An Emulation of the KEYNOTE-189 Trial Using Electronic Health Records

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Background & Objective

- Evidence generated from routinely collected healthcare data, or real-world evidence (RWE), can support decision-making among clinicians, regulators, payors, and patients.
- Despite its advantages, leveraging healthcare data collected from routine practice to study drug effectiveness remains controversial.
  - RWE investigations are susceptible to many biases, including channeling bias, immortal time bias, and unmeasured confounding.
- To better understand the settings in which RWE can provide reliable conclusions on cancer treatment effectiveness, a framework modeled after a prior initiative[1] was created and described for systematically emulating randomized controlled trials (RCTs) in oncology.[2]
- We report–the results of the pilot emulation of the KEYNOTE-189 trial[3] using an electronic health record (EHR) database.

Methods

- This retrospective study leveraged a US EHR database linked with a tumor registry.
- Patients with metastatic non-squamous non-small cell lung cancer were included; patients with prior first-line treatment for metastatic disease, primary non-lung malignancies, and EGFR/ALK mutations were excluded.
- Overall survival in initiators of pembrolizumab and chemotherapy vs. chemotherapy alone were compared in intent-to-treat analyses, with several sensitivity and post-hoc analyses conducted to contextualize the main results.
- The mortality hazard ratio and 12-month survival probabilities were estimated using Cox regression and the Kaplan-Meier estimator, respectively.
- Inverse probability of treatment weighting was used to control for potential baseline confounders.

Results

Table 1. Patient Characteristics in the KEYNOTE-189 RCT vs. RWE Study

	RCT		RWE[a]	
Patient Characteristic	Pembrolizumab + Chemotherapy (N = 410)	Placebo + Chemotherapy (N = 206)	Pembrolizumab + Chemotherapy (N = 571)[b]	Chemotherapy Only (N = 1,274)[b]
Age				
<65 years - no. (%)	197 (48.0)	115 (55.8)	266 (46.7)	672 (52.7)
Male sex - no. (%)	254 (62.0)	109 (52.9)	275 (48.3)	656 (51.5)
Region - no. (%)				
Europe	243 (59.3)	131 (63.6)	0 (0.0)	0 (0.0)
North America	111 (27.1)	46 (22.3)	571 (100.0)	1,274 (100.0)
East Asia	4 (1.0)	6 (2.9)	0 (0.0)	0 (0.0)
Other Region	52 (12.7)	23 (11.2)	0 (0.0)	0 (0.0)
Performance Status - no. (%)				
0	186 (45.4)	80 (38.8)	170 (29.8)	342 (26.8)
1	221 (53.9)	125 (60.7)	207 (36.3)	466 (36.6)
2	1 (0.2)	0 (0.0)	112 (19.5)	270 (21.2)
3	0 (0.0)	0 (0.0)	82 (14.4)	196 (15.4)
Histologic Features - no. (%)				
Adenocarcinoma	394 (96.1)	198 (96.1)	511 (89.5)	1140 (89.5)
Other	16 (3.9)	8 (3.9)	60 (10.5)	134 (10.5)
Brain Metastases - no. (%)	73 (17.8)	35 (17.0)	15 (2.6)	59 (4.6)
PD-L1 Tumor Proportion Score - no. (%)				
<1%	127 (31.0)	63 (30.6)	187 (32.7)	409 (32.1)
≥1%	260 (63.4)	128 (62.1)	383 (67.1)	865 (67.9)
1-49%	128 (31.2)	58 (28.2)	239 (41.9)	533 (41.8)
≥50%	132 (32.2)	70 (34.0)	144 (25.3)	332 (26.1)
Unavailable or Missing	23 (5.6)	15 (7.3)	N/A	N/A
Previous Therapy for Non-Metastatic Disease				
Thoracic Radiotherapy	28 (6.8)	20 (9.7)	163 (28.6)	380 (29.8)
Neoadjuvant or Adjuvant Therapy	30 (7.3)	20 (9.7)	2 (0.3)	8 (0.7)
None	352 (85.9)	166 (80.6)	406 (71.1)	886 (69.5)

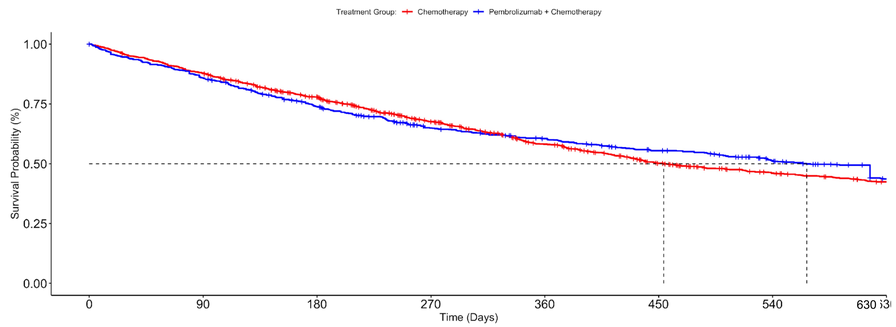
Abbreviations: RCT = Randomized-controlled trial, RWE = Real-world evidence
[a]Estimates shown are following application of inverse probability treatment (IPT) weights in the first imputed dataset. Age, race, marital status, body mass index, performance status, PD-L1 tumor proportion score, and creatinine clearance were imputed. Figures may not add to 100% due to rounding.
[b]Sample sizes shown are the sum of the IPT weights.

Table 2. Estimates of Overall Survival in the RCT vs. RWE Study

Estimate	Mortality Hazard Ratio (95% CI)	12-Month Survival Probability (95% CI)	
		Pembrolizumab Combination	Chemotherapy Only
KEYNOTE-189 (ITT)	0.49 (0.38, 0.64)	0.69 (0.64, 0.74)	0.49 (0.42, 0.56)
RWE (ITT)	0.95 (0.78, 1.16)	0.60 (0.54, 0.65)	0.58 (0.55, 0.62)
RWE (PP)	1.15 (0.96, 1.37)	0.72 (0.42, 1.00)	0.58 (0.18, 1.00)

ITT= Intent-to-treat, PP = Per-protocol; RWE= Real-world evidence

Figure 1. Kaplan-Meier Survival Estimates in RWE Study



Results (continued)

- There were 589 pembrolizumab initiators and 1,265 chemotherapy-only initiators.
- The mortality hazard ratio was 0.95 (95% CI: 0.78, 1.16) in the ITT analysis of the RWE study versus 0.49 (95% CI: 0.38, 0.64) in the RCT.
- The 12-month survival probabilities were 0.60 (95% CI: 0.54, 0.65) vs. 0.58 (95% CI: 0.55, 0.62) in the pembrolizumab and chemotherapy groups, respectively, compared with 0.69 (95% CI: 0.64, 0.74) and 0.49 (95% CI: 0.42, 0.56) in the RCT.
- In the RWE study, results were robust to sensitivity analyses.
- Substantial treatment crossover was observed in the real-world setting (11.1% of comparator group patients)
- A post-hoc subgroup analysis of *de novo* metastatic patients (N_{wgt} = 468), identified using the linked tumor registry only, was aligned with the RCT (HR: 0.52, 95% CI: 0.28, 0.96).

Conclusion

- Results of this EHR-based emulation were incongruous with those of the benchmark RCT, but consistent with other investigators' emulation attempts.
- Key drivers of misalignment included the inability to fully operationalize important eligibility criteria including performance status, potentially inaccurate date of metastatic disease due to reliance on ICD-codes, uncontrolled confounding by indication and other unmeasured or inadequately measured confounders such as PD-L1 tumor proportions score.
- Additionally, differences in treatment crossover between real-world and RCT settings may explain these findings.
- These results will be used to refine feasibility explorations for future CARE emulations and should be considered when designing RWE studies for oncology treatment questions.

References

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