Early Endpoints in Oncology: Increasingly Common in Clinical Trials Yet Frequently Challenged in Health Technology Appraisals (HTAs)

ISPOR EU Copenhagen, 14 November 2023 | 13:45 - 14:45

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University of Sheffield

PRECISIONheor

It’s Time for a Poll!

Which of the following best describes the organization you are currently working in?

1. Pharmaceutical/Biotech industry
2. HTA/payer organization
3. Research organization (academic and/or consulting)

Navigate to this session in the meeting app to participate!

It’s Time for a Poll!

How many intermediate endpoints have been accepted by IQWIG/G-BA as a valid surrogate endpoint for a final endpoint?

1. 0
2. Less than 5
3. 6 to 10
4. More than 10

Navigate to this session in the meeting app to participate!

OS Is the Gold Standard

Can Something Other Than Gold Be Accepted For Good Reasons?

Ying Zheng, Senior Director,
Global Health Economics and Value Assessment, Sanofi

Disclaimer

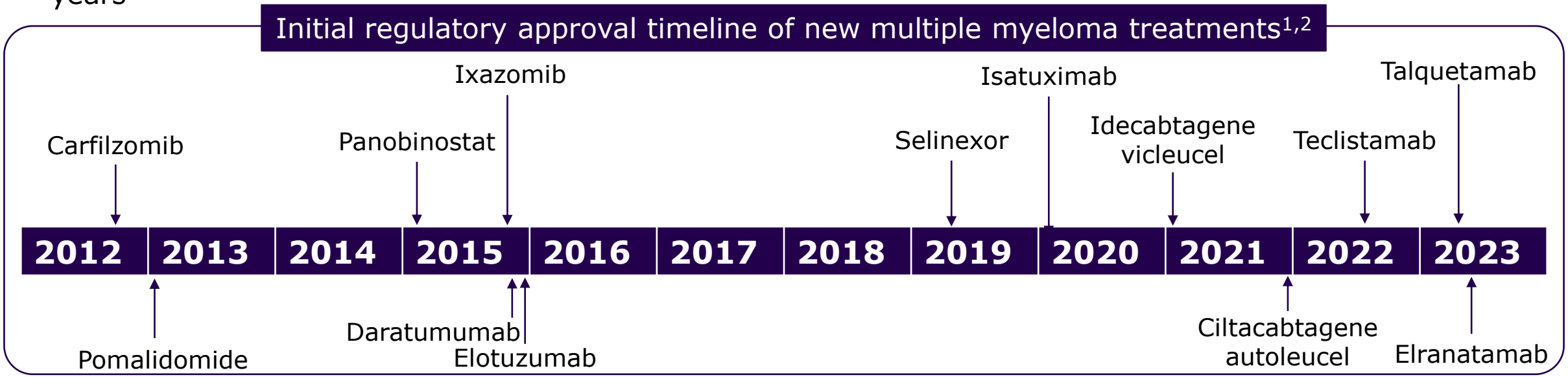
I am an employee of Sanofi

The presentation reflects my views—not Sanofi's

Novel Oncolytic Treatments Are Changing Treatment Landscape and Patient Outcomes

With the expansion of new treatment options and emergence of new treatment classes[1,2]

1. Possibility for patients to go through several lines (up to 6–7) in certain oncology areas
   - Pharmaceutical treatment options for multiple myeloma expanded from bortezomib (2003) and lenalidomide (2006) to over 10 new molecular entities multiplied by combination therapies
2. New treatments & new combinations of treatments prolong patient survival from several months to several years



1. Kaplan DA. Multiple Myeloma: Top 10 Advances in the Past 10 Years, Available at: https://www.targetedonc.com/view/multiple-myeloma-top-10-advances-in-the-past-10-years. Last accessed on 10 Oct 2023. **2.** Toogood S. Targeted Therapy, Immunotherapy Propel 10 Years of Progress in NSCLC. Available at: Targeted Therapy, Immunotherapy Propel 10 Years of Progress in NSCLC (targetedonc.com). Last accessed on 10 Oct 2023.

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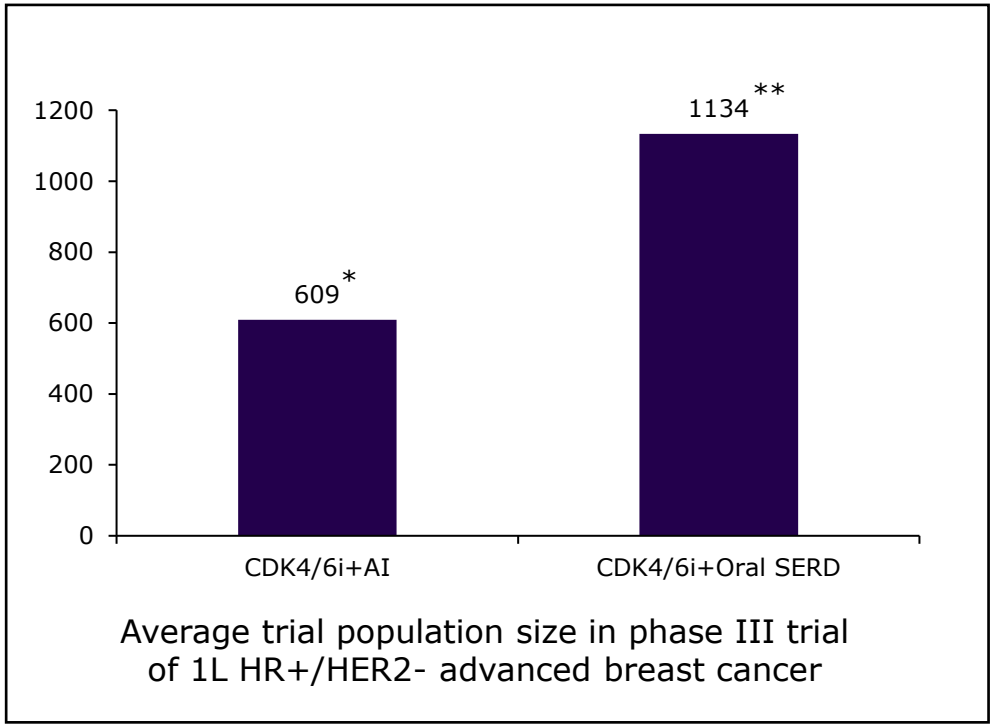
Practical Challenges in Measuring OS Benefits (1/2)

More recent trials require longer follow up time and/or larger patient population size, which increases the cost of the clinical trials and burden on measuring OS endpoints



Average trial population size in phase III trial of 1L HR+/HER2- advanced breast cancer

Clinical trials in newly diagnosed multiple myeloma who were ineligible for autologous stem-cell transplantation

	NCT00111319[1,2]		MAIA[3–5]	
Treatment	Bortezomib, melphalan (M), prednisone (P)	M, P	Daratumumab, lenalidomide (L), dexamethasone (d)	L, d
Patient number	344	338	368	369
Start year	2004		2014	
Follow-up (median)	16.3 months, significant TTP, PFS, OS		28.0 months, significant PFS 56.2 months, significant OS	

*Average trial population of PALOMA-2, MONALEESA-2, MONARCH 3
**Average of AMEERA5, persevERA Breast Cancer, SERENA-4
Note: For adjuvant BC trial of CDK4/6i, the sample size is over 5000.
1L, first line; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitors; d, dexamethasone; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; M, melphalan; OS, overall survival; P, prednisone; PFS, progression-free survival; R, lenalidomide; SERD, selective estrogen receptor degrader; TTP, time to progression.
1. VELCADE/Melphalan/Prednisone Versus Melphalan/Prednisone in Patients With Previously Untreated Multiple Myeloma (NCT00111319). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT00111319. Last access on 10th Oct 2023. **2.** Velcade. Full prescribing information. Available at: https://www.velcade.com/files/pdfs/VELCADE_PRESCRIBING_INFORMATION.pdf. Last accessed on 10th Oct 2023. **3.** Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma (NCT02252172). Available at: https://clinicaltrials.gov/study/NCT02252172. Last accessed on 10th Oct 2023. **4.** Facon T, et al. *N Engl J Med.* 2019; 380:2104–2115. 5. Facon T, et al. *Lancet*. 2021. 22(11):1582–1596.

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Practical Challenges in Measuring OS Benefits (2/2)

OS data is more prone to be impacted by

1. Treatment cross-over and/or subsequent treatments
   - Ibrutinib in 1L CLL[1]
     - OS HR in ITT = 0.44 (0.21–0.92)
     - OS HR adjusting for crossover using rank-preserving structural failure time = 0.30 (0.13–0.66)
2. Imbalance in patient drop off and missing data
   - Palbociclib + Letrozole in 1L advance breast cancer[2]
     - OS HR in ITT = 0.956 (0.777, 1.177)
     - OS HR accounting for imbalance in missing survival data = 0.869 (0.706, 1.069)
3. Trial design considerations
   - Trade off in preserving alpha for OS vs. testing other endpoints like ORR or PRO earlier
   - Ethical and practical challenges if cross-over is not allowed
   - Single arm trial design

1L, first line; CLL, chronic lymphocytic leukemia; HR, hazard ratio; ITT, intention-to-treat; ORR, overall response rate; OS, overall survival; PRO, patient-reported outcomes.

1. Coutre S, et al. *Haematologica*. 2018. 103(6):e249–e251. **2.** Finn R, et al. *J Clin Oncol*. 2022. 40(17):LBA1003–LBA1003.

Early Endpoints in Use or in Development

	Time to event	Response rates		Patient reported outcome		
Definition	Time from randomization until occurrence of a pre-defined, disease specific event	The proportion of patients who achieve a pre-defined outcome in response to a treatment; can be complete response, partial response or stable disease		Information on the impact of disease, symptoms or treatment on patient's quality of life (QoL); participation in activities of daily living and healthcare resource use		
Segmentation	Disease-state-related	Non-biomarker	Tumor marker/ Biomarker	Cancer agnostic measures	Cancer specific measures	Symptom specific measures
Examples	• PFS • TTP • Disease-free survival (DFS) • Event-free survival (EFS) • Relapse-free survival (RFS) • Metastasis-free survival (MFS)	• ORR *Complete response* *Partial response* *Pathological complete response* • Disease control rate • Clinical benefit rate	• Minimal / measurable residual disease (MRD)* • ctDNA*	• PROMIS • QLQ-C30** • EQ-5D • FACT-G • SF-36 • MD Anderson Symptom • Inventory (activities of daily living)	• QLQ-BR23** (breast) • QLQ-CR2** (colorectal) • FACT-C (colorectal) • QLQ-LC13** (lung) • NSCLC-SAQ (lung)	• SBQ** (symptom burden) • KESS (constipation) • IIED / FSFI (sexual function) • PDQ (pain)

*Some biomarkers may be used as predictors of event-related outcomes, e.g., MRD for PFS and ctDNA for DFS
** Modules of the EORTC PROs tool
^ PROs can also be measures of time to event, e.g., time to deterioration, or response, e.g., percentage of patients with improved HRQoL
ctDNA, circulation tumor deoxyribonucleic acid; DFS, disease-free survival; EFS, event-free survival; EORTC, European organisation for research and treatment of cancer; EQ-5D, EuroQoL- 5 dimension; FACT, functional assessment of cancer therapy; FSFI, female sexual function index; IIED, international index of erectile dysfunction; HRQoL, health-related quality of life; KESS, knowles-eccersley-scott symptom questionnaire; MFS, metastasis-free survival; MRD, minimal/measurable residual disease; NSCLC-SAQ, NSCLC symptom assessment questionnaire; ORR, overall response rate; PDQ, pain disability questionnaire; PFS, progression-free survival; PRO, patient-reported outcomes; PROMIS, patient reported outcomes measurement information system; QLQ, quality of life questionnaire; QoL, quality of life; RFS, relapse-free survival; SBQ, symptom burden questionnaire; SF-36, short form-36; TTP, time to progression.

1. Improving the understanding, acceptance and use of oncology–relevant endpoints in HTA body / payer decision-making. Available at: https://www.efpia.eu/media/t2nlhr0k/improving-the-understanding-acceptance-and-use-of-oncology-relevant-endpoints.pdf. Last accessed on 10 Oct 2023.

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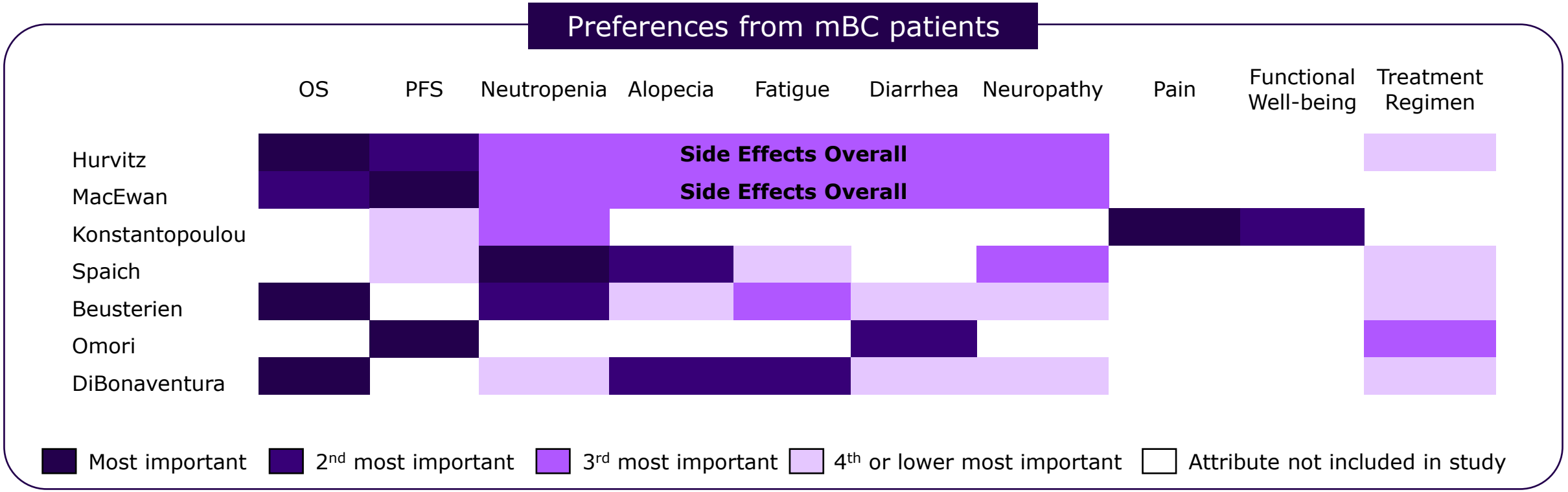
Patient Relevance of Early Endpoints

While quantity of life is important, quality of life is equally or more important. As cancer patients' survival improves, there is increased emphasis on the impact of disease and treatment on overall wellbeing and pain

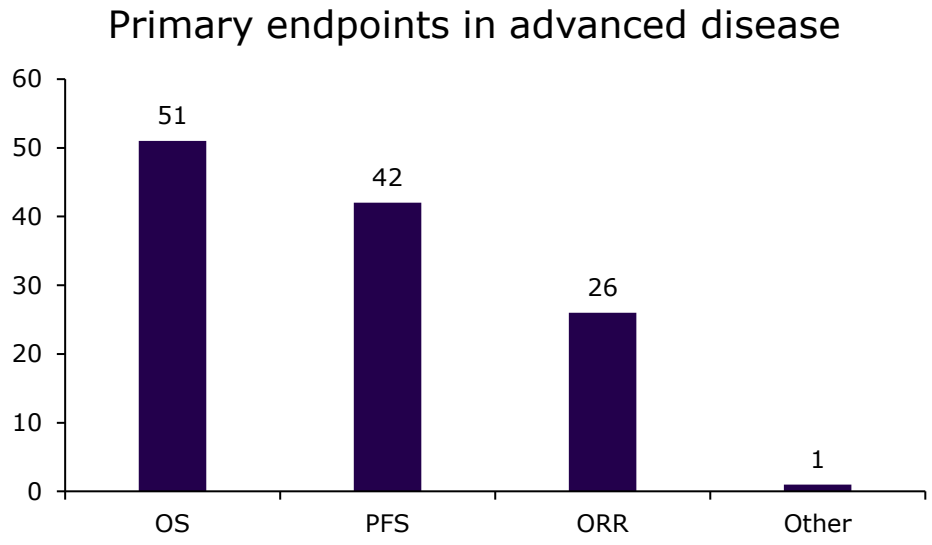


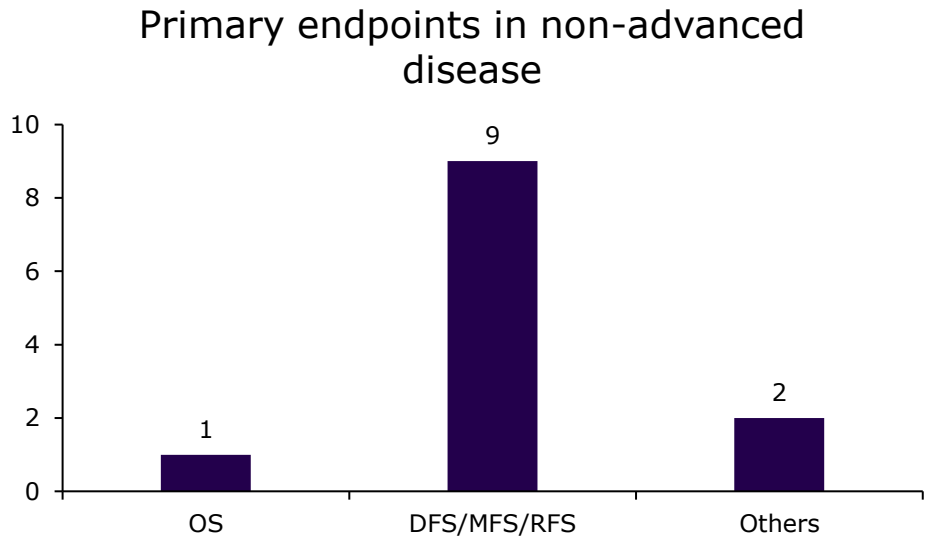
mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival.

1. Harding V, et al. *Br J Cancer.* 2013. 201;109(6): 1543-1548. **2.** MacEwan JP, et al. *MDM Policy & Practice.* 2019. 4(1):2381468319855386. **3.** Konstantopoulou T, et al. *ISPOR Europe* 2019. **4.** Spaich S et al. *Frontiers in Oncology*. 2018;(535). **5.** Beusterien K, et al. *International Journal of Women's Health.* 2012;4: 279-287. **6.** Omori et al. *Breast Cancer.* 2019; 26: 652-663. **7.** DiBonaventura MD et al. *Am Health Drug Benefits*. 2014;7(4): 386-396.

Primary Endpoints in Oncology Approvals by EMA (2015–2020)

Primary endpoints in oncology





33 studies have co-primary endpoints and 26 out of 33 have OS as co-primary endpoint

DFS, disease-free survival; EMA, European Medical Agency; MFS, metastasis-free survival; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival.

1. Falcone R, et al. *Cancers (Basel).* 2022. 14(4):889.

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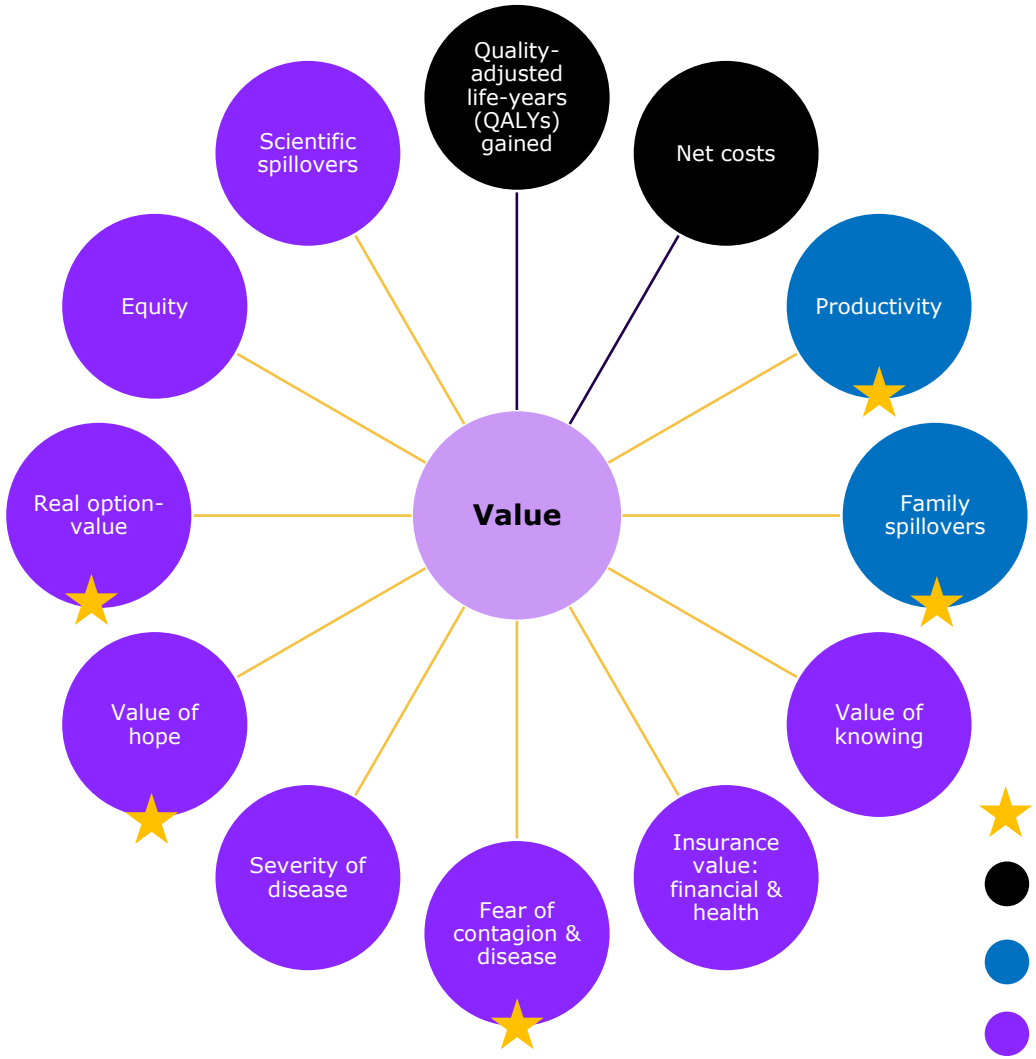
Value of Early Endpoints Reflects Novel Elements of ISPOR Value Flower



DFS?

PFS?

MRD?

Denotes novel elements captured/reflected by early endpoints

Core elements of value

Common but inconsistently used elements of value

Potential novel elements of value

Value element included in the traditional payer or health plan perspective

Value element also included in societal perspective

Adapted from Lakdawalla D et al. *Value Health*. 2018; 21(2):131-139.
DFS, disease-free symptoms; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; MFS, metastasis-free survival; PFS, progression-free survival; QALY, quality-adjusted life-years.
Goring S. et al. Novel Elements of the Value Flower: Fake or Truly Novel? Available at: https://www.ispor.org/publications/journals/value-outcomes-spotlight/vos-archives/issue/view/navigating-the-changing-heor-publishing-landscape/novel-elements-of-the-value-flower-fake-or-truly-novel. Last accessed on 10th Oct 2023.

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Value of Access to Innovative Cancer Treatment Early

Retrospective database study of 12 oncology drugs between 2011–2018 in EU 28 countries

- Marketing approval for the cancer drugs came on average **242 days later** in Europe than in the US
- The average time to market in Europe was **403 days (range 17–1187 days)**
- The delay in patient access of ipilimumab and abiraterone may have led to **a potential loss of more than 30,000 life years**

cancers

MDPI

Article

Unequal Access to Newly Registered Cancer Drugs Leads to Potential Loss of Life-Years in Europe

Carin A. Uyl-de Groot [1,*], Renaud Heine [1], Marieke Krol [2] and Jaap Verweij [3]

1 Erasmus School of Health Policy & Management, Erasmus University Rotterdam, Burg Oudlaan 50, 3062 PA Rotterdam, The Netherlands; heine@eshpm.eur.nl
2 IQVIA, Herikerbergweg 314, 1101 CT Amsterdam, The Netherlands; Marieke.Krol@iqvia.com
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* Correspondence: uyl@eshpm.eur.nl; Tel.: +31-10-408-8555

EU, Europe; US, United States.

1. Uyl-de Groot CA, et al. *Cancers (Basel).* 2020. 12(8):2313.

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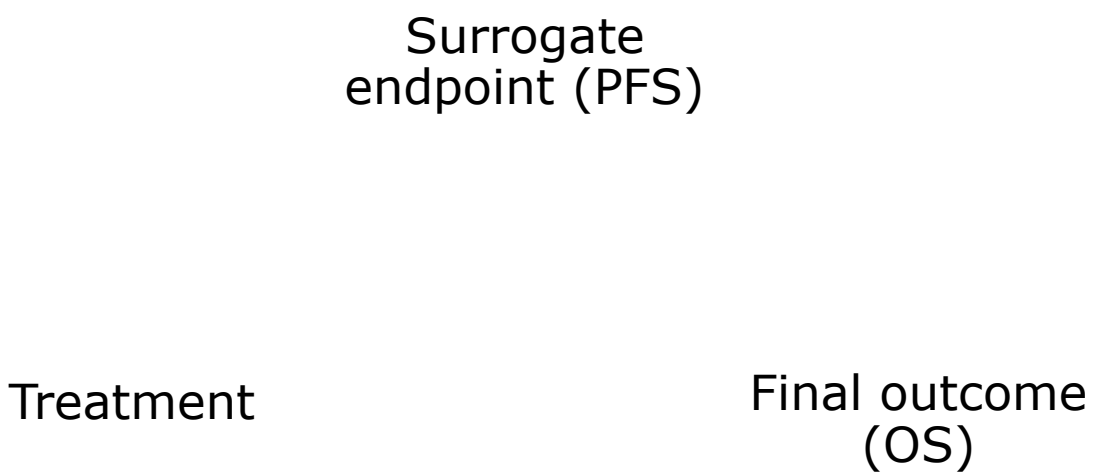
Early Endpoints as Surrogate for Final Endpoints (OS): Level of Evidences

- **Level 3:** Biological plausibility ☑
- **Level 2**: Consistent association between surrogate endpoint and final outcomes
- **Level 1**: The technology's effect on the surrogate endpoint corresponds to commensurate effect on the final outcome



OS, overall survival; PFS, progression-free survival.

1. Buyse M, et al. 2022. *Oncologist*;27(4):266–271.

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Early Endpoints as Surrogate for Final Endpoints (OS): Patient-Level (Individual-Level) Surrogacy

- **Level 3:** Biological plausibility
- **Level 2**: Consistent association between surrogate endpoint and final outcomes
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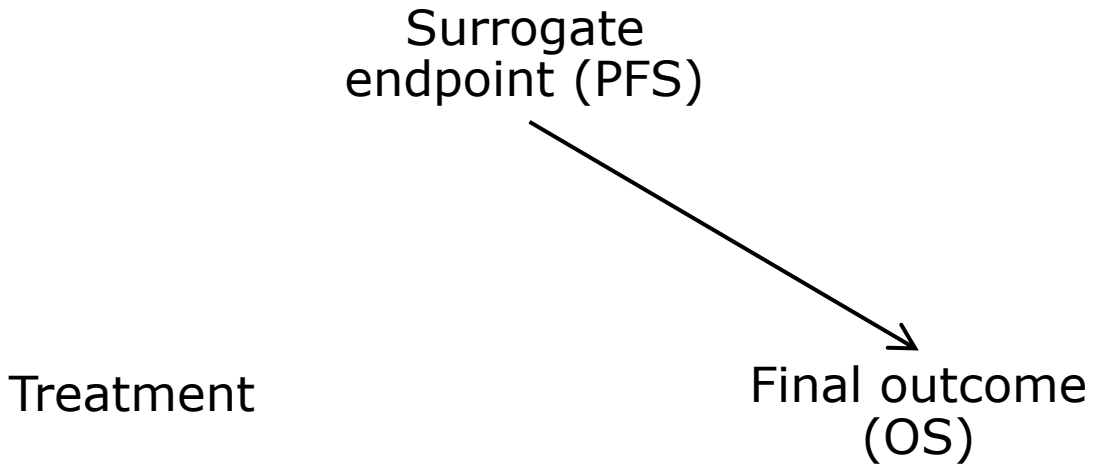

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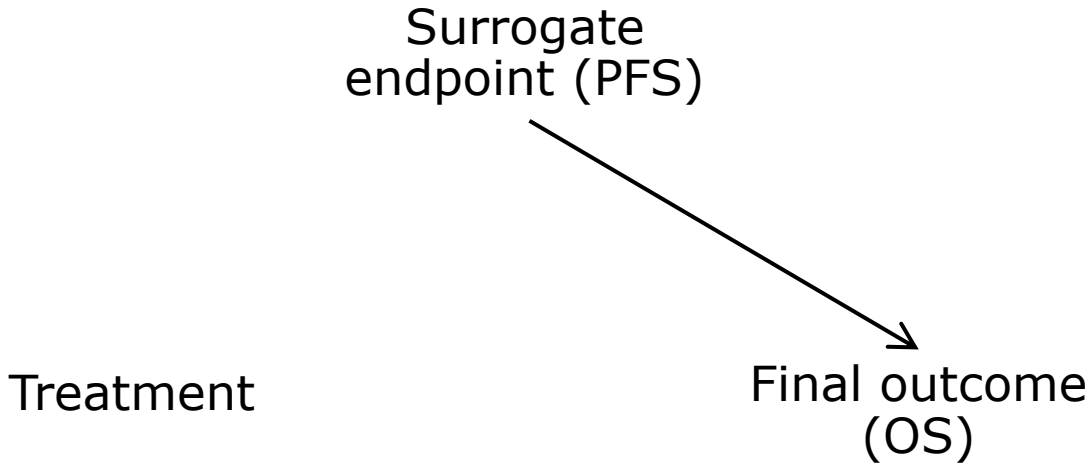

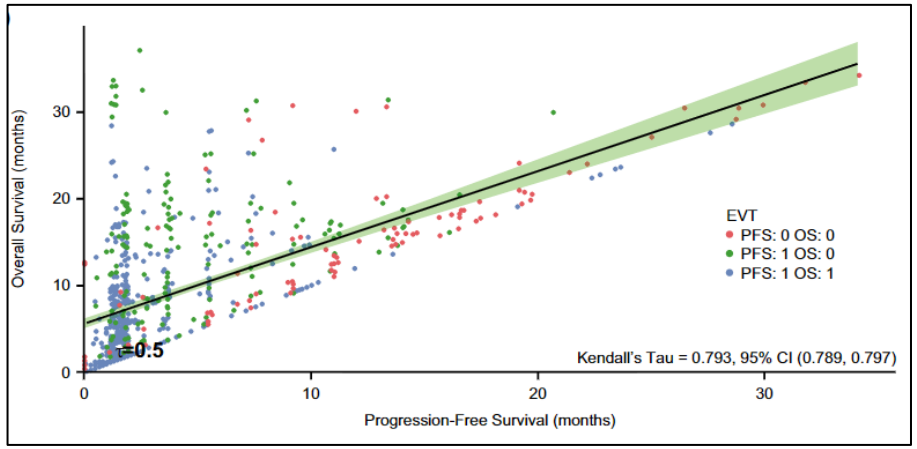

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Early Endpoints as Surrogate for Final Endpoints (OS): Trial-Level Surrogacy-Causal Surrogate

- **Level 3:** Biological plausibility
- **Level 2**: Consistent association between surrogate endpoint and final outcomes
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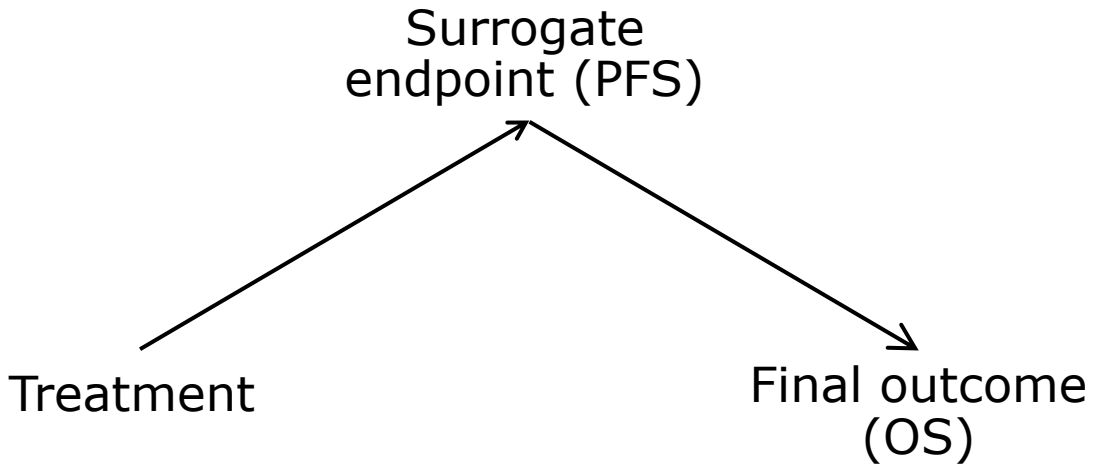

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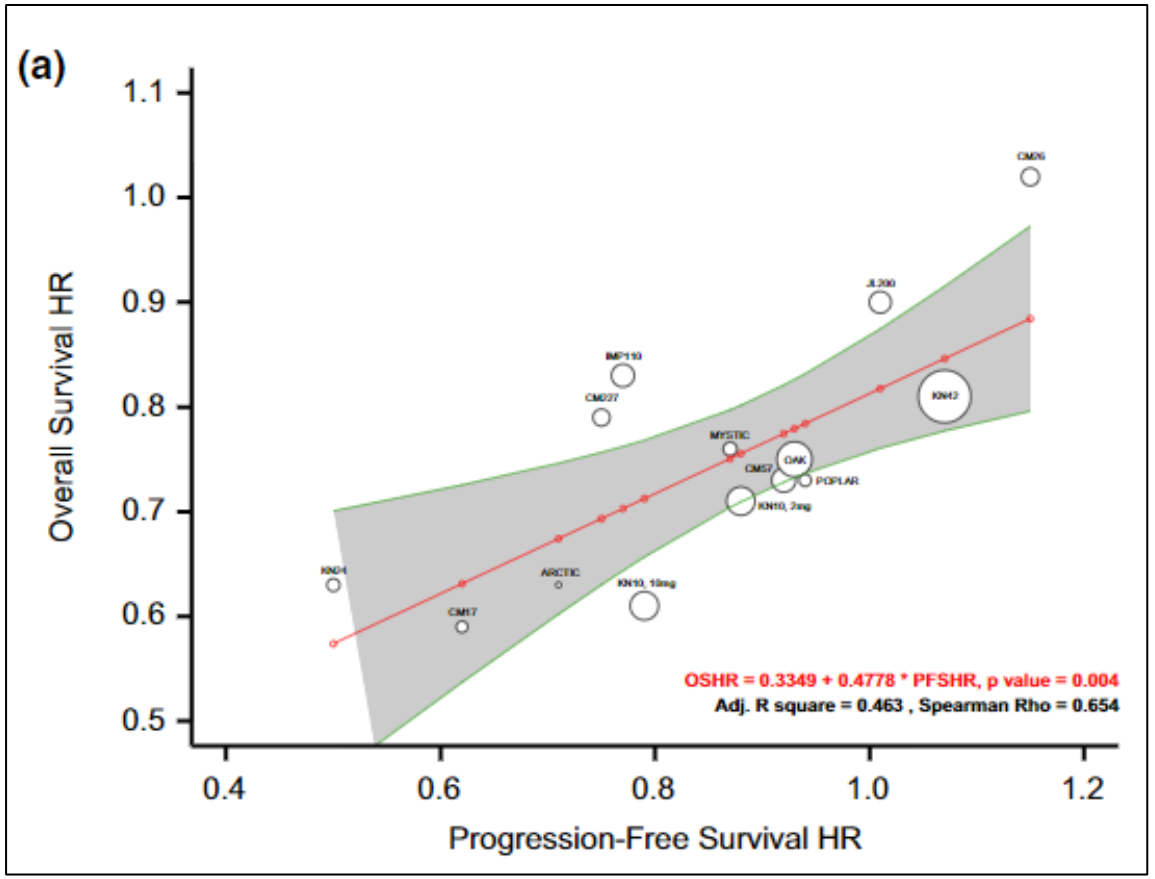

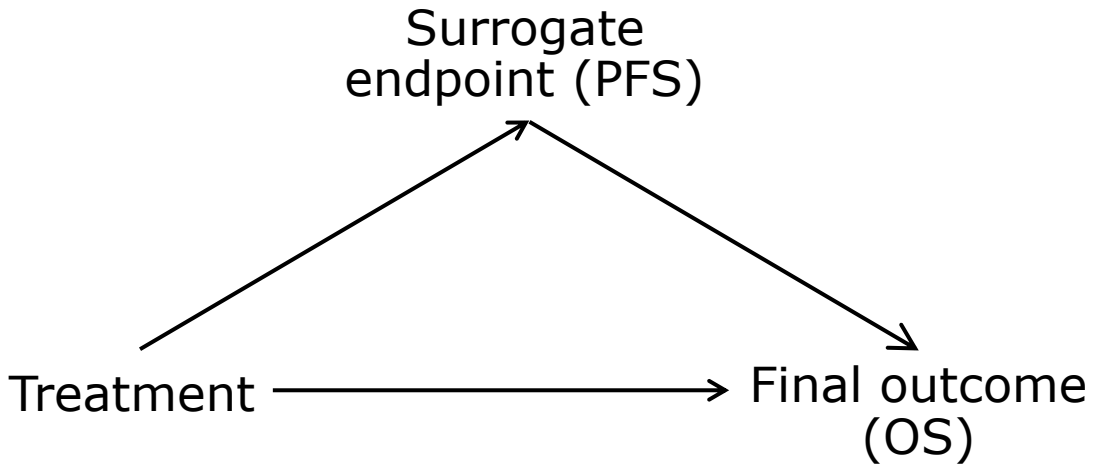

HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

1. Buyse M, et al. 2022. *Oncologist*;27(4):266–271.

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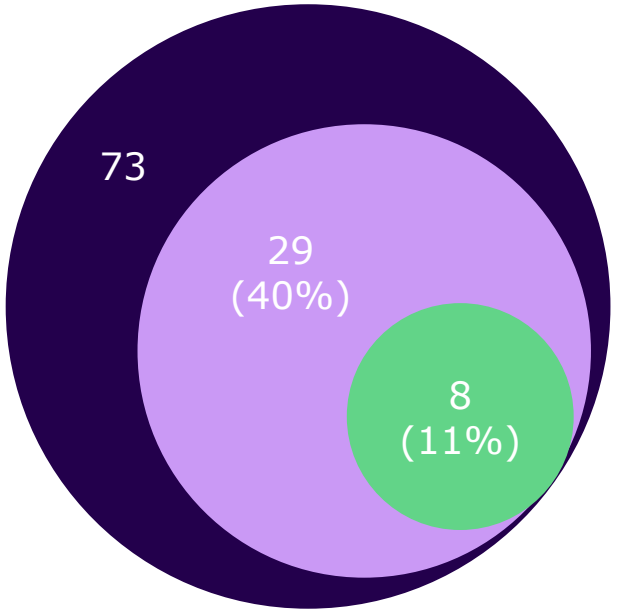
Challenges of Surrogacy Validation for Early Endpoints: Lack of Specific and Consistent Guidance Across HTA Agencies

Surrogate Endpoints in Health Technology Assessment: An International Review of Methodological Guidelines



# of HTAs surveyed from Europe, Australia and Canada

Detailed methodological guidance on surrogate endpoints

with methodological guidelines that made **specific reference to consideration of surrogate outcomes**

HTA, health technology assessment.

1. Grigore B, et al. *Pharmacoeconomics*. 2020 Oct;38(10):1055–1070.

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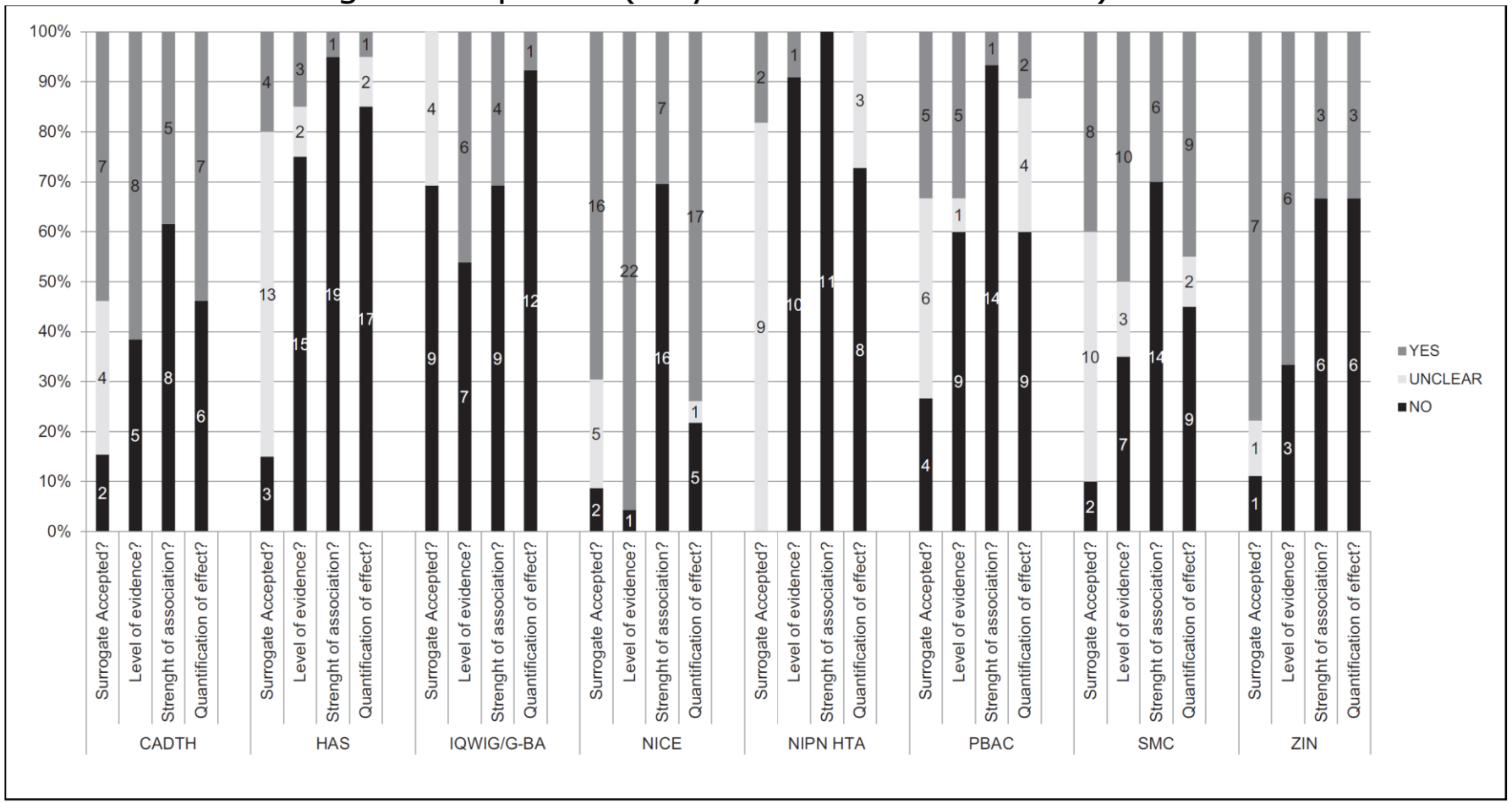
Challenges of Surrogacy Validation for Early Endpoints: Variability in Acceptance and Scrutiny of Surrogate Endpoints Across HTAs

Overall, there was low level of agreement across the 8 HTA agencies on acceptability and steps of validation on surrogate endpoints (May 2013 and June 2018)



HTA, health technology assessment.

1. Ciani O, et al. *Med Decis Making.* 2021;41(4):439–452.

Challenges of Surrogacy Validation for Early Endpoints: No Strong Evidence of Association Between Accepting the Surrogate Endpoint and Coverage Recommendation

Technology	Indication	Surrogate endpoints /Final endpoints	NICE	HIS/SMC	HAS	PBAC	CADTH	IQWiG/ G-BA	ZiN	NIPN	HTA Agencies
Axitinib	Advanced RCC after failure of prior systemic treatment	PFS/OS							-		7
Bortezomib	Previously untreated MCL	PFS/OS				-	-	-	-	-	3
Bortezomib	Induction therapy in MM before ASCT	Response rate, PFS/OS						-	-	-	5
Bosutinib	Previously untreated CML	Major cytogenetic response/OS				-			-		6
Brentuximab vedotin	CD30-positive Hodgkin lymphoma	PFS/OS					-		-	-	5
Cobimetinib (in combo with vemurafenib)*	Unresectable or metastatic BRAF V600 mutation positive melanoma	PFS/OS							-		7
Dasatinib	Untreated CML	Complete cytogenetic response, major molecular response/OS			-		-	-	-		3
Dasatinib	Imatinib-resistant or intolerant CML						-	-			5
Degarelix	Advanced hormone-dependent prostate cancer	Prostate specific antigen Testosterone levels/OS					-	-			6
Imatinib	Adjuvant treatment of gastrointestinal stromal tumors	RFS/OS			-		-	-	-		3
Pertuzumab	Neoadjuvant treatment of HER2-positive breast cancer	Pathological complete response, iDFS & PFS/OS							-		7
Ribociclib	1L HR+/HER2- aBC	PFS/OS									8

Approved for reimbursement Restricted reimbursement Rejected - Not assessed

aBC, advanced breast cancer; ASCT, autologous stem cell transplantation; CADTH, Canadian Agency for Drugs and Technologies in Health; CML, chronic myeloid leukemia; G-BA, Gemeinsamer Bundesausschuss – Germany; HAS, Haute Autorité de Santé – France; HIS, Health Improvement Scotland; iDFS, invasive disease-free survival; IQWiG, Institute for Quality and Efficiency in Health Care; MCL, mantle cell lymphoma; MM, multiple myeloma; NICE, National Institute for Health and Care Excellence; NIPN, National Institute of Pharmacy and Nutrition, OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee; PFS, progression-free survival; RCC, renal cell carcinoma; RFS, relapse-free survival; SMC, Scottish medical consortium; ZIN, Zorginstituut Nederland.

1. Ciani O, et al. *Med Decis Making.* 2021;41(4):439–452.

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It’s Time for a Poll!

In your opinion, what is the biggest value of using early endpoints in oncology

1. The standalone value of these endpoints as clinically meaningful and patient relevant
2. Acceleration in the approval and access to innovative treatments
3. A surrogate for final endpoint (OS)

Navigate to this session in the meeting app to participate!

OS, overall survival.

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In Summary

1. Expansion of new treatment options and novel mechanism of action make measuring OS more and more challenging if not impossible
2. Early endpoints like PFS can be important measures of clinical benefit and are considered meaningful and relevant by regulators and patients
3. There is a need for HTA's perspective on early endpoints to evolve with new reality in oncology to minimize delays in patients' access to innovative treatments (waiting for mature OS is no longer an option!)
4. A strong & open-minded collaboration is needed between different stakeholders to establish clear and realistic evidence requirement and provide specific methodology guidance on measuring the value of early endpoints (standalone or as a surrogate endpoints)

HTA, health technology assessment; OS, overall survival; PFS, progression-free survival.

Thanks for listening!