

Validation of Crossover Adjustment Outcomes in a Randomized Clinical Trial (RCT) using Real-world Evidence (RWE) in Non-small Cell Lung Cancer (NSCLC)

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Background

- Crossover is allowed in some randomized controlled trials (RCT), which may bias estimates of relative treatment effect.
- Several crossover correction methodologies may be applied, such as the rank-preserving structural failure time model, inverse probability of censoring weights and the two-stage method.
- These methods aim to adjust survival for patients who crossover, which allows for a more accurate estimation of the relative treatment effect.

Objective

- The aim of this study was to demonstrate the importance of validation of estimated survival outcomes from RCTs against survival using real-world data.

Key Results

- Crossover-adjusted analysis overestimated survival compared to real-world evidence (RWE) but demonstrated similar survival up to 10 months of follow-up.

Discussion/Conclusions

- Survival differences between the RWE and RCT studies might be explained by differences in quality of care, subsequent treatment after crossover, inclusion and exclusion criteria (e.g., programmed death-ligand 1 (PD-L1) status), limited patient numbers in the tail, or methodological issues regarding the two-stage method.
- Validation against RWE remains important for the prediction of clinically plausible survival.
- Further research is needed as RWE studies are non-controlled, non-randomized and observational, which limits head-to-head comparisons with RCTs and requires caution when interpreting results.

Methods

- Patients receiving chemotherapy from a German RWE² study and KEYNOTE-024¹ were compared on baseline characteristics and estimated overall survival (OS).
- Estimated survival before and after crossover adjustment was compared to survival based on RWE² in stage IV non-small cell lung cancer (NSCLC).
- In KEYNOTE-024¹, pembrolizumab was compared to chemotherapy in patients with stage IV NSCLC with a PD-L1 tumor proportion score of ≥50%.
 - The chemotherapy arm from KEYNOTE-024¹ included 151 patients and was corrected for crossover using the two-stage method.
- The RWE study² included 108 patients with stage IV NSCLC treated with chemotherapy.
 - The observational period was 6.33 years in the RWE² study (February 2010 to June 2016).
- Patient characteristics of KEYNOTE-024¹ and RWE² were compared on age, sex, histology and smoking status.
- Crossover from chemotherapy to the pembrolizumab group in KEYNOTE-024¹ was permitted in the event of disease progression.

Results

- Baseline characteristics in the KEYNOTE-024¹ and RWE² studies were similar (Table 1).
- PD-L1 status was ≥50% in KEYNOTE-024, but not reported for RWE.
- Other baseline characteristics such as Eastern Cooperative Oncology Group performance status score and prior received treatment were not consistently reported between both studies, which limited a direct comparison of the study populations (Table 2).
- Survival of RWE and RCT crossover-adjusted chemotherapy arms was almost identical up to month 10 of follow-up (Figure 1), which was confirmed by the area under the curve (AUC) and median OS (Table 3).

Table 1. Baseline characteristics

	Chemotherapy KEYNOTE-024 (n=151)	Chemotherapy RWE (n=108)
Age (years)	Median (range) 66.0 (38–85)	Mean (SD) 63.9 (10.6)
Sex (male) – n (%)	95 (62.9)	60 (55.6)
Histology – n (%)		
Squamous	27 (17.9)	25 (23.1)
Non-squamous	124 (82.1)	76 (70.4)
Smoking status – n (%)		
Current	31 (20.5)	Current/former
Former	101 (66.9)	81 (75.0)
Never	19 (12.6)	11 (10.2)
Region of enrollment	Global	Germany (Europe)

Type of chemotherapy regimen

KEYNOTE-024: carboplatin + pemetrexed, cisplatin + pemetrexed, carboplatin + gemcitabine, cisplatin + gemcitabine, or carboplatin + paclitaxel
RWE: platinum compounds, vinorelbine, pemetrexed, taxanes (docetaxel, paclitaxel), etoposide, gemcitabine
Abbreviations: RWE, real-world evidence; SD, standard deviation

References

1. Reck et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol. 2019 Mar 1;37(7):537-546. doi: 10.1200/JCO.18.00149. DOI. Epub 2019 Jan 8. PMID: 30620668

2. Schad et al. Overall survival of stage IV non-small cell lung cancer patients treated with Viscum album L. in addition to chemotherapy, a real-world observational multicenter analysis. PLoS One. 2018 Aug 27;13(8):e0203058. DOI: 10.1371/journal.pone.0203058. Erratum in: PLoS One. 2022 Aug

Results (cont.)

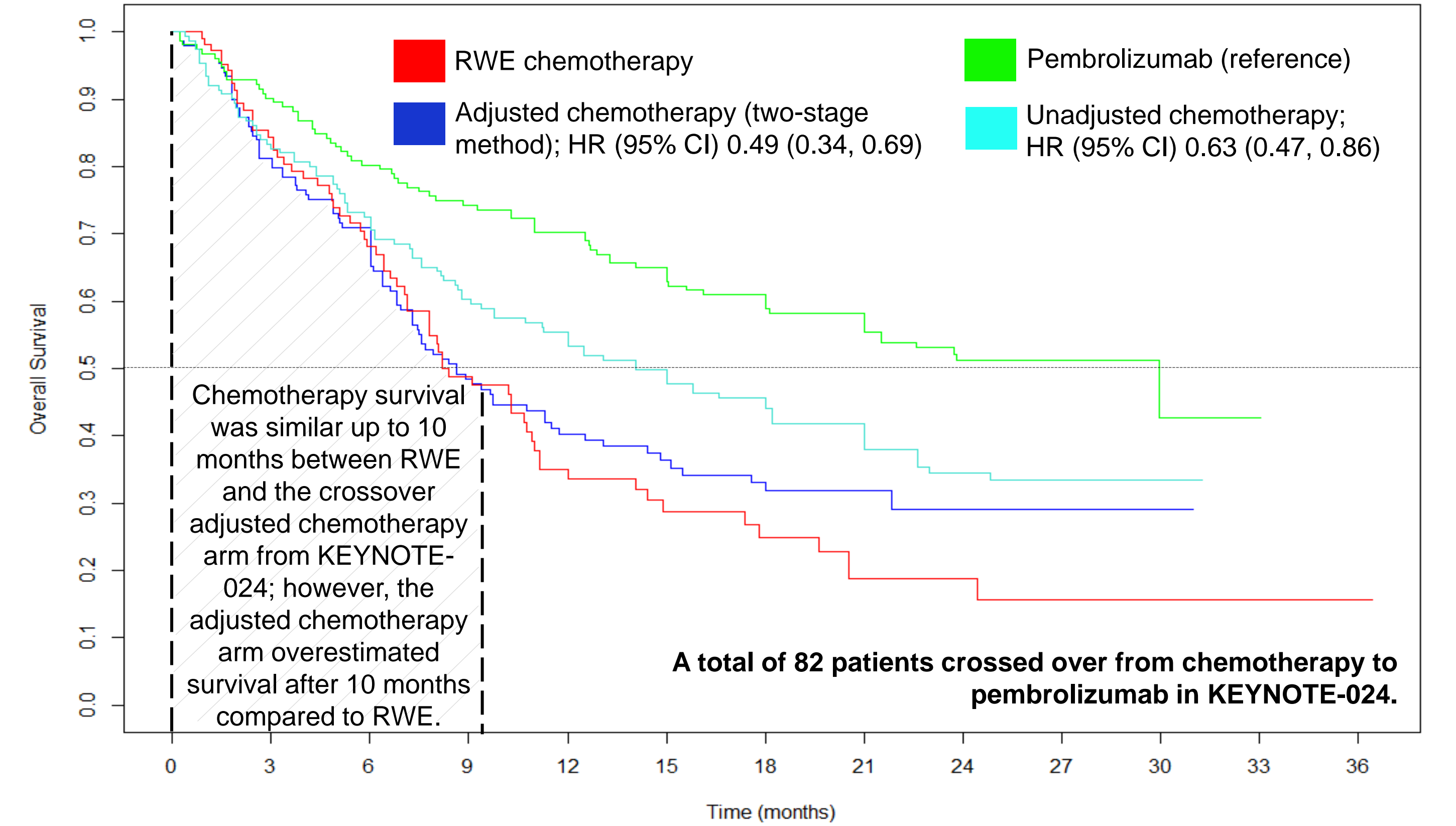
Table 2. Availability of other reported baseline characteristics

	Chemotherapy KEYNOTE-024 (n=151)	Chemotherapy RWE (n=108)
Body mass index	X	✓
Cancer-directed surgery	X	✓
Radiation therapy	X	✓
Prior neoadjuvant therapy	✓	X
Prior adjuvant therapy	✓	X
ECOG performance status score	✓	X

Abbreviations: ECOG, Eastern Cooperative Oncology Group; RWE, real-world evidence

- After 10 months, survival for the crossover-adjusted chemotherapy arm flattened; survival of chemotherapy in clinical practice did not flatten (Figure 1).
- Crossover-adjusted survival was observed to provide a better prediction of RWE survival compared to the unadjusted survival (Figure 1).
- Hazard ratios demonstrated a larger benefit for pembrolizumab when adjusting for crossover (Figure 1).

Figure 1. Reconstructed OS Kaplan-Meier curves for chemotherapy arms from RWE and KEYNOTE-024 vs. pembrolizumab



	0	3	6	9	12	15	18	21	24	27	30	33	36
RWE chemotherapy	108	58	24	13	6	2	2						
Pembrolizumab	154	136	121	112	106	96	89	83	52	22	5	0	NR
Unadjusted chemotherapy	151	123	107	88	80	70	61	55	31	16	5	0	NR
Adjusted chemotherapy	151	120	99	65	45	34	28	25	13	9	2	0	NR

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reported; RWE, real-world evidence

Table 3. AUC and median OS

Treatment arm	AUC until 10 months	AUC until 30 months	Median overall survival (months, 95% CI)
RWE chemotherapy (reference)	7.32 months	12.06 months	8.0 (7.0, 11.0)
Crossover-adjusted chemotherapy	7.16 months	13.74 months	8.7 (7.3, 11.5)
Crossover-unadjusted chemotherapy	7.66 months	16.07 months	14.2 (9.8, 19.0)

Abbreviations: AUC, area under the curve; CI, confidence interval; RWE, real-world evidence

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