since diagnosis to treatment initiation, smoking history and biomarker status (*ALK*, *ROS1*, *EGFR* and *PD-L1*) and compared models using likelihood ratio tests using 5% significance level.

We performed several sensitivity analyses. First, we extended the enrolment window for US data to 1 October 2015 to reflect when immunotherapies first became available for aNSCLC in the USA and repeated the primary analysis. Second, rather than excluding people with missing ECOG PS scores in the US data, we imputed ECOG PS assuming best (ECOG PS 0 or 1) and worst (ECOG PS 2+) and repeated the primary analysis. Third, we repeated the main analysis using data from Pilleron *et al* for comparison. The study by Pilleron *et al* included adult patients with aNSCLC treated with chemotherapy between 2014 and 2017 in the UK followed until the end of 2018 and presented results by disease stage (III, IV) and age (≤75, >75 years). We selected US patients from the same time period and standardised the US study population to match the average characteristics of patients in stage IV in terms of age, sex, race (white, non-white) and baseline ECOG PS score. Additional details for the study by Pilleron *et al* can be found in online supplemental table 1.

Finally, we undertook a post hoc analysis to explore the potential role of time-period effects on observed differences in outcomes for patients treated with 1L chemotherapy, hypothesising that the earlier and faster uptake of immunotherapies in the USA may impact comparability. To explore this, we compared OS for patients in the UK with patients in the US receiving 1L chemotherapy regimens before the widespread availability of immunotherapies, that is, those initiating 1L treatment between 1 June 2012 and 31 March 2014.

Patient and public involvement

None.

RESULTS

The UK cohort included 1003 patients meeting the inclusion criteria, with 69.6%, 17.8% and 12.6% of patients initiating chemotherapy, immunotherapy and targeted therapy, respectively. After applying inclusion criteria, the US cohort included 3819 patients initiating 1L therapy (online supplemental figure 1). Of these patients, 60.6%, 21.9% and 17.5% initiated chemotherapy, immunotherapy and targeted therapy, respectively (table 1 and online supplemental table 2).

Age and sex distributions were similar in the US and UK populations regardless of 1L therapy (table 1). The median age was 68 years (range 28–93) for UK patients and 69 years (IQR 61–76; range 21–81) for US patients. 541 (53.9%) patients in the UK were male compared with 2013 (52.7%) in the USA. Most patients in the two cohorts had ECOG PS scores of 0 or 1 (759 (75.7%) in the UK vs 2786 (73.0%) in the USA). The proportion of patients with ECOG PS scores of 0 or 1 was higher in the

Table 1 Baseline characteristics and details of follow-up for patients in the UK and USA by 1L drug class

Characteristic	Overall		1L chemo		1L IO monotherapy		1L targeted therapy	
	UK (n=1003)	USA (n=3819)	UK (n=698)	USA (n=2313)	UK (n=179)	USA (n=836)	UK (n=126)	USA (n=670)
Proportion of study pop., %	100	100	69.6	60.6	17.8	21.9	12.6	17.5
Median follow-up (range*), months	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)	2013 (52.7)	395 (56.6)	1311 (56.7)	94 (52.5)	439 (52.5)	52 (41.3)	263 (39.3)
Female	462 (46.1)	1806 (47.3)	303 (43.4)	1002 (43.3)	85 (47.5)	397 (47.5)	74 (58.7)	407 (60.7)
Tumour 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)	2684 (70.3)	391 (56.0)	1460 (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)	2786 (73.0)	513 (73.5)	1714 (74.1)	157 (87.7)	556 (66.5)	89 (70.6)	516 (77.0)
2+	244 (24.3)	1033 (27.0)	185 (26.5)	599 (25.9)	22 (12.3)	280 (33.5)	37 (29.4)	154 (23.0)
EGFR status, No. (%)								
Mutation positive	108 (10.8)	556 (14.6)	1 (0.1)	65 (2.8)	0 (0.0)	11 (1.3)	107 (84.9)	480 (71.6)
Mutation negative	•	2078 (54.4)	•	1333 (57.6)	•	613 (73.3)	•	132 (19.7)
Unknown/missing	•	1185 (31.0)	•	915 (39.6)	•	212 (25.4)	•	58 (8.7)
ALK status, No. (%)								
Rearrangement present	19 (1.9)	97 (2.5)	0 (0.0)	8 (0.3)	0 (0.0)	5 (0.6)	19 (15.1)	84 (12.5)
Rearrangement not present	•	2332 (61.1)	•	1302 (56.3)	•	604 (72.2)	•	426 (63.6)
Unknown/missing	•	1390 (36.4)	•	1003 (43.4)	•	227 (27.2)	•	160 (23.9)
PDL1 status,† No. (%)								
PD-L1 positive	182 (18.1)	1486 (38.9)	3 (0.4)	586 (25.3)	179 (100)	669 (80.0)	0 (0.0)	231 (34.5)
PD-L1 negative/not detected	•	728 (19.1)	•	535 (23.1)	•	39 (4.7)	•	154 (23.0)
Unknown/missing	•	1605 (42.0)	•	1192 (51.5)	•	128 (15.3)	•	285 (42.5)

This table presents variables that were common between the US and UK analyses. Additional variables that were measured in the US study only can be found in online supplemental table 2.
*Lester *et al* (2021) only reported range.
†In the US analysis, patients were considered PD-L1 positive if the PD-L1 tumour proportion score was≥1% or if there was a reference to PD-L1 positivity in the medical chart.
ALK, anaplastic lymphoma kinase; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IO, immunotherapy; 1L, first line; PDL1/PD-L1, programmed cell death ligand 1.

UK compared with the USA for patients initiating immunotherapies and lower for those initiating targeted therapies. The mix of lung cancer histology types differed slightly between the countries, with the proportion of patients with non-squamous cell disease being lower in the UK compared with the US cohort (641 (63.9%) vs 2684 (70.3%)), but missing data on histology were greater in the UK. Biomarker prevalence rates were not comparable due to the different classifications used. Median follow-up was 9.0 months in the USA vs 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 with the USA: 287 (29%) patients in the UK versus 1835 (48%) in the USA (online supplemental table 3), though this may partly be driven by differences in censoring rates and how the 2L combination therapies were classified. Excluding 2L combination therapies consisting of more than one drug class for patients in the USA leads to a switching rate of 40%. This pattern is observed regardless of 1L drug class.

Conditional on receiving 2L therapy, the proportion of people receiving immunotherapies was comparable (52% in the UK vs 49% in the USA) but patients in the UK were more likely to receive other chemotherapy regimens (36% in the UK vs 18% in the USA) and less likely to receive targeted therapy (12% in the UK vs 16% in the USA). As shown in online supplemental table 3, conditional on the 1L therapy received, there were large differences in the proportion of UK versus US patients who went on to receive 2L therapies.

The median OS across all therapies was 9.5 months (95% CI 8.8 to 10.7) in the UK compared with 10.4 months (95% CI 9.7 to 11.0) in the USA prior to population adjustment (standardisation) (table 2). After population adjustment, median OS in the USA (9.6 months (95% CI 9.0 to 10.2)) was more similar to median OS in the UK, indicating the importance of matching patient characteristics across both countries. Adjusted median OS was similar in the UK and USA for 1L chemotherapy (8.1 months (95% CI 7.4 to 8.9) in the UK vs 7.7 months (95% CI 7.1 to 8.3) in the USA), immunotherapy (14.0 months (95% CI 10.7 to 20.6) in the UK vs 13.9 months (95% CI 11.0 to 17.1) in the USA) and targeted therapy (20.2 months (95% CI 16.0 to 30.5) in the UK vs 21.6 months (95% CI 18.5 to 23.7) in the USA). Similar patterns were observed for RMST at 12 and 24 months.

OS curves exhibited a similar shape for each 1L drug class over the duration of follow-up (figure 1). In general, the OS curves were similar and overlapping in all treatment groups once the data were adjusted to match patient characteristics. For 1L chemotherapy—irrespective of adjustment (standardisation)—the OS curves overlap until about 12 months, after which OS estimates are lower in the UK versus the USA. OS is very similar in the 1L immunotherapy and 1L targeted therapy groups after adjustment while differing prior to adjustment.

Extending the study period for US data to 1 October 2015 led to small reductions in OS but did not qualitatively affect study results (online supplemental table 4). Imputing all missing ECOG PS scores as 0 or 1 did not materially change the results while imputing as 2 or more led to higher estimates of median OS (online supplemental table 5). For the comparison with Pilleron *et al*, median OS for patients receiving 1L chemotherapy was similar for the UK and US cohorts after standardisation for those aged less than 75 years (7.7 months (95% CI 7.5 to 7.9) for the UK vs 8.1 months (95% CI 7.8 to 8.5) for the USA) and those 75 years or older (7.9 months (95% CI 7.5 to 8.2) for the UK vs 7.6 months (95% CI 7.0 to 8.4) for the USA) (online supplemental table 6).

Table 2 Median OS and RMST at 12 and 24 months in the UK and USA by 1L drug class

Analysis	Summary	US unweighted	US weighted*	UK
Overall	mOS (95% CI)	10.4 (9.7 to 11.0)	9.6 (9.0 to 10.2)	9.5 (8.8 to 10.7)
	12 months RMST (SE)	8.0 (0.07)	7.8 (0.07)	8.2 (0.13)
	24 months RMST (SE)	12.3 (0.15)	11.9 (0.15)	12.0 (0.27)
Chemo	mOS (95% CI)	8.1 (7.5 to 8.7)	7.7 (7.1 to 8.3)	8.1 (7.4 to 8.9)
	12 months RMST (SE)	7.5 (0.09)	7.4 (0.10)	7.7 (0.16)
	24 months RMST (SE)	10.9 (0.18)	10.6 (0.19)	10.5 (0.3)
IO mono.	mOS (95% CI)	10.2 (8.5 to 11.6)	13.9 (11.0 to 17.1)	14.0 (10.7 to 20.6)
	12 months RMST (SE)	7.6 (0.16)	8.31 (0.17)	8.79 (0.31)
	24 months RMST (SE)	12.3 (0.34)	13.64 (0.36)	14.23 (0.69)
Targeted	mOS (95% CI)	23.7 (22.4 to 27.1)	21.6 (18.5 to 23.7)	20.2 (16.0 to 30.5)
	12 months RMST (SE)	10.1 (0.14)	9.8 (0.15)	9.8 (0.34)
	24 months RMST (SE)	17.3 (0.33)	16.4 (0.35)	16.3 (0.77)

*US data standardised to reflect average characteristics of patients in the UK for age, sex, ECOG PS score (0–1 or 2+) and histology (squamous cell, non-squamous cell, unknown).
chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IO mono, immunotherapy monotherapy; 1L, first line; mOS, median overall survival; OS, overall survival; RMST, restricted mean survival time.

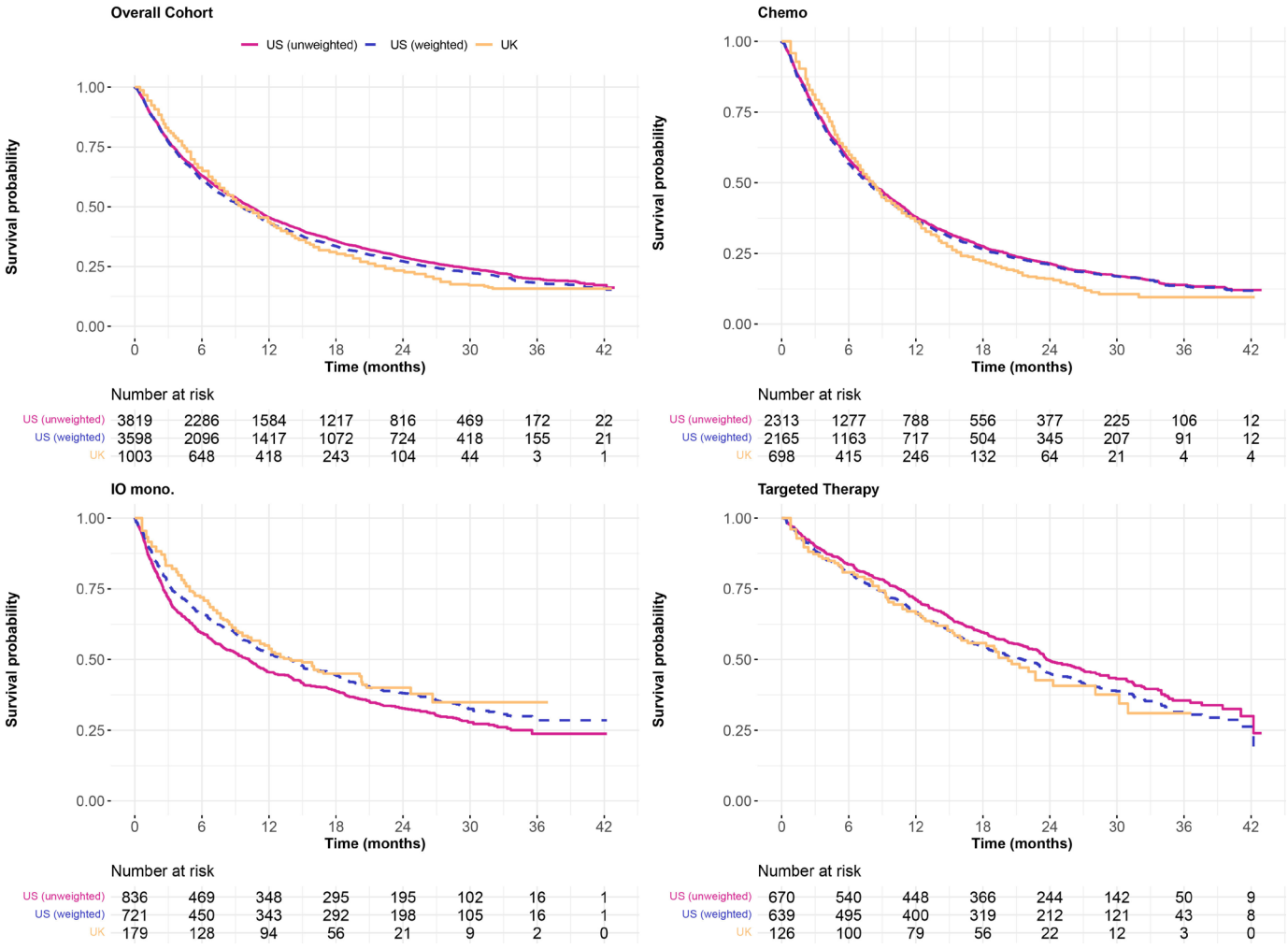

Figure 1 OS curves for the UK and USA before and after standardisation by 1L drug class. US data standardised to reflect average characteristics of patients in the UK for age, sex, ECOG PS score (0–1 or 2+) and histology (squamous cell, non-squamous cell, unknown). 1L, first line; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IO mono, immunotherapy monotherapy; OS, overall survival.

The probability of survival at 6 months was also similar but survival at 12 months was 5 percentage points higher for the US cohort compared with the UK cohort. TTD from the US cohort standardised to UK characteristics was 3.0 (95% CI 2.9 to 3.0), 4.6 (95% CI 4.0 to 6.0) and 9.7 (95% CI 9.0 to 10.9) months for patients receiving 1L chemotherapy, immunotherapy and targeted therapy, respectively (online supplemental table 7). In a post hoc analysis, we 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 standardisation, for the UK and the USA (see online supplemental figure 2).

DISCUSSION

We compared OS for patients receiving 1L treatment for aNSCLC in the UK and the USA and found that, after adjusting for a set of common demographic and clinical characteristics, estimates of OS were similar between countries for those initiating 1L immunotherapy and targeted therapies. Estimates were similar for those initiating 1L chemotherapy for the first 12 months, after which some divergence was observed by visual inspection with OS higher in the USA versus the UK. This suggests that, in this population, it may be reasonable to use data from the USA to improve our understanding of OS for patients in the UK, where relevant local data are currently unavailable or limited. This could be useful to HTA decision-makers when evaluating US data. The ability to make use of international data where local data are currently unavailable or limited could help address decision uncertainties such as real-world outcomes, long-term survival and time on treatment.

In addition to finding that US patients receiving 1L chemotherapy had a higher OS than UK patients after approximately 12 months, we observed a similar phenomenon in the US comparison with Pilleron *et al*.[10] This could reflect real differences in long-term OS but could also be explained by other factors such as time-period

effects, differences in censoring patterns, differences in subsequent treatment patterns or differences in the distributions of unmeasured prognostic factors of OS across the two settings. In a post hoc analysis, we found some indication of a time period effect with OS curves similar to when restricting US data to the period before the widespread use of immunotherapies in the USA. The importance of the introduction of immunotherapies is evidenced in Snee *et al*, where we see higher survival over time for patients initiating therapy between 2013 and 2017 vs 2007 and 2012.[18]

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, specific products, patient subgroups or outcomes is unclear and should be explored further. Of note, a previous study in the same indication found OS results from the USA were similar to OS results from Canada (Ramagopalan *et al*),[8] although with greater differences identified for 1L immunotherapy than for chemotherapy.

A key limitation of the study relates to the UK data used for comparison. First, the study included data from only nine sites and its representativeness to the general UK population is unknown. However, we found similar results for 1L chemotherapy when using aggregate data reported from the national SACT registry.[10] Second, we did not have access to full details of the study design in the original UK retrospective study, for instance, how combination therapies consisting of more than one drug class were considered in classifying 1L and 2L therapies (except for immunotherapy which was stated to be monotherapy only). Third, we only had aggregate data for comparison. This limited our ability to further adjust for patient characteristics or subsequent lines of therapy. Fourth, the UK data had access to only a limited set of demographic and clinical characteristics and the definitions did not always align with those from the US data. During the time of the study, there were differences between the countries in biomarker testing threshold scores for use of immunotherapy, though additional sensitivity analysis did not find this to meaningfully change the study results (see online supplemental table 8). There may be additional prognostic variables for which adjustment could improve the comparability of OS between the UK and USA (online supplemental tables 9–11). However, it is worth noting that, despite these limitations, we found OS results to be comparable between the UK and the USA. Currently, with the limited availability of representative and clinically orientated local patient-level data sources, this is more likely to reflect the context in which such studies will be used to inform decision-making. Finally, it was not suitable to compare TTD, due to meaningful differences in the definitions used (online supplemental table 12), which is an important outcome for health economic analyses. Future work should assess the transportability of TTD and other HTA-relevant outcomes.

These results should help inform HTA reviewers when assessing the relevance of US data in the evaluation of aNSCLC therapies.

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Competing interests At the time of this study, SK, PM, BB, TJR, BA, JK and AS reported employment with Flatiron Health, which is an independent member of the Roche Group. BA conducted this work as an employee of Flatiron Health. PM, BB, TJR, BA, JK and AS reported stock ownership in Roche. All other authors declared no competing interests.

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