Use of Real-World Data to Support Comparative Effectiveness in Single-Arm Trial-Based Oncology Health Technology Assessments in Japan

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Background

- Single-arm trials (SATs) are increasingly used to support oncology health technology assessments.
- Without a concurrent control arm, SAT-based evaluations require external evidence to estimate comparative efficacy. Real-world data (RWD) provide a pragmatic potential source of external comparator data.
- Japan's Center for Outcomes Research and Economic Evaluation for Health (C2H) guidelines recognize RWD as a potential evidence source, and RWD have been accepted as part of the evidence package in SAT-based oncology evaluations.[1]

Objectives

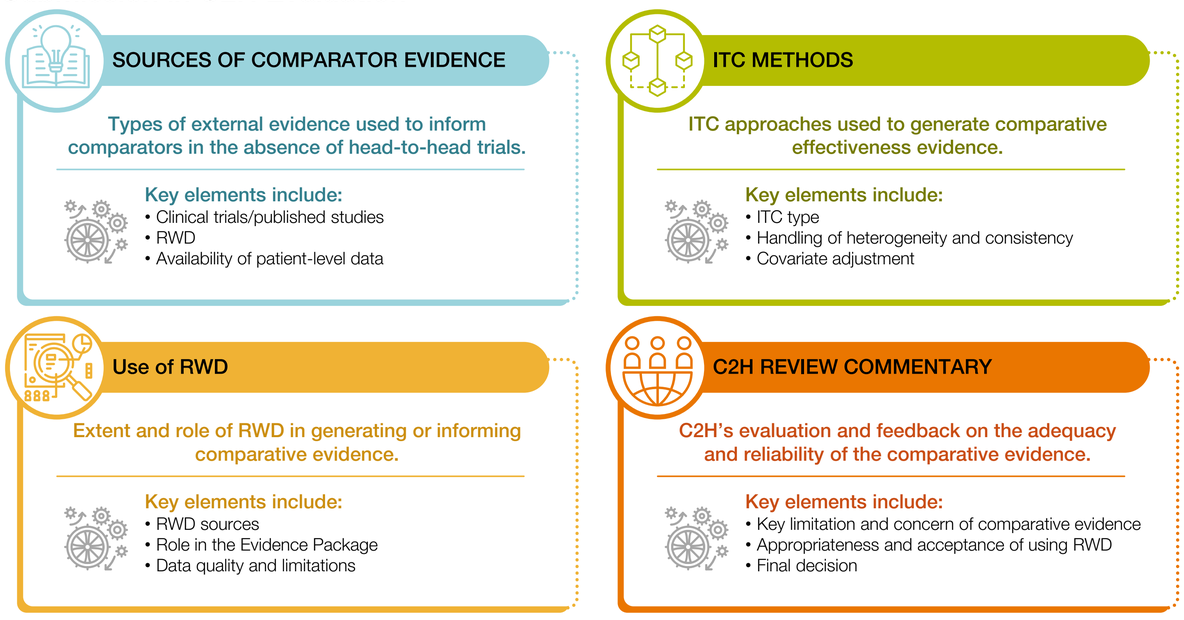
- To characterize SAT-based oncology submissions in C2H evaluations, with a focus on sources of comparator evidence, including the use of RWD, indirect treatment comparison (ITC) methods, and C2H review commentary on comparative evidence.

Methods

Data Extraction

- Full-text screening of C2H Summary Reports was conducted by one investigator, with data extraction validated by a second investigator.
- For each eligible SAT-based evaluation, data were extracted on (1) sources of comparator evidence; (2) ITC methods; (3) specific use of RWD; and (4) C2H review commentary on comparative evidence (**Figure 1**).

Figure 1. Key Aspect of Review and Data Extraction from SAT-based Oncology Submission in C2H Evaluation

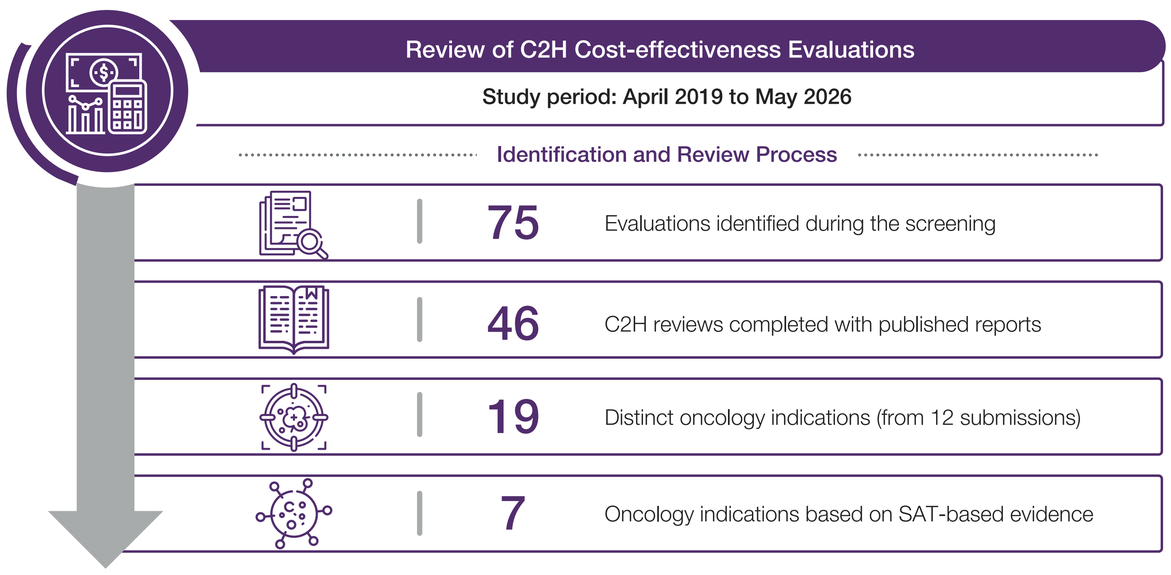


Abbreviations: C2H = Japan's Center for Outcomes Research and Economic Evaluation for Health; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; RCT = randomized controlled trial; RWD = real-world data; SAT = single-arm trial.

Results

- Of the 75 evaluations identified, 46 were completed, and 12 focused on oncology treatments across 19 distinct indications. Of these, 37% (7/19) relied on SATs for clinical evidence, and all SAT-based evaluations used suboptimal external trials to derive comparative efficacy estimates (**Figure 2**).

Figure 2. Review of C2H Submissions



Abbreviation: C2H = Center for Outcomes Research and Economic Evaluation for Health; SAT = single-arm trial.

Results (cont.)

- Among SAT-based evaluations, ITCs using individual patient-level data (IPD) or pseudo-IPD from external trials were generally preferred (90%) over naive comparisons against aggregated data.
- Three evaluations[2-4] used observational study based on RWD to inform comparative efficacy for the external comparators through unanchored matching-adjusted indirect comparisons (MAICs) using aggregated data (**Table 1**).

Table 1. Summary of SAT-based C2H Submission

Drug (C2H ID)	Indication and SAT-based Trial	Comparator Evidence	ITC Approach
Selpercatinib (C2H2113)[5]	NSCLC (LIBRETTO-001)	Platinum + pemetrexed + pembrolizumab (KEYNOTE-189; RCT)	ITC informed by propensity score-matched IPD
	Thyroid cancer with a RET gene fusion (LIBRETTO-001)	Lenvatinib (SELECT; RCT)	Naive indirect comparison conducted based on pseudo-IPD
	Medullary thyroid cancer with a RET mutation (LIBRETTO-001)	NR	NR
Tisagenlecleucel (C2H1902)[2]	R/R B-ALL (pooled B2101J, ELIANA, ENSIGN)	Blinatumomab (RIALTO; SAT); inotuzumab (Bhojwani 2018, RWD)[6]	Unanchored MAIC (IPD & aggregated data)
	R/R DLBCL (JULIET)	Salvage chemotherapy (CORAL extension studies)	Unanchored MAIC based on pseudo-IPD
Elranatamab (C2H2403)[3]	Multiple myeloma (MagnetisMM-3)	Elotuzumab + pomalidomide + dexamethasone (LocoMMotion; RWD)[7]	Unanchored MAIC (aggregated data)
Epcoritamab (C2H2307)[4]	LBCL (EPCORE NHL-1)	Salvage chemotherapy (SCHOLAR-1; RWD)[8]	Unanchored MAIC (aggregated data)

Abbreviations: C2H = Center for Outcomes Research and Economic Evaluation for Health; ID = identification; IPD = individual patient-level data; ITC = indirect treatment comparison; LBCL = large B-cell lymphoma; MAIC = matching-adjusted indirect comparison; NR = not reported; NSCLC = non–small cell lung cancer; R/R B-ALL = relapsed/refractory B-cell acute lymphoblastic leukemia; R/R DLBCL = relapsed/refractory diffuse large B-cell lymphoma; RCT = randomized controlled trial; RET = rearranged during transfection; RWD = real-world data; SAT = single-arm trial.

- These studies demonstrate that prospective observational or pooled historical real-world evidence can provide credible evidence in rare, high-unmet-need settings; however, comparability with the pivotal SATs remains a key limitation due to differences in patient populations, treatment eras, data collection, and potential confounding/selection bias (**Table 2**).

Table 2. Summary of RWD Used as Evidence for Comparative Efficacy

Study	Disease	Study Purpose	Design/Data Source	Strength	Limitation
LocoMMotion (N=248)	Triple-class-exposed RRMM	Evaluate effectiveness and safety of real-world therapies	Prospective, multinational observational study; routine clinical practice	Contemporary benchmark for comparison with single-arm trials in this population	Nonrandomized; predates newer therapies; potential selection bias and TEAE underreporting; small subgroups
SCHOLAR-1 (N=636)	Refractory DLBCL	Establish a historical benchmark for refractory disease	Retrospective pooled analysis of two clinical trials and two observational cohorts	Large patient-level dataset; harmonized refractory definition and robust subgroup analyses	Retrospective, heterogeneous data sources; older treatment era may limit applicability to contemporary patients
Bhojwani 2018 (N=51)	Pediatric R/R ALL	Evaluate InO safety and efficacy in a heavily pretreated pediatric population	Retrospective, multicenter compassionate-use cohort	Multicenter evidence in a rare, heavily pretreated pediatric population	Small, uncontrolled cohort; heterogeneous treatment history and potential selection bias

Abbreviations: DLBCL = diffuse large B-cell lymphoma; InO = inotuzumab ozogamicin; R/R ALL = relapsed/refractory acute lymphoblastic leukemia; RRMM = relapsed/refractory multiple myeloma; RWD = real-world data; TEAE = treatment-emergent adverse event.

- ITC approaches, including MAIC (66.7%, 4 out of 6), naive comparison (16.7%, 1 out of 6), and network meta-analysis (16.7%, 1 out of 6), were employed to generate comparative efficacy.
- One indication was excluded because it was not included in the C2H cost-effectiveness analysis due to its small proportion of the overall population.
- Although the review committee generally accepted ITC evidence submitted in SAT-based evaluations, there were concerns regarding the high uncertainty associated with comparative evidence derived from external trials, given the nature of the SAT design.

Conclusions

- Single-arm designs preclude head-to-head comparisons and anchored MAICs, necessitating external comparators with limited ability to address cross-study differences and residual confounding.
- External trials are the primary source of comparative evidence for SAT-based oncology evaluations in C2H, but substantial uncertainty remains.
- RWD may offer an alternative external comparator when suitable comparator trial data are unavailable, provided appropriate methods are used to address population differences and confounding.

References

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