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

SUPPLEMENTARY MATERIALS

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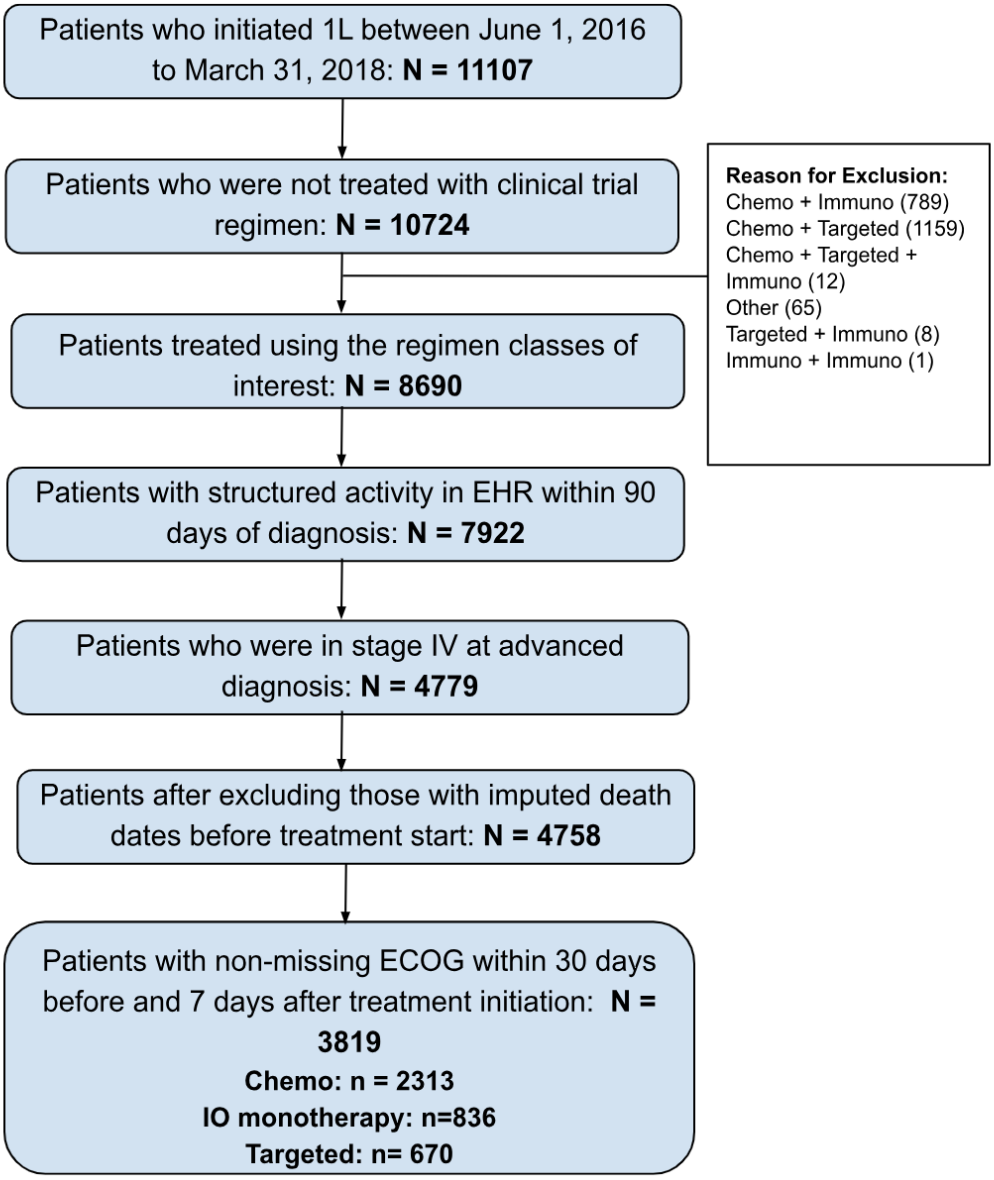
Supplementary Table 1. Pragmatic literature review

	UK publication		
Factor	**Lester et al. (2021)**	**Snee et al. (2021)**	**Pilleron et al. (2023)**
Peer-reviewed	Yes	Yes	No (Preprint)
Used in our analysis	Yes	No	Sensitivity analyses
Data Source	9 NHS Trusts and hospitals around the UK	Leeds Teaching hospitals	UK SACT dataset
Population of interest	Patients with stage IV advanced NSCLC	People with NSCLC	Patients with advanced NSCLC in Stages III and IV (analyses stratified by stage)
Sample Size	1003	3739	20,716
Treatment of interest	1L chemo, immunotherapy and targeted therapy	NA	Chemotherapy (Cytotoxic)
Index date anchor	1L treatment initiation	Disease diagnosis	1L treatment initiation
Study Period	2016–2019 (Enrol: 2016 to 2018)	2007–2018 (Enrol: 2007–2017)	2014–2018 (Enrol: 2014–2017)
Patient characteristics available at index	Age Sex ECOG PS Histology TNM Stage Biomarkers (high missingness)	Age Sex WHO performance status Histology TNM stage	Age Sex ECOG PS Ethnicity Treatment intent(curative vs palliative)
Death Ascertainment	Methodology not mentioned	Linkage of EMR to the Office of National Statistics death certificates	Linkage of SACT data to data from the National Cancer Registration and Analysis Service (NCRAS) data
OS Analysis	Whole cohort regardless of treatment Stratified by treatment	First stratified by disease stage(I, II, III, IV) Within each stage stratum, they stratified by tumour histology (squamous, nonsquamous,...) and year of diagnosis	First stratified by disease stage (III vs IV) Within each stage stratum, they stratified by age (< 75 vs 75+)

Search-term in pubmed: (advanced non-small lung cancer OR aNSCLC OR advanced NSCLC OR metastatic non-small lung cancer OR met aNSCLC) AND (treatment pattern OR treatment guideline OR practice pattern OR treatment practice) AND (overall survival OR OS OR survival OR outcomes OR discontinuation OR ttd OR time on treatment OR ToT) AND (United Kingdom OR UK OR England). Filters applied: 2011 to 2022, Classical Article, Clinical Study, Comparative Study, Guideline, Meta-Analysis, Observational Study, Practice Guideline, Preprint, Review, Systematic Review. 1L=first-line. chemo=chemotherapy. ECOG PS=Eastern Cooperative Oncology Group performance status. EMR=electronic medical record. NA=not applicable. NHS=National Health Service. NSCLC=non-small cell lung cancer. OS=overall survival.

SACT=systemic anti-cancer therapy. WHO=World Health Organization.



Supplementary Figure 1. Flow diagram of inclusion and exclusion criteria applied to the real-world cohort.

21 patients were excluded because their imputed death date preceded treatment start. In Flatiron Health date of death is provided at the month granularity for privacy reasons. For the analysis, the date of death is imputed to be the 15th of the month. 1L=first-line therapy. Chemo=chemotherapy. ECOG PS=Eastern Cooperative Oncology Group performance status. EHR=electronic health record. Immuno/IO=immunotherapy. Targeted=targeted therapy.

Supplementary Table 2. Baseline characteristics and details of follow-up for patients in the UK and US by 1L drug class (Including variables that were only available in the US analysis)

	Overall		1L Chemo		1L IO monotherapy		1 L targeted therapy	
Characteristic	**UK (n=1003)**	**US (n=3819)**	**UK (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 (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)
Race/Ethnicity, No. (%)								
Asian	••	117 (3.1)	••	35 (1.5)	••	17 (2.0)	••	65 (9.7)

	Overall		1L Chemo		1L IO monotherapy		1 L targeted therapy	
Characteristic	**UK (n=1003)**	**US (n=3819)**	**UK (n= 698)**	**US (n=2313)**	**UK (n = 179)**	**US (n=836)**	**UK (n = 126)**	**US (n=670)**
Black or African American	••	354 (9.3)	••	235 (10.2)	••	75 (9.0)	••	44 (6.6)
White	••	2678 (70.1)	••	1651 (71.4)	••	608 (72.7)	••	419 (62.5)
Other Race	••	333 (8.7)	••	185 (8.0)	••	66 (7.9)	••	82 (12.2)
Missing/Unknown	••	337 (8.8)	••	207 (8.9)	••	70 (8.4)	••	60 (9.0)
Practice Type, No. (%)								
Community	••	3241 (84.9)	••	1985 (85.8)	••	725 (86.7)	••	531 (79.3)
Academic	••	521 (13.6)	••	290 (12.5)	••	104 (12.4)	••	127 (19.0)
Both	••	57 (1.5)	••	38 (1.6)	••	7 (0.8)	••	12 (1.8)
Time from advanced diag. to treatment initiation (months)								
Median (IQR)	••	1.15 (0.76–1.74)	••	1.15 (0.72–1.68)	••	1.25 (0.85–1.97)	••	1.12 (0.79–1.61)
Smoking History, No. (%)								
History of smoking	••	3200 (83.8)	••	2095 (90.6)	••	765 (91.5)	••	340 (50.7)
No history of smoking	••	610 (16.0)	••	213 (9.2)	••	70 (8.4)	••	327 (48.8)
Unknown/Not documented	••	9 (0.2)	••	5 (0.2)	••	1 (0.1)	••	3 (0.4)
***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)

	Overall		1L Chemo		1L IO monotherapy		1 L targeted therapy	
Characteristic	**UK (n=1003)**	**US (n=3819)**	**UK (n= 698)**	**US (n=2313)**	**UK (n = 179)**	**US (n=836)**	**UK (n = 126)**	**US (n=670)**
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)
***ROS1* Status, No. (%)**								
Rearrangement present	••	33 (0.9)	••	8 (0.3)	••	1 (0.1)	••	24 (3.6)
Rearrangement not present	••	1917 (50.2)	••	1024 (44.3)	••	504 (60.3)	••	389 (58.1)
Unknown/Missing	••	1869 (48.9)	••	1281 (55.4)	••	331 (39.6)	••	257 (38.4)
***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)

*Lester et al.,(2021) only reported range. ALK=anaplastic lymphoma kinase. chemo=chemotherapy. ECOG PS=Eastern Cooperative Oncology Group performance status. EGFR=epidermal growth factor receptor.

	Overall		1L Chemo		1L IO monotherapy		1 L targeted therapy	
Characteristic	**UK (n=1003)**	**US (n=3819)**	**UK (n= 698)**	**US (n=2313)**	**UK (n = 179)**	**US (n=836)**	**UK (n = 126)**	**US (n=670)**

IO=immunotherapy. ROS1=ROS proto-oncogene 1, receptor tyrosine kinase. PDL1/PD-L1=programmed cell death ligand 1. **In the US analysis, patients were considered PD-L1 positive if the PD-L1 tumour proportion score was ≥ 1% or if there was reference to PD-L1 positivity in the medical chart.

Supplementary Table 3. Treatment switching from first to second line therapies in UK and US

	1L therapy			
	Any	Chemo	IO	Targeted
UK				
Any 2L	287 (29%)	229 (33%)	28 (16%)	30 (24%)
Conditional on 2L				
Chemo	104 (36%)	74 (32%)	26 (93%)	4(13%)
IO	148 (52%)	146(64%)	2 (7%)	0 (0%)
Targeted	35 (12%)	9(4%)	0 (0%)	26 (87%)
US				
Any 2L	1835 (48%)	1245 (54%)	234 (28%)	356 (53%)
Conditional on 2L				
Chemo	330 (18%)	201 (16%)	105 (45%)	24 (7%)
IO	896 (49%)	827 (66%)	38 (16%)	31 (9%)
Targeted	317 (17%)	65 (5%)	9 (4%)	243 (68%)
Other*	292 (16%)	152 (12%)	82 (35%)	58 (16%)

*Combination regimens and other treatments. This data is unknown for the UK.
chemo=chemotherapy. IO=immunotherapy. 1L=first-line. 2L=second-line.

Supplementary Table 4. Overall survival and restricted mean survival time for the extended US cohort

Analysis	Summary	US unweighted	US weighted	UK
Overall (N=5106)	mOS (95% CI)	9.86 (9.30–10.4)	9.23 (8.71–9.79)	9.5(8.8–10.7)
	RSMT at:			
	12 months	7.92(0.06)	7.78(0.06)	8.24(0.13)
	24 months	12.11(0.13)	11.79(0.13)	12.01(0.27)
Chemo (N= 3340)	mOS (95% CI)	7.89 (7.39–8.34)	7.46 (7.06–8.05)	8.1(7.4–8.9)
	RSMT at:			
	12 months	7.45(0.08)	7.32(0.08)	7.69(0.16)
	24 months	10.83(0.15)	10.55(0.16)	10.50(0.3)
IO mono. (N= 892)	mOS (95% CI)	9.63 (7.95–11.2)	13.4 (10.9–15.7)	14.0(10.7–20.6)
	RSMT at:			
	12 months	7.57(0.16)	8.26(0.17)	8.79(0.31)
	24 months	12.11(0.33)	13.50(0.35)	14.23(0.69)
Targeted (N= 874)	mOS (95% CI)	23.1 (21.0–24.9)	20.0 (17.2–22.9)	20.2(16.0–30.5)
	RSMT at:			
	12 months	9.98(0.12)	9.67(0.13)	9.77(0.34)
	24 months	16.92(0.29)	16.08(0.30)	16.30(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. CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. IO=immunotherapy. IO mono=immunotherapy monotherapy. mOS=median overall survival. RMST=restricted mean survival time. se=standard error. Targeted=targeted therapy.

Supplementary Table 5. Results for sensitivity analysis imputing missing ECOG PS scores

Scenario	Prevalence ECOG PS 0 or 1 after imputation (Before = 73%)	Unweighted mOS (95% CI)	Weighted mOS (95% CI)
Best (impute missing ECOG PS as 0 or 1)	78.3%	10.48 (9.89–11.04)	9.20 (8.71–9.86)
Worst (impute missing ECOG PS of 2 or more)	58.6%	10.48 (9.89–11.04)	10.32 (9.72–11.01)

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). CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. mOS=median overall survival.

Supplementary Table 6. OS results for 1L chemotherapy for US data using UK data from Pilleron et al. 2021

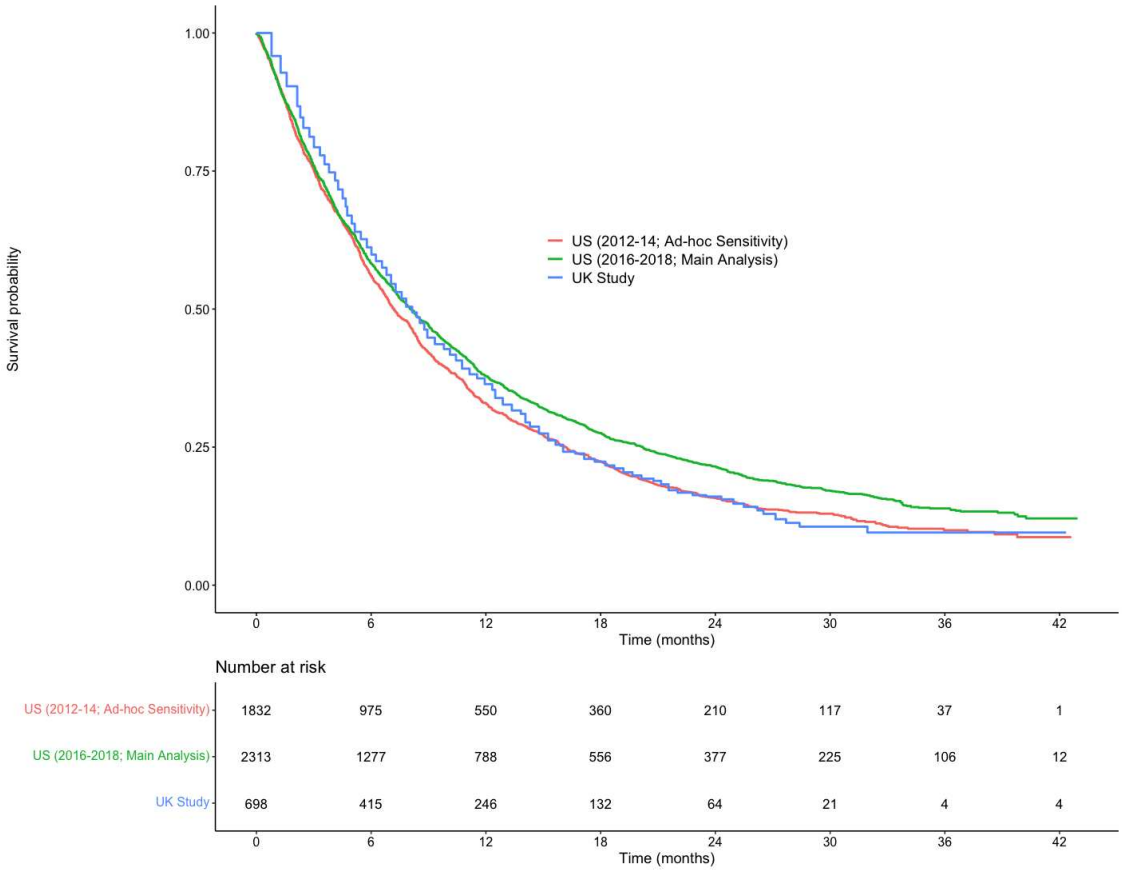
Analysis	Variable	US unweighted	US weighted	UK (Pilleron et al.)
Age < 75	mOS (95% CI)	7.9 (7.6–8.2)	8.1 (7.8–8.5)	7.7 (7.5–7.9)
	Survival prob est. (%) at			
	6 months	59 (58–60)	60 (58–61)	59.7 (58.7–60.6)
	12 months	37 (36–38)	38 (36–39)	33.2 (32.3–34.1)
Age ≥ 75	mOS (95% CI)	7.1 (6.8–7.7)	7.6 (7.0–8.4)	7.9 (7.5–8.2)
	Survival prob est. (%) at			
	6 months	56 (54–59)	58 (55–61)	60.4 (58.4–62.5)
	12 months	35 (33–37)	38 (35–41)	33.4 (31.5–35.4)

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. CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. mOS=median overall survival. OS=overall survival.

Supplementary Table 7. Time to treatment discontinuation (TTD) from US Flatiron data before and after standardisation by 1L drug class

	Median rwTTD (95% CI)			
Analysis	**Overall**	**Chemo**	**Immuno**	**Targeted**
US Unweighted	3.7 (3.5–3.8)	3.0 (2.9–3.0)	4.6 (4.0–6.0)	9.7 (9.0–10.9)
US Weighted	3.4 (3.2–3.6)	3.0 (2.8–3.0)	6.2 (4.8–7.4)	9.2 (8.5–10.2)

US data standardised to reflect average characteristics of patients in the UK for age, sex, ECOG score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknown). 1L=first-line. chemo=chemotherapy. CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. IO=immunotherapy. rwTTD=real-world time to treatment discontinuation. Targeted=targeted therapy.



Supplementary Figure 2. Post-hoc analysis comparing standardised OS for patients initiating 1L chemotherapy using data from the US between 2012–2014.

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).

Supplementary Table 8. Transportability analysis for immunotherapy exposed cohort with tumour proportion score of ≥ 50%

Analysis	Summary	US PDL1 50+ unweighted	US PDL1 50+ weighted	UK
IO mono.	mOS (95% CI)	11.6(10.0–14.9)	14.9 (11.7–18.9)	14.0 (10.7–20.6)
	12 months RMST (se)	8.01 (0.19)	8.48 (0.19)	8.79 (0.31)
	24 months RMST (se)	13.12 (0.40)	14.03 (0.42)	14.23 (0.69)

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). CI=confidence interval. IO mono=immunotherapy monotherapy. mOS=median overall survival. RMST=restricted mean survival time. se=standard error.

Supplementary Table 9. Full and reduced models for US for any 1L treatment

		Full Model		Reduced Model	
Variable		Log(HR)	95% CI	Log(HR)	95% CI
Sex					
Female		••	••	••	••
Male		0.23	0.16–0.31	0.25	0.17–0.33
Age at treatment initiation		0.01	0.00–0.01	0.01	0.00–0.01
Race					
White		••	••	••	••
Non-white		-0.08	-0.18–0.01	••	••
Missing/Unknown		0.12	-0.01–0.26	••	••
Practice Type					
Community		••	••	••	••
Academic		-0.10	-0.21–0.02	••	••
Both		-0.80	-1.2–-0.37	••	••
Time from diagnosis to treatment initiation (months)		-0.03	-0.04–-0.01	••	••
1L initiation year					
	2016	••	••	••	••
	2017	-0.03	-0.12–0.05	••	••
	2018	-0.09	-0.22–0.04	••	••
1L Regimen Class					
Chemo		••	••	••	••
Immuno		-0.21	-0.31–-0.11	-0.26	-0.35–-0.16
Targeted		-0.28	-0.48–-0.07	-0.69	-0.80–-0.57
ECOG PS					
0–1		••	••	••	••
2+		0.61	0.53–0.70	0.61	0.53–0.70
Tumor Pathology					
Squamous		••	••	••	••
Non-squamous		-0.13	-0.23–-0.04	-0.19	-0.27–-0.10
Not otherwise specified		0.17	-0.01–0.36	0.14	-0.04–0.32

	Full Model		Reduced Model	
Variable	Log(HR)	95% CI	Log(HR)	95% CI
Smoking History				
History of smoking	••	••	••	••
No history of smoking	-0.09	-0.22–0.03	••	••
Unknown/Not documented	1.30	0.58–2.1	••	••
***EGFR* Status**				
Mutation positive	••	••	••	••
Mutation negative	0.38	0.17–0.60	••	••
Unknown/Missing	0.49	0.26–0.73	••	••
***ALK* Status**				
Rearrangement present	••	••	••	••
Rearrangement not present	0.69	0.33–1.0	••	••
Unknown/Missing	0.53	0.16–0.91	••	••
***ROS1* Status**				
Rearrangement present	••	••	••	••
Rearrangement not present	0.50	-0.04–1.0	••	••
Unknown/Missing	0.64	0.09–1.2	••	••
***PD-L1* Status**				
PD-L1 positive	••	••	••	••
PD-L1 negative/not detected	0.15	-0.01–0.31	••	••
Unknown/Missing	0.07	-0.07–0.20	••	••
Likelihood-ratio test	**chi-square(df=17)= 90.3, p<0.001**			
Concordance Index	**0.647**		**0.636**	

1L=first-line. ALK=anaplastic lymphoma kinase. chemo=chemotherapy. CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. EGFR=epidermal growth factor receptor. HR=hazard ratio. Immuno=immunotherapy. PD-L1=programmed cell death ligand 1. ROS1=ROS proto-oncogene 1, receptor tyrosine kinase. Targeted=targeted therapy.

Supplementary Table 10. Full model for overall survival in the US by 1L drug class

		Chemo		Immunotherapy		Targeted	
Variable		Log(HR)	95% CI	Log(HR)	95% CI	Log(HR)	95% CI
Sex							
Female		••	••	••	••	••	••
Male		0.23	0.13–0.32	0.29	0.11–0.46	0.22	0.00–0.44
Age at treatment initiation		0.00	0.00–0.01	0.00	-0.01–0.01	0.02	0.01–0.04
Race							
White		••	••	••	••	••	••
Non-white		-0.13	-0.25–-0.01	-0.07	-0.29–0.15	0.13	-0.11–0.38
Missing/Unknown		0.13	-0.04–0.29	0.23	-0.07–0.52	0.03	-0.36–0.42
Practice Type							
Community		••	••	••	••	••	••
Academic		-0.02	-0.16–0.13	-0.37	-0.65–-0.08	-0.11	-0.39–0.17
Both		-0.78	-1.3–-0.28	-0.05	-1.0–0.95	-2.00	-4.0–-0.05
Time from diagnosis to treatment initiation (months)		-0.04	-0.06–-0.01	-0.02	-0.04–0.01	-0.04	-0.09–0.02
1L initiation year							
	2016	••	••	••	••	••	••
	2017	-0.02	-0.12–0.09	-0.19	-0.45–0.06	-0.01	-0.24–0.22
	2018	-0.03	-0.18–0.13	-0.34	-0.67–-0.02	-0.12	-0.50–0.25
ECOG PS							
0–1		••	••	••	••	••	••
2+		0.57	0.46–0.67	0.71	0.54–0.88	0.71	0.47–0.94
Tumor Pathology							
Squamous		••	••	••	••	••	••
Non-squamous		-0.06	-0.17–0.05	-0.31	-0.52–-0.10	-0.64	-1.2–-0.09
NOS		0.20	-0.02–0.41	-0.11	-0.51–0.29	0.34	-0.44–1.1
Smoking History							
History of smoking		••	••	••	••	••	••
No history of smoking		-0.03	-0.21–0.14	0.04	-0.26–0.35	-0.36	-0.58–-0.14
Unknown/Not documented		1.90	0.87–2.9	0.53	-1.5–2.5	0.33	-1.1–1.7

	Chemo		Immunotherapy		Targeted	
Variable	Log(HR)	95% CI	Log(HR)	95% CI	Log(HR)	95% CI
***EGFR* Status**						
Mutation positive	••	••	••	••	••	••
Mutation negative	0.33	0.02–0.64	-0.86	-1.6–-0.16	0.51	0.17–0.85
Unknown/Missing	0.40	0.05–0.74	-0.41	-1.1–0.31	0.63	0.23–1.0
***ALK* Status**						
Rearrangement present	••	••	••	••	••	••
Rearrangement not present	0.69	-0.20–1.6	0.15	-1.0–1.3	0.65	0.19–1.1
Unknown/Missing	0.71	-0.19–1.6	-0.29	-1.5–0.94	0.68	0.17–1.2
***PD-L1* Status**						
PD-L1 positive	••	••	••	••	••	••
PD-L1 negative/not detected	0.09	-0.12–0.30	0.31	-0.10–0.72	0.27	-0.21–0.76
Unknown/Missing	-0.03	-0.22–0.17	0.05	-0.16–0.26	0.44	-0.01–0.89
Concordance Index	0.61		0.64		0.68	

1L=first-line. ALK=anaplastic lymphoma kinase. chemo=chemotherapy. CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. EGFR=epidermal growth factor receptor. HR=hazard ratio. NOS=not otherwise specified. PD-L1=programmed cell death ligand 1. Targeted=targeted therapy.

Supplementary Table 11. Reduced models for OS in the US by 1L drug class

	Chemo		Immuno		Targeted	
Variable	Log(HR)	95% CI	Log(HR)	95% CI	Log(HR)	
Sex						
Female	••	••	••	••	••	••
Male	0.24	0.14–0.33	0.26	0.09–0.43	0.29	0.08–0.51
Age at treatment initiation	0.00	0.00–0.01	0.01	0.00–0.01	0.03	0.02–0.04
ECOG PS						
0–1	••	••	••	••	••	••
2+	0.57	0.47–0.68	0.68	0.51–0.85	0.64	0.41–0.87
Tumor Pathology						
Squamous	••	••	••	••	••	••
Non-squamous	-0.12	-0.22–-0.02	-0.33	-0.51–-0.14	-0.84	-1.4–-0.29
NOS	0.18	-0.04–0.39	-0.15	-0.54–0.24	0.24	-0.53–1.0
Concordance Index	0.59		0.63		0.65	

1L=first-line. chemo=chemotherapy. CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. EGFR=epidermal growth factor receptor. HR=hazard ratio. Immuno=immunotherapy. NOS=not otherwise specified. PD-L1=programmed cell death ligand 1. Targeted=targeted therapy.

Supplementary Table 12. The difference in the definition of rwTTD in the US and UK analyses

	Definition of Endpoint in data source	
Endpoint	**Flatiron Health**	**Lester et al. 2021**
rwTTD	Time from 1L treatment initiation to treatment discontinuation (for any reason including death). **Start date:** first drug episode for the drug of interest within a given line of therapy (LOT) **End date:** last drug episode for the drug of interest within a given LOT Time at risk is time elapsed between start and end dates of a LOT A patient is treated as uncensored if ANY of the following three events are observed in the data: The patient advanced to a new LOT. Because rwTTD is defined within a given LOT, evidence of advancement to a new LOT mandates the discontinuation of the treatment offered under the preceding line. The patient has not advanced to a new LOT, but has a recorded date of death. Mortality should be treated as confirmatory of treatment discontinuation. The patient has not advanced to a new LOT and has no recorded date of death, but has sufficient evidence of confirmed structured activity after the last drug episode for the drug(s) of interest. In the absence of a more definitive condition like LOT advancement or evidence of death, inference of treatment discontinuation from structured EHR data is necessary. A prolonged period (e.g., 120 days) of confirmed structured activity following the last recorded drug episode may be considered reasonable evidence of treatment discontinuation because it suggests that the patient is still being followed at the treating clinic; thus, one can assume consistent capture of treatment data. As such, it is unlikely that the cessation of new drug episodes is the result of missing data.	Time from 1L treatment initiation to treatment discontinuation (for any reason including death). ["...in patients who discontinued treatment but were still alive, the treatment *end date was recorded as the start date of the last treatment cycle* because a definitive end date of the last cycle was not available, and the last cycle start date was the latest date when it was certain that treatment was continuing."]

1L=first-line therapy. EHR=electronic health records. LOT=line of therapy. rwTTD= real-world time to treatment discontinuation.