Are Real-World Survival Outcomes in Metastatic Breast Cancer Transportable Between the US and Austria?

Harlan Pittell, PhD[1]; Uwe Siebert, MD, MPH, MSc, ScD[2]; Per-Olof Thuresson, MSc, PharmD[3]; Lu Chen, PhD[3]; Carol Hawkes, MSc, PhD[4]; Danalyn Byng, MSc, PhD[5]; Gabriel Rinnerthaler, MD[6]; Simon Peter Gampenrieder, MD[6]; Richard Greil, MD[6]; Mohamed S. Ali, PharmD, SM[1]; Philani Mpofu, PhD[1]; Elsie Horne, PhD[7]; Qianyi Zhang, MS[1]; Amit Samani, PhD, MD[7]; Blythe Adamson, PhD, MPH[1]

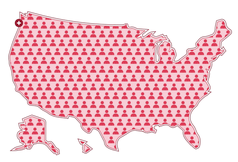
[1]Flatiron Health, New York, NY, USA; [2]UMIT TIROL – University for Health Sciences and Technology, Hall in Tirol, Austria; [3]Roche/Genentech, Basel, Switzerland; [4]Daiichi Sankyo, Uxbridge, UK; [5]Daiichi Sankyo, Munich, Germany; [6]AGMT, Salzburg, Austria; [7]Flatiron Health, London, UK

Background

- HTA bodies generally prefer local evidence, but when not available, may rely on real-world evidence (RWE) from other countries.
- It remains uncertain whether such evidence is truly **transportable** across countries with differing populations, care delivery, and data capture.
- Given the global burden of **breast cancer,** understanding where survival estimates align across settings is critical for evidence-based policy decisions.
- **Objective**: Assess whether **real-world overall survival (OS)** outcomes in metastatic breast cancer (mBC) are transportable between the **US and Austria**, building on prior work using UK data and complementary analyses of treatment timing (Poster HSD26).

Using External Data to Address Evidence Gaps in Target Populations

Evidence gap in *target population*: small sample size, limited long-term outcomes, or restricted use of treatment of interest.



External data from another country (*source population*) may help address this gap.

Methods

Analyses were prespecified in a publicly available protocol registered on the ISPOR Open Science Framework (OSF)[1]. Harmonized real-world data from Austria and the US were used for comparative analysis of outcomes.

Data sources:

- **Austria – AGMT (Austrian Group Medical Tumor Therapy) Registry:** nationwide, prospective registry capturing patient characteristics, treatments, and outcomes across Austrian oncology centers[2]
- **US – Flatiron Health Research Database:** derived from deidentified electronic health records from US community oncology and academic practices[3]

Study population: Adults diagnosed with mBC between Jan 2015 and Sep 2024, follow-up through Dec 2024 (Austria: n = 1,292; US: n = 21,215)

Main outcome: Overall survival was measured from start of first-line (1L) systemic therapy to death, with censoring at data cutoff

Transportability analysis:

- A pooled logistic regression model was fitted on the US cohort to estimate survival probabilities adjusted for clinical characteristics and 1L treatment type.
- Inverse odds of sampling weights (IOSW) were used to align the distribution of baseline characteristics in the US cohort with those of the Austrian cohort.
- The US model coefficients were then applied to the Austria cohort to generate predicted survival curves, overall and by tumor subtype.
- Predicted and observed OS curves were compared, and the **mean absolute difference** in 5-year survival was calculated to quantify agreement.

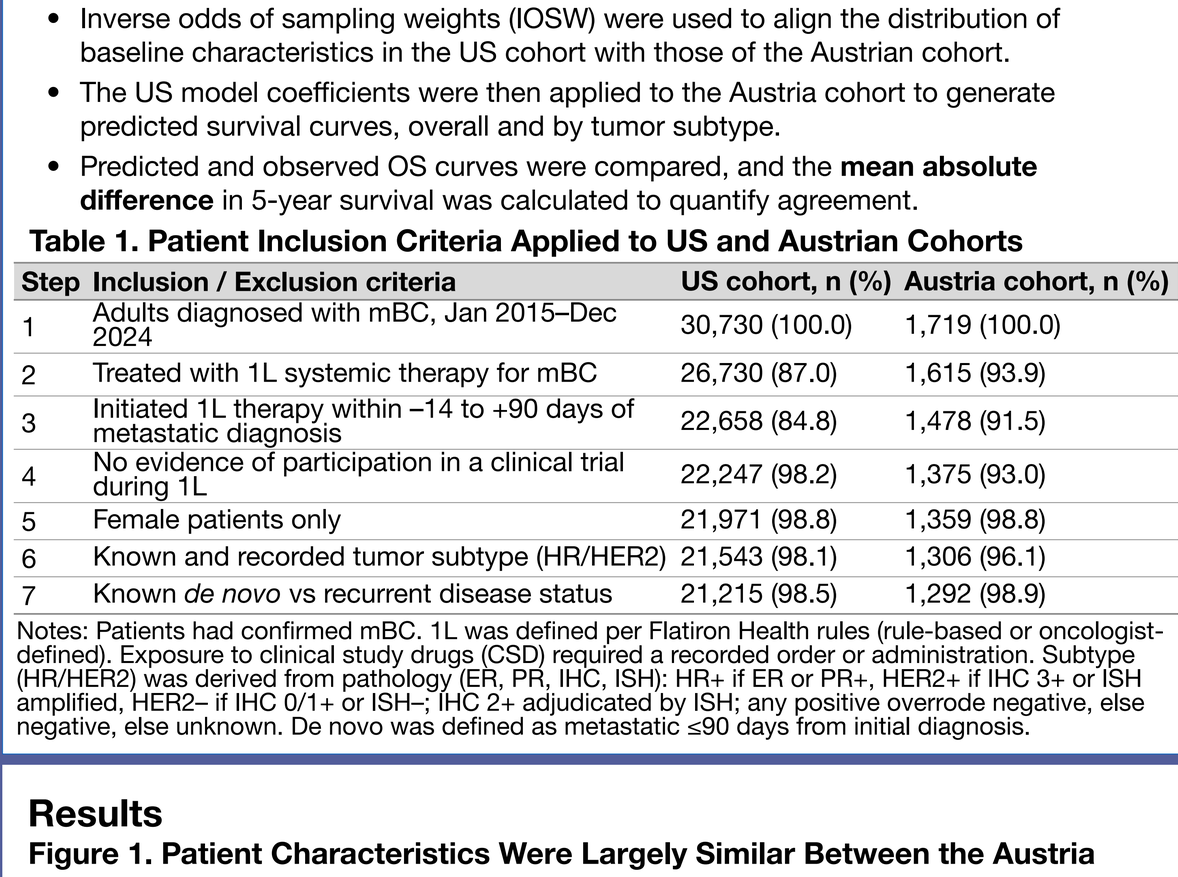
Table 1. Patient Inclusion Criteria Applied to US and Austrian Cohorts

Step	Inclusion / Exclusion criteria	US cohort, n (%)	Austria cohort, n (%)
1	Adults diagnosed with mBC, Jan 2015–Dec 2024	30,730 (100.0)	1,719 (100.0)
2	Treated with 1L systemic therapy for mBC	26,730 (87.0)	1,615 (93.9)
3	Initiated 1L therapy within –14 to +90 days of metastatic diagnosis	22,658 (84.8)	1,478 (91.5)
4	No evidence of participation in a clinical trial during 1L	22,247 (98.2)	1,375 (93.0)
5	Female patients only	21,971 (98.8)	1,359 (98.8)
6	Known and recorded tumor subtype (HR/HER2)	21,543 (98.1)	1,306 (96.1)
7	Known *de novo* vs recurrent disease status	21,215 (98.5)	1,292 (98.9)

Notes: Patients had confirmed mBC. 1L was defined per Flatiron Health rules (rule-based or oncologist-defined). Exposure to clinical study drugs (CSD) required a recorded order or administration. Subtype (HR/HER2) was derived from pathology (ER, PR, IHC, ISH): HR+ if ER or PR+, HER2+ if IHC 3+ or ISH amplified, HER2– if IHC 0/1+ or ISH–; IHC 2+ adjudicated by ISH; any positive overrode negative, else negative, else unknown. De novo was defined as metastatic ≤90 days from initial diagnosis.

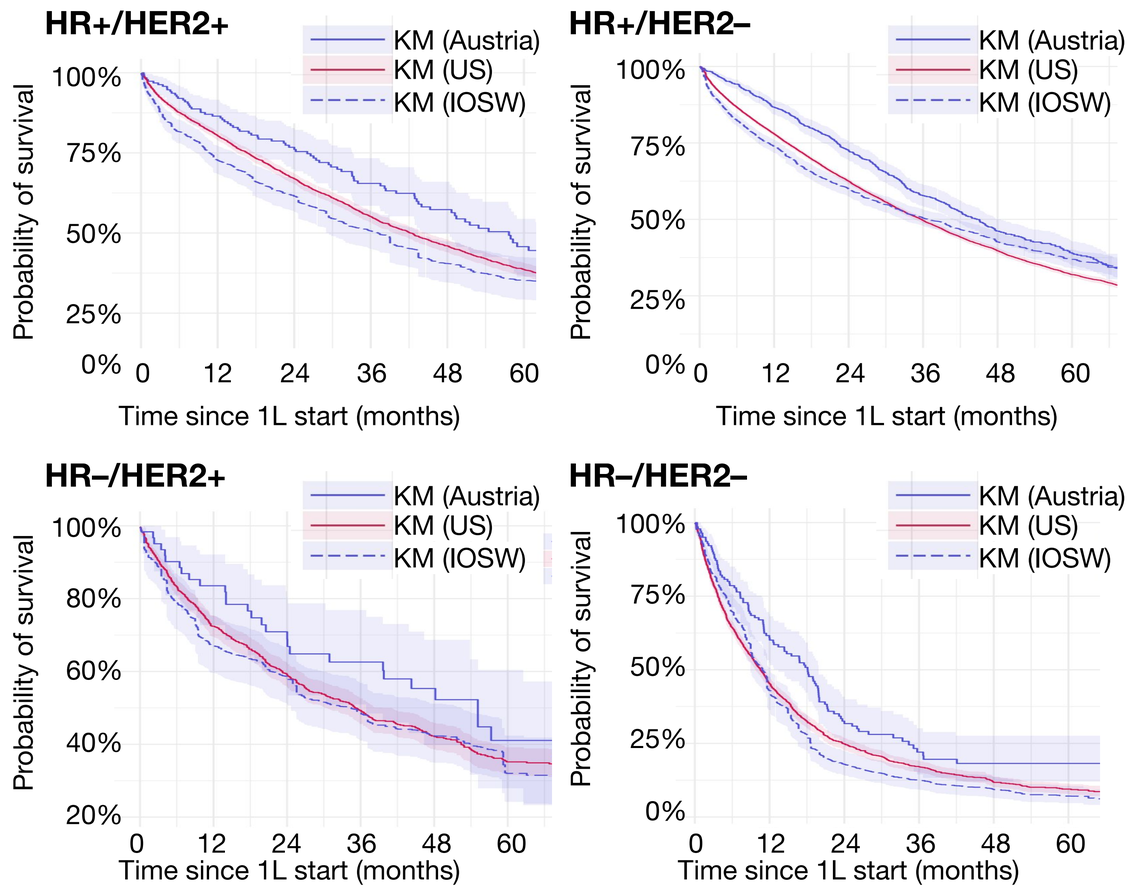
Results

Figure 1. Patient Characteristics Were Largely Similar Between the Austria and US Cohorts, With Only Minor Differences in BMI and Recurrent mBC



- Predicted survival curves for Austria underestimated observed Austrian survival in the overall breast cancer population and across subtypes. The degree of underestimation was more pronounced than when the Austrian observed survival was compared with the unadjusted US survival curves.
- Mean absolute differences over 5 years between predicted (US IOSW) and observed (Austria) survival were 8.10 months (6.37, 9.84) overall and by subtype:
  - HR+/HER2+: 13.73 (6.62, 15.55)
  - HR+/HER2–: 5.61 (4.04, 7.43)
  - HR–/HER2+: 9.37 (5.61, 29.59)
  - HR–/HER2–: 10.91 (7.77, 15.29)

Figure 2. US-Based Predictions Underestimate 5-Year Overall Survival in Austrian mBC Cohorts Across Subtypes



Notes: Each plot presents Kaplan–Meier survival curves by tumor subtype, showing observed survival for the US and Austrian cohorts, as well as predicted survival for the Austrian cohort based on the US model. Predictions were generated using a pooled logistic regression model fit on the US cohort, adjusted for age group, *de novo*/recurrent presentation, number and location of metastatic sites, BMI, and 1L class (chemotherapy, anti-HER2 therapy, CDK4/6 inhibitors, hormone therapy, and other immunotherapy). We examined five-year survival, an endpoint widely recognised as clinically meaningful and relevant for evaluating outcomes in mBC. IOSW approach adjusts US data to look like Austrian data.

Differences between predicted and observed survival in the Austria cohort suggest that **further evaluation is needed to assess the transportability** of real-world survival outcomes between countries and **explore methodologies for benchmarking.**

Discussion

Unadjusted survival was shorter in the US cohort than in the Austria cohort and the difference *widened* after standardization to the Austrian population data. Such differences likely reflect a combination of clinical, data capture, and healthcare system factors rather than true prognostic differences. These findings underscore the need for a more formal methodological framework to assess and quantify transportability of real-world outcomes across healthcare contexts.

Limitations

- **Data source differences:** The Austrian registry and US EHR data differ in completeness, follow-up duration, and capture of comorbidities and treatment intent, which may influence observed survival independently of underlying outcomes. These data may not also generalize to their respective source and target populations.
- **Residual confounding:** Important prognostic variables such as comorbidities, functional status, and genomic markers were unavailable or inconsistently measured across datasets.
- **Model scope:** The pooled logistic regression was developed in the US cohort; external application assumes covariate effects are stable across systems, which may not hold.

Future directions

Future work should evaluate fit-for-purpose data selection and cross-country comparability, including completeness of metastatic diagnoses, therapy capture, and system-level factors influencing care delivery. Developing and validating a standardized framework for transportability assessment, alongside methodological extensions such as multilevel modeling or adjustment for care setting, may improve interpretability of international RWD comparisons.

References: [1] Acquaah V, Pittell H, Mpofu PB, Horne E, Adamson B. US-Austria (Flatiron/AGMT) mBC Transportability Study Protocol and Statistical Analysis Plan. doi:10.17605/OSF.IO/S7ZR2; [2] AGMT_MBC Registry. Accessed October 7, 2025. http://agmt.at/mbc-registry/?lang=en [3] Flatiron Health. Database Characterization Guide. Flatiron.com. Published March 18, 2025. Accessed October 6, 2025. https://flatiron.com/database-characterization

Acknowledgments: Darren Johnson (Flatiron Health) for publication management. Data first presented at ISPOR Europe on 9-12 November 2025. The AGMT_MBC Registry is supported by grants from Roche, Daiichi Sankyo, Novartis, Pfizer, Caris Life Sciences, Eli Lilly, Seagen, Gilead, and AstraZeneca.
Disclosures: This study was sponsored by Flatiron Health, Inc.—an independent member of the Roche Group. During the study period, HP, MSA, PM, EH, QZ, AS, and BA reported employment with Flatiron Health, Inc. and stock ownership in Roche. DB and CH, employment and ownership of Daiichi Sankyo stock.
Author contact information: harlan.pittell@flatiron.com

Scan for abstract and digital poster