The Use of Surrogate Endpoints in Health Technology Assessments for Chronic Cancers

Rhiannon I. Campden, Ph.D.[1], Jiayue Yu, M.Sc.[1], Christiana Tzonev, M.Sc.[1], Mihaela Musat, Ph.D.[2], Deepika Thakur, M.Pharm[1]
[1]Cytel Inc., Toronto, Canada; [2]Cytel Inc., Waltham, Massachusetts, USA

HTA210

Background

IQWiG and EUnetHTA are the only health technology assessment (HTA) agencies to provide prescriptive guidelines on the use of a surrogate endpoint (i.e., an endpoint used as a substitute for a direct measure of survival or of how a patient feels, or functions).[1,4]

Previous studies have highlighted inconsistencies in the level of evidence and statistical validation methods used to assess surrogate endpoints in HTA submissions.[2,3]
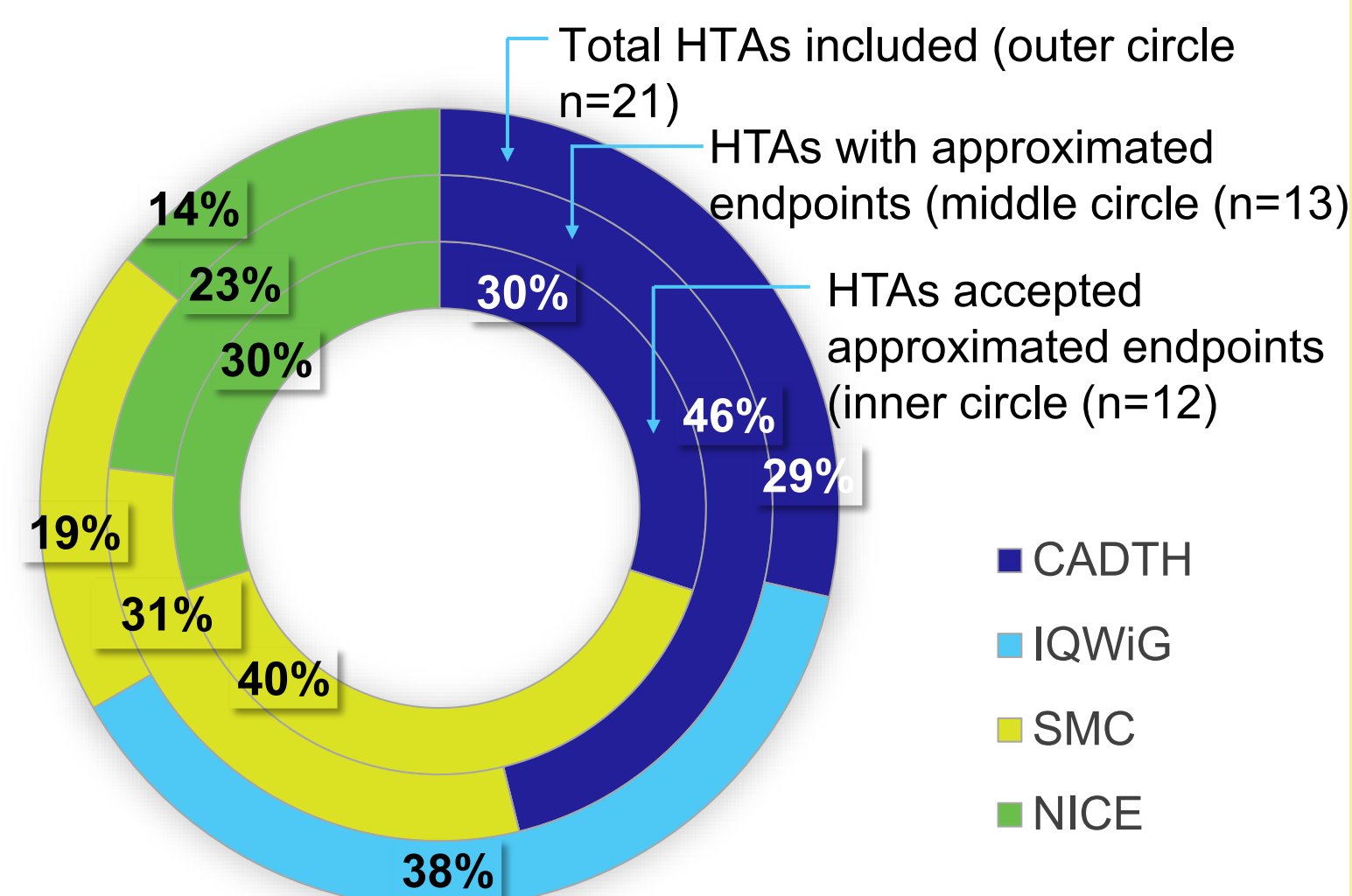
Objective

To investigate the use of surrogate endpoints in HTA submissions for chronic cancers after 2019 to study the use and acceptance of surrogate endpoints.

Key Results

13/21 HTAs reported approximated (either surrogate or extrapolated) endpoints; 10/13 approximated endpoints were accepted (*Figure 1*).

Extrapolated survival endpoints were used more frequently in our dataset than surrogate endpoints; only 2/13 HTAs reported the use of surrogate endpoints.

7/13 HTAs reported validating the approximated endpoints.

Figure 1. Summary of included HTAs.

Total HTAs included (outer circle n=21)
HTAs with approximated endpoints (middle circle (n=13)
HTAs accepted approximated endpoints (inner circle (n=12)

Legend: CADTH, IQWiG, SMC, NICE

Conclusions

In chronic cancers, extrapolated endpoints are more commonly used than surrogate endpoints.

Inconsistencies were observed in the validation of approximated outcomes.

Feedback from HTA agencies suggests that validation of surrogate and extrapolated endpoints is important to replace the primary endpoint and understand the benefits of an intervention in treating chronic cancer.

Preferential use of extrapolated endpoints over surrogate endpoints due to stricter guidelines or lack of validation is unclear.

Methods

HTAs on chronic cancers were included as these indications have longer survival outcomes and would require surrogate endpoints if survival outcomes are immature.

HTAs on chronic cancers published between 2019 and May 2022 from CADTH, NICE, IQWiG, and SMC, were reviewed for the use of surrogate or extrapolated endpoints (*Figure 2*).
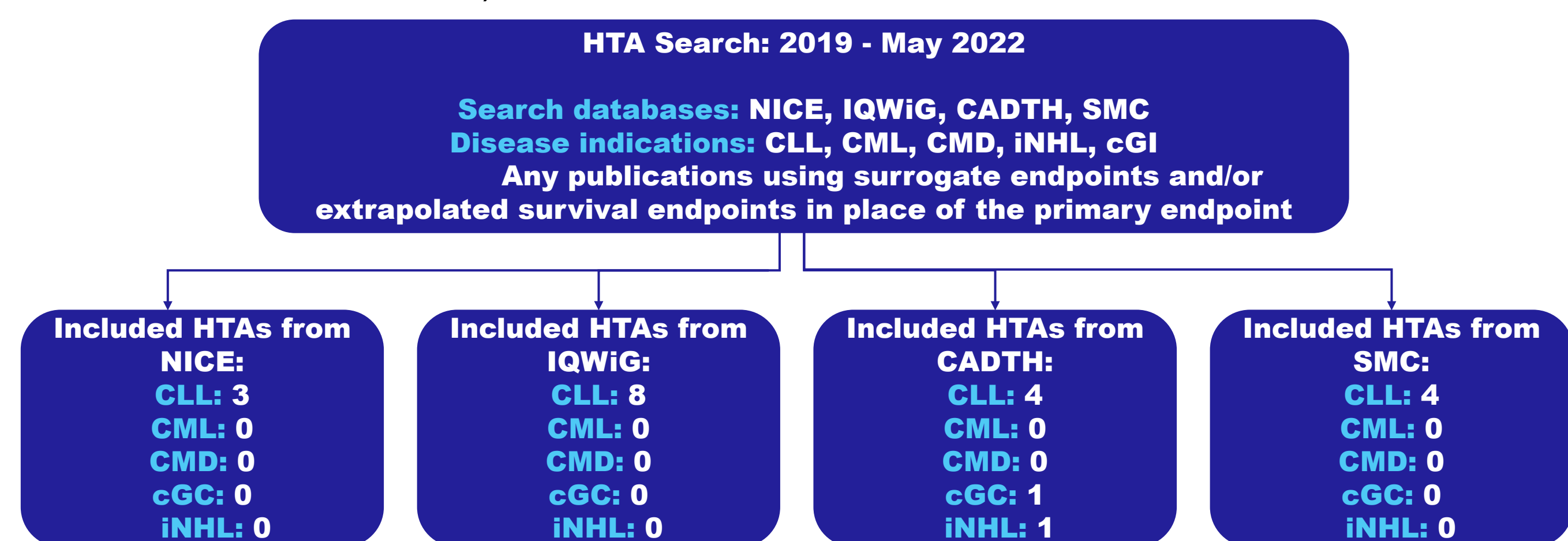
The indications of interest were:

- chronic lymphocytic leukemia (CLL)
- chronic myeloid leukemia (CML)
- chronic myeloproliferative disease (CMD)
- chronic gastrointestinal cancer (cGC)
- indolent non-Hodgkin's lymphoma (iNHL)

HTAs were included if an endpoint other than the mature primary outcome was used, i.e., if either a surrogate endpoint or an extrapolated endpoint was used in place of the primary outcome.

Results

Figure 2. Results of HTA search. Numbers of HTAs included from each agency (NICE, IQWiG, CADTH, and SMC) for the indications of CLL, CML, CMD, cGC, and iNHL.

HTA Search: 2019 - May 2022
Search databases: NICE, IQWiG, CADTH, SMC
Disease indications: CLL, CML, CMD, iNHL, cGI
Any publications using surrogate endpoints and/or extrapolated survival endpoints in place of the primary endpoint

Included HTAs from NICE:
CLL: 3
CML: 0
CMD: 0
cGC: 0
iNHL: 0

Included HTAs from IQWiG:
CLL: 8
CML: 0
CMD: 0
cGC: 0
iNHL: 0

Included HTAs from CADTH:
CLL: 4
CML: 0
CMD: 0
cGC: 1
iNHL: 1

Included HTAs from SMC:
CLL: 4
CML: 0
CMD: 0
cGC: 0
iNHL: 0

- 21 HTAs were identified: 6 from CADTH, 8 from IQWiG, 4 from SMC, and 3 from NICE (*Figure 3A*).
- Of the 21 HTAs, 13 reported the use of surrogate endpoints or extrapolated endpoints: 6 from CADTH, 4 from SMC, and 3 from NICE (*Figure 3B*). No studies that were submitted to IQWiG reported the use of surrogate endpoints.

Figure 3. Distribution of the number of HTAs in chronic cancers by indication

A. All identified HTAs   **B.** HTAs that included surrogate / extrapolated endpoints
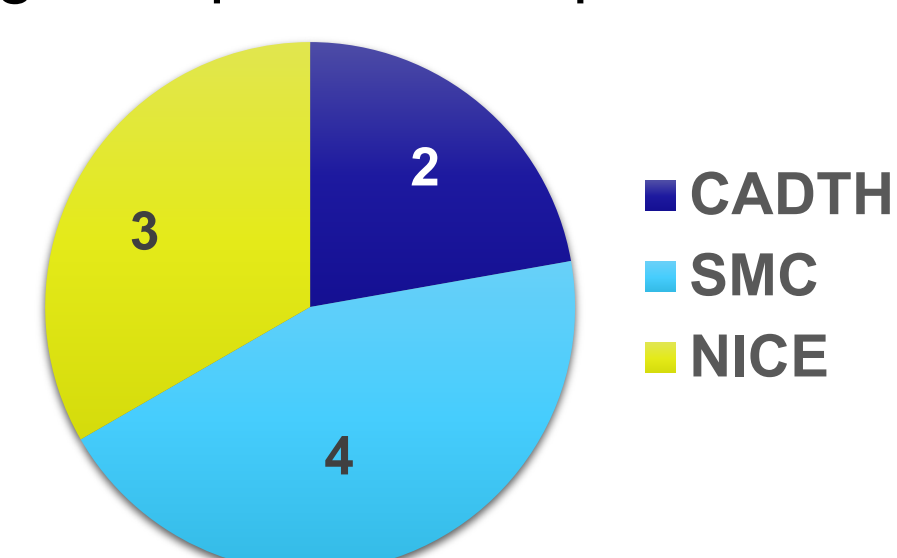

Legend: CADTH, IQWiG, SMC, NICE
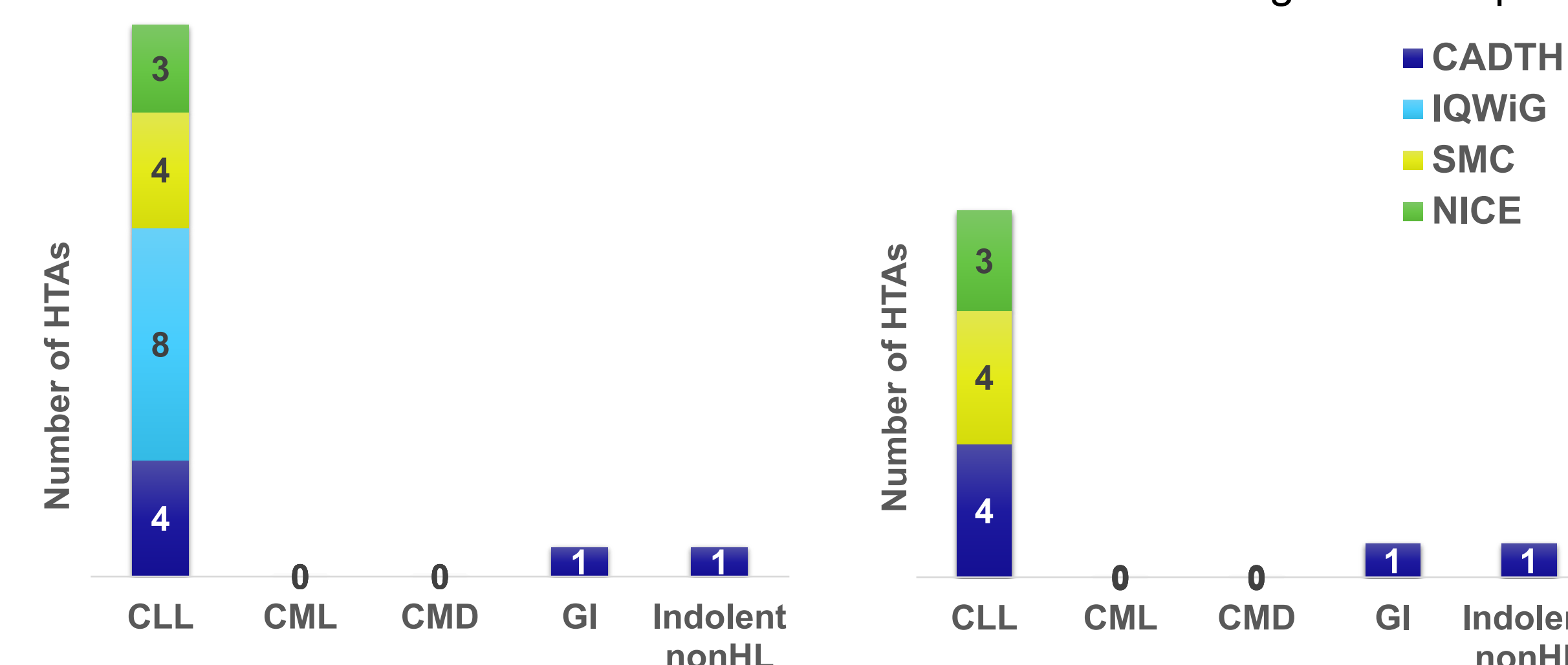
- Out of the 13 HTAs that reported the use of approximated endpoints, 9 HTAs on CLL accepted the extrapolated endpoints: 2 from CADTH, 4 from SMC, and 3 from NICE (*Figure 4*).
- In CLL 3 HTAs from NICE, 1 HTA from CADTH, and 3 HTAs from SMC validated the use of extrapolated or estimated survival outcomes.
- Two HTAs from CADTH used progression-free survival (PFS) in iNHL or durable response in cGC as surrogate endpoints for overall survival (OS). No details on validation of endpoints was reported.
- Both reports noted there was a high degree of uncertainty in the measure; however, only the HTA on iNHL was accepted.

Figure 4. HTAs in chronic lymphocytic leukemia accepting extrapolated endpoints

Legend: CADTH (2), SMC (4), NICE (3)

Results

All HTAs that accepted surrogate endpoints or extrapolated endpoints (10/13) contained a disclaimer within the regulatory body's response indicating uncertainty in the economic model based on immature survival data or equivalence and not the superiority of the intervention (*Table 1*).

- 50% of HTAs including surrogate endpoints were accepted
- 0% of HTAs that were accepted included validated surrogate endpoints
  - no surrogate endpoints validated
- 100% of HTAs including validated extrapolated endpoints were accepted

Table 1. Summary of the use and acceptance of surrogate / extrapolated endpoints in HTAs

Indication	HTA source	Intervention	Year	Outcomes used in cost effectiveness model*	Approximated endpoint validated	Approximated endpoint accepted by agency in cost-effectiveness model	HTA accepted	Comments on acceptance
CLL	NICE	Acalabrutinib	2021	Approximated OS	Yes (Error estimation)	Yes	Yes	Equivalence not superiority claimed.
CLL	NICE	Venetoclax + obinutuzumab	2020	Approximated OS	Yes (Parametric model)	Yes	Yes	Equivalence not superiority claimed.
CLL	NICE	Venetoclax + rituximab	2019	Approximated OS, PFS	Yes (Parametric model)	Yes	Yes	NR
CLL (1L+)	CADTH	Acalabrutinib	2020	Approximated OS, PFS	Yes (Parametric model)	Yes	Yes	Notes uncertainty in the data due to immature survival endpoints.
CLL (treatment naïve)	CADTH	Acalabrutinib	2020	TTD, TTP based on PFS and OS from other trial data	No	No	Yes	Noted that there is no clinical data to support the economic analysis.
CLL	CADTH	Venetoclax + rituximab	2019	PFS, approximated OS	No	No	Yes	Uncertainty in effectiveness estimates.
CLL	CADTH	Venetoclax + obinutuzumab	2020	Approximated OS, PFS	No	Yes	Yes	NR
CLL	SMC	Acalabrutinib	2021	Approximated OS	No	Yes; restricted use		Survival data not mature and therefore could not be tested.
CLL	SMC	Venetoclax	2020	Approximated OS, PFS	Yes (Parametric model)	Yes	Yes; restricted use	Notes uncertainty due to immature survival data.
CLL	SMC	Venetoclax	2019	Approximated OS, PFS	Yes (Parametric model)	Yes	Yes	Notes uncertainty due to immature survival data leading to implausibly high survival data.
CLL	SMC	Venetoclax + obinutuzumab	2022	TTNT, approximated OS	Yes (Parametric model)	Yes	Yes; restricted use	Notes uncertainty due to immature survival data.
cGC	CADTH	Xermelo	2019	Durable response	No	NR	No	Uncertainty in the model based on immature survival data.
iNHL	CADTH	Lenalidomide + rituximab	2021	PFS	No	Yes	Yes	Uncertainty in the cost estimates and other parameters given the indirect comparative data.

Abbreviations: 1L+ – one prior line of therapy; CADTH – Canadian Agency for Drugs and Technologies in Health; CLL – chronic lymphocytic leukemia; cGC – chronic gastrointestinal cancer; HTA – Health Technology Assessment; iNHL – indolent non-Hodgkin's lymphoma; NICE – The National Institute for Health and Care Excellence; NR – not reported; OS – overall response; PFS – progression free survival; SMC – Scottish Medicines Consortium; TTD – time to death; TTP – time to progression; TTNT – time to next treatment. *Approximated includes extrapolated, predicted, and estimated OS and PFS.

- Eleven HTAs on CLL for venetoclax, venetoclax plus rituximab, venetoclax plus obinutuzumab, or acalabrutinib used extrapolated OS or PFS (*Figure 5*).
  - In 9 of these HTAs, the extrapolation method was considered acceptable; however, only 7 validated and reported the extrapolation method.
  - Validation methods included fitting parametric models or estimating prediction error (Akaike information criterion; NICE HTA on Acalabrutinib 2021)
    - Parametric models included:
      - Log-log distribution
      - Weibull distribution
      - Gompertz distribution

Figure 5. HTAs in chronic lymphocytic leukemia using extrapolated OS or PFS

Extrapolation methods accepted: n=9
Extrapolation method validated: n=7
Validation via parametric model n=6
Validation via prediction error estimation n=1
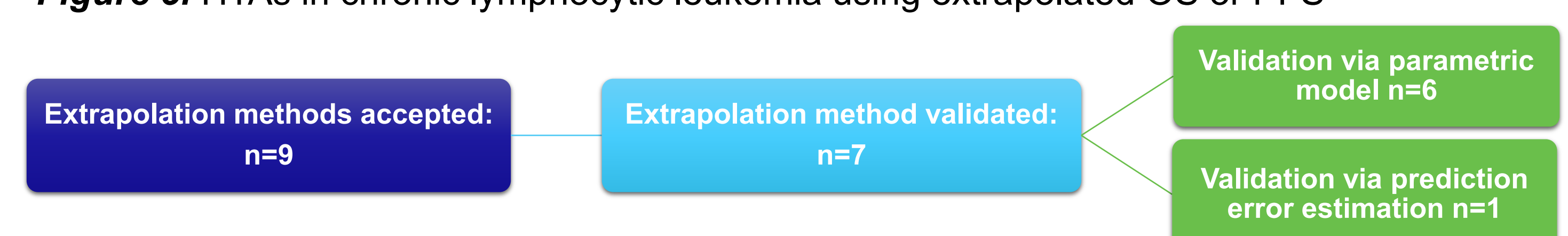
Strengths/Limitations

- The methodology followed a systematic approach for identifying the evidence for chronic cancers.
- The search was limited to HTA submissions in English, which may introduce language bias.
- SMC submissions provide limited information on how extrapolated endpoints were calculated.
- Supplements from G-BA (Gemeinsamer Bundesausschuss) HTAs may provide additional information; however, the original G-BA HTAs are non-English (in German).
- Variations in how approximated endpoints were referred to in HTAs was observed (term used: estimate, extrapolate, predict)

References/Abbreviations

[1] US Food and Drug Administration. https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development [2] Pinto et al. Value in Health. 2020; 23(3):319-327. [3] Ciani et al. Medical Decision Making. 2021; 41(4):439-452. [4] Grigore et al. PharmacoEconomics. 2020; 38:1055-1070.
Abbreviations: CADTH – Canadian Agency for Drugs and Technologies in Health; cGC – chronic gastrointestinal cancer; CLL – chronic lymphocytic leukemia; CMD – chronic myeloproliferative disease; CML – chronic myeloid leukemia; EUnetHTA – European Network of HTA organizations; G-BA – Gemeinsamer Bundesausschuss; HTA – Health Technology Assessment; iNHL – indolent non-Hodgkin's lymphoma; IQWiG – The independent Institute for Quality and Efficiency in Health Care; NICE – The National Institute for Health and Care Excellence; NR – not reported; OS – overall survival; PFS – progression free survival; SMC – Scottish Medicines Consortium; TTD – time to death; TTP – time to progression; TTNT – time to next treatment.

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