Comparative Effectiveness Using External Controls for Single-Arm Trials of Pembrolizumab in Tumor-Agnostic Indications Leveraging Real-World Data

Poster No. RWD19

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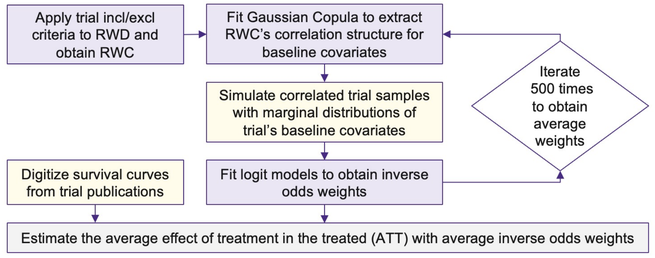
BACKGROUND

- Tumor-agnostic drugs, typically approved based on single-arm basket trials, create challenges for assessing comparative effectiveness due to lack of comparators and differing standards of care (SoC) across tumor types.
- We compared progression-free (PFS) and overall survival (OS) of patients with 8 microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) metastatic cancers treated with pembrolizumab (trial data) versus chemotherapy (external controls) .

METHODS

- We applied inclusion/exclusion criteria from MSI-H/dMMR trials (KEYNOTE 164 and KEYNOTE 158) to TriNetx electronic health record database to derive eight real-world control cohorts (RWC).
- The RWC included 9,267 patients who received SoC chemotherapies, had not received anti-PD-(L)1/2 therapies, and had progressed on ≥1 line of systemic therapy.
- Index date was defined as the date of index treatment initiation (i.e., chemotherapy received in second- or later-line).
- Imbalances of known covariates were adjusted with inverse odds weighting.
- Adjusted hazard ratios (HRs) were obtained for PFS and OS using weighted Cox regression for colorectal cancer (CRC) and endometrial cancer (EC) given available Kaplan-Meier data.

Figure 1. Overview of key study processes



RWD, real-world data; RWC, real-world control.

Definition of the primary endpoints in the RWC:

- OS: the interval between index treatment and the date of death.
- Proxy for PFS: the interval between index treatment and either the discontinuation date, the day before the next line of therapy, or the date of death, whichever occurred first.

RESULTS

Table 1. Baseline and prognostic factors of trial cohort versus real-world cohort

Characteristics	KEYNOTE 164 Cohort B (CRC) N=63, n (%)	Real-world cohort (CRC) N=3104, n (%)	KEYNOTE 158 (non-CRC) N=233, n (%)	Real-world cohort (non-CRC) N=6163, n (%)
Age, years Median (range)	59 (23-83)	61 (20-90)	60 (20-87)	65 (18-90)
Female sex	30 (52)	1346 (43.4)	137 (59)	4566 (74.1)
Performance status				
0	22 (35)	NA	113 (49)	NA
1	41 (65)	NA	120 (52)	NA
Prior lines of therapy				
0	0 (0)	0 (0)	7 (3)	0 (0)
1	24 (38)	2552 (82.2)	87 (37)	5041 (81.8)
2	20 (32)	355 (11.4)	61 (26)	648 (10.5)
≥3	19 (30)	197 (6.3)	78 (34)	474 (7.7)
Prior (neo)adjuvant therapy	17 (27)	653 (21.0)	55 (24)	1150 (18.7)
Tumor types				
CRC	63 (100)	3104 (100)	0 (0)	0 (0)
Endometrial	0 (0)	0 (0)	49 (21)	1089 (17.7)
Gastric	0 (0)	0 (0)	24 (10)	524 (8.5)
CCA	0 (0)	0 (0)	22 (9)	421 (6.8)
Pancreatic	0 (0)	0 (0)	22 (9)	1514 (24.6)
Small intestine	0 (0)	0 (0)	19 (8)	213 (3.5)
Ovarian	0 (0)	0 (0)	15 (6)	2178 (35.3)
Brain	0 (0)	0 (0)	13 (6)	224 (3.6)
Other	0 (0)	0 (0)	69 (30)	558 (9.1)
Race				
Asian	14 (22)	92 (3.0)	NA	140 (2.3)
Black	7 (11)	453 (14.6)	NA	798 (12.9)
White	42 (67)	2298 (74.0)	NA	4667 (75.7)
Other	0 (0)	261 (8.4)	NA	558 (9.1)

CCA, cholangiocarcinoma; CRC, colorectal cancer; NA, not available.

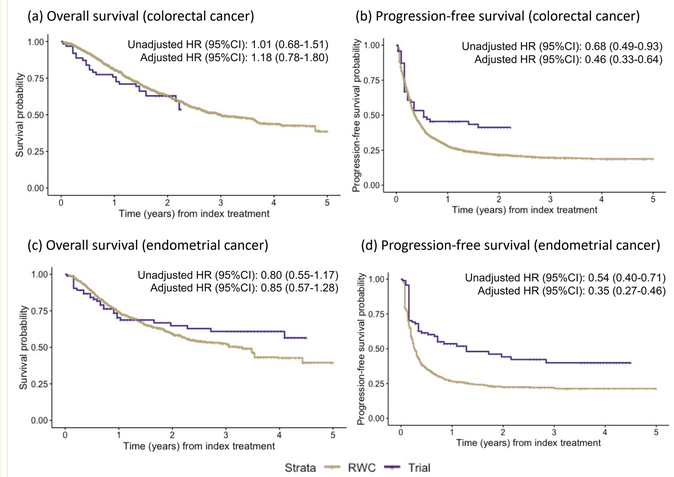
Table 2. Survival outcomes of trial cohort versus real-world cohort

Tumor type	Median OS (95%CI)		Median PFS (95%CI)	
	Trial (Pembro)	RW Control (Chemo)	Trial (Pembro)	RW Control (Chemo)
CRC	37.5* (19.2, NR)	34.3 (31.5, 39.5)	4.1 (2.1, 18.9)	4.4 (4.1, 4.7)
Endometrial	51.7* (27.2, NR)	36.3 (29.4, NR)	13.1 (4.3, 34.4)	3.2 (3.0, 3.7)
Gastric	11 (5.8, 31.5)	16.5 (13.8, 20.3)	3.2 (2.1, 12.9)	3.9 (3.2, 4.5)
CCA	19.4 (6.5, NR)	11.7 (10.0, 13.6)	4.2 (2.1, 24.9)	4.4 (3.7, 5.1)
Pancreatic	3.7 (2.1, 9.8)	10.1 (9.4, 11.0)	2.1 (1.9, 3.4)	4.2 (3.9, 4.6)
Small intestine	NR (16.2, NR)	21.8 (15.6, 31.5)	23.4 (4.3, NR)	4.0 (3.2, 5.4)
Ovarian	33.6 (11.0, NR)	28.5 (25.8, 30.8)	2.2 (2.0, 6.2)	2.8 (2.7, 2.9)
Brain	5.6 (1.5, 16.2)	10.3 (8.6, 12.4)	1.1 (0.7, 2.1)	4.7 (3.7, 6.2)

CRC, colorectal cancer; CCA, cholangiocarcinoma; OS, overall survival; PFS, progression-free survival; Pembro, pembrolizumab; Chemo, chemotherapies; NR, not reached; RW, real-world; CI, confidence interval;
* Estimated from fitting log-normal distribution to the digitized KM curve data.
Patients lost to follow-up or without the relevant event by the end of the study period were censored at the date of last confirmed activity date.

- Real-world patients tend to be older, white, and only had one prior line of therapy compared to the trial cohort (**Table 1**).
- Compared to patients receiving pembrolizumab, patients receiving chemotherapy for colorectal (37.5 months extrapolated and not reached at 39 months vs. 34.3), endometrial (51.7 months extrapolated and not reached at 56 months vs. 36.3), cholangiocarcinoma (19.4 vs. 11.7), small intestine (not reached at 56 months vs. 21.8), and ovarian cancers (33.6 vs. 28.5) had shorter median OS, whereas patients with gastric (11 vs. 16.5), pancreatic (3.7 vs. 10), and brain cancers (5.6 vs. 10.3) had longer median OS (**Table 2**).
- After inverse odds weighting, baseline imbalance was improved for all covariates with the standardized mean differences achieving <0.1.

Figure 3. Survival after adjustment with inverse odds weights in the trial cohort versus the real-world cohort



+, Censored; HR, hazard ratio; CI, confidence interval; RWC, real-world cohort.

LIMITATIONS

- ❑ The real-world endpoint based on time to discontinuation may underestimate PFS if discontinuation happens for reasons other than progression, such as toxicity.
- ❑ MSI-H/dMMR status was not available in the TriNetx database, and thus was not included in the analysis. Prior literature showed that MSI-H/dMMR status is not a significant prognostic factor for non-anti-PD-(L)1/2 treatments in the advanced/metastatic setting.

CONCLUSIONS

Patients with MSI-H/dMMR advanced/metastatic CRC and EC receiving pembrolizumab were associated with significant prolonged PFS but not OS than real-world patients receiving chemotherapies.

2023 International Society for Pharmacoeconomics and Outcomes Research Annual Meeting, Boston MA