Table Suppl 1: Oncology Products Approved by Health Canada 2020-2021: Comparison of use of RWE to FDA and EMA – by Product						
		Health Canada designation	Dates of SBD publication	Health Canada use of RWE, N=29	FDA use of RWE N=29	EMA use of RWE N=25
Generic Name	Brand Name			By Categories (1-5) See Method, Fig 2 and Table S2 for definition		
sacituzumab govitecanhziy	Trodelvy	NOC PR	12/23/2021	RWE not used	3	5
Sotorasib	Lumakras	NOCc	12/7/2021	5	1	Report Not Available
Brexucabtagene autoleucel	Tecartus	NOC PR	12/6/2021	5	3	3
Infigratinib	Truseltiq	NOCc	11/30/2021	RWE not used	2	Report Not Available
Pralsetinib	Gaverto	NOCc	11/26/2021	RWE not used	5	3
Tafasitamab	Minjuvi	NOCc	11/25/2021	2	1	1
Idecabtagene vicleucel	ABECMA	NOCc	11/22/2021	RWE not used	1	1
Tepotinib	Tepmetko	NOCc	10/21/2021	4	2	1
Selpercatinib	Retevmo	NOCc	11/9/2021	RWE not used	4	RWE not used
Zanubrutinib	Brukinsa	NOC PR	7/15/2021	RWE not used	RWE not used	5
Trastuzumab deruxtecan	Enhertu	NOCc	7/9/2021	2	1	1
Binimetinib	Mektovi	NOC	6/8/2021	RWE not used	RWE not used	RWE not used
Encorafenib	Braftovi	NOC	6/8/2021	RWE not used	RWE not used	RWE not used
Isatuximab	Sarclise	NOC	12/16/2020	RWE not used	2	RWE not used
Fedratinib	inrebuc	NOC	10/22/2020	RWE not used	5	5
Polatuzumab vedotin	Polivy	NOCc	10/8/2020	RWE not used	RWE not used	3
Tucatinib	Tukysa	NOC PR	10/1/2020	RWE not used	5	5
Ripretinib	Qinlock	NOC PR	9/22/2020	RWE not used	5	RWE not used
Decitabine and cedazuridine	Inqovi	NOC PR	9/21/2020	5	3	Report not available
Sonidegib	Odomzo	NOC	8/11/2020	RWE not used	RWE not used	RWE not used
Entrectinib	Rozlytrek	NOCc	7/6/2020	RWE not used	3	1
Sonidegib	Daurizmo	NOC	7/10/2020	RWE not used	3	RWE not used
Gemtuzumab ozogamicin	Mylotarg	NOC	7/10/2020	5	1	2
Darolutamide	Nubeqa	NOC	6/29/2020	RWE not used	5	RWE not used
Gilteritinib	Xospata	NOC	3/23/200	RWE not used	5	3
Neratinib	Nerlynx	NOC	1/29/2020	RWE not used	RWE not used	RWE not used
Erdafitinib	Balversa	NOCc	1/28/2020	RWE not used	1	Report Not Available
Talazoparib	Talzenna	NOC	1/21/2020	RWE not used	RWE not used	RWE not used
Acalabrutinib	Calquence	NOC	1/13/2020	RWE not used	5	RWE not used

NOC = Notice of Compliance; NOC PR = Notice of Compliance with Priority review; NOCc = NOC with conditions

Table Suppl 2 : Oncology Products Approved by Health Canada 2020-2021 comparisons to FDA & EMA % (Fig 2a) and Examples to support categories from review documents

RWE Categories – Oncology Drugs	Number on bar charts Figure 2a	Health Canada % (n) N=29	FDA % (n) N=29	EMA % (n) N= 25	**Examples to demonstrate regulatory activities included in categories[#]**
Review of retrospective/prospective real-world studies *and* use of historical control for patient population/endpoint comparisons	**1**	0	21.7 (6)	20.0 (5)	FDA: 1) Natural history studies demonstrated patients had poor response to standard of care. 2) Results from 3 real-world, retrospective natural history studies using databases in the United States showed that patients with mutations had similar demographic and clinical characteristics compared to patients in studies and treatment significantly improved responses than real world studies
Review of retrospective/prospective Real World studies for efficacy/safety	**2**	6.9 (2)	10.3 (3)	4.0 (1)	Health Canada: To evaluate the efficacy, an observational, retrospective cohort study was used. This study sought to match patients using propensity score methods to the cohort enrolled in the pivotal, Phase II trial. The purpose of the study was to compare the responses observed among patients who received drug 1 versus those who received the combination of 1+2 (active treatment) followed by monotherapy of 2. The comparison had a positive outcome but was not used in the regulatory decision making
Review and use of historical data for efficacy/safety	**3**	0	17.2 (5)	16.0 (4)	EMA: In order to assess the performance of the comparator arm, the applicant provided an updated review of historical studies regarding the comparator arm, Overall, the observed efficacy results in the treatment arm are not considered to deviate substantially from those of the historical trials and any difference is likely to be attributed to the differences in study population and study design.
Mention the review of RWE in therapeutic context – not clear whether it was used for decision making	**4**	3.4 (1)	3.4 (1)	0 (0)	Health Canada: Efficacy results placed in the context of 1) intra-study comparisons in the pivotal study before and after initiation of active treatment and 2) published evidence on available therapies for NSCLC used to treat the disease suggested increased clinical benefit with active treatment, primarily based on response rates. However, definitive conclusions could not be drawn. Real-world effectiveness outcomes were also inconclusive.
Mention of the review of historical data in therapeutic context– not clear whether it was used for decision making	**5**	13.8 (4)	24.1 (7)	16.0 (4)	FDA: Patients with active brain metastases have been historically excluded from breast cancer clinical trials; however, this study permitted enrollment of patients with treated and progressing brain lesions and untreated brain lesions, as well as patients with treated and stable brain lesions.

Minor edits including removing drug and study names

Table Suppl 3: Non-Oncology Orphan Products Approved by Health Canada 2020-2021: Comparison of use of RWE to FDA and EMA – by Product

Generic Name	Brand Name	Health Canada Designation	Dates of SBD publication	Health Canada Use of RWE	FDA us of RWE	EMA Use of RWE
				By Categories (1-5) See Method, Fig 2 and Table S3 for definition		
Elexacaftor, Tezacaftor, and Ivacaftor	Trikafta	NOC PR	8/5/2021	2	5	1
Ponesimod	Ponvory	NOC	8/5/2021	RWE not used	RWE not used	Report Not available
Risdiplam B45	Evrysdi	NOC PR	7/21/2021	3	3	1
Voretigene neparvovec	Luxturna	NOC	5/17/2021	RWE not used	1	RWE not used
Triheptanoin	Dojolvi	NOC PR	5/3/2021	RWE not used	1	Report Not available
Fostamatinib	Tavalisse	NOC PR	3/31/2021	RWE not used	5	3
Onasemnogene abeparvovec	Zolgensma	NOC PR	3/10/2021	2	1	1
Mecasermin	Increlex	NOC	3/25/2021	3	4	2
Obiltoxaximab	Anthim	NOC	1/28/2021	RWE not used	RWE not used	5
Givosiran	Givlaari	NOC	1/21/2021	RWE not used	5	3
Luspatercept	Reblozyl	NOC PR	11/30/2020	RWE not used	RWE not used	RWE not used
Amifampridine	Firdapse	NOC PR	10/30/2020	2	4	3
Amifampridine	Ruzurgi	NOC PR	10/22/2020	2	1	RWE not used
Satralizumab	Enspryng	NOC PR	9/21/2020	RWE not used	RWE not used	RWE not used
Tafamidis meglumine	Vyndaqel	NOC PR	5/21/2021	RWE not used	5	5
Ravulizumab	Ultomiris	NOC	3/2/2020	RWE not used	5	5
Caplacizumab	Cablivi	NOC PR	5/29/2020	RWE not used	RWE not used	RWE not used
Siponimod	Mayzent	NOC	4/29/2020	2	RWE not used	RWE not used
Ozanimod	Zeposia	NOC	12/2/2020	RWE not used	5	5

NOC = Notice of Compliance; NOC PR = Notice of Compliance with Priority Review

Table Suppl 4: Oncology Products Approved by HC 2020-2021 comparisons to FDA & EMA % (Fig 2b) and Examples to support categories from review documents

RWE Categories: Non oncology orphan drugs (Figures 2b)	Number on bar charts Figure 2b	HC % (n) N=19	FDA % (n) N= 19	EMA % (n) N=17	**Examples to demonstrate regulatory activities included in categories[#]**
Review of retrospective/prospective real-world studies and use of historical control for patient population/endpoint comparisons	**1**	0	21.0 (4)	17.6 (3)	EMA: RWE: The choice of outcome measures will also be determined by how widely available their use is in a real-world setting and their inclusion in the core dataset of the registries selected for inclusion Historical data: The benchmark was based on the associated upper limit of the 90% CI from the historical data. When a pre-defined benchmark could be determined for the secondary endpoint, hypothesis testing was performed.
Review of retrospective/prospective Real World studies	**2**	26.3 (5)	0	5.9 (1)	Health Canada: Additional supportive efficacy data were obtained from an ongoing registry. The European (EU) Registry is a descriptive, multicentre, observational, prospective, open-ended, non-interventional, post-authorization surveillance registry study designed to obtain real world evidence for the safety and effectiveness of treatment in children
Review and use of historical data	**3**	10.5 (2)	5.30 (1)	17.6 (3)	Health Canada: The product was approved in Europe since 2009 and in the United States of America since 2018. Therefore, postmarket safety data contributed greatly to the understanding of the safety profile of the product. The overall, cumulative subject exposure to the product is 302 patients based upon data from completed interventional clinical studies up to the data lock point for this submission. These include 163 healthy volunteers and 139 patients
Mention the review of RWE – not clear whether it was used for decision making	**4**	0	15.8 (3)	0	FDA: Death rates were lower for treated subjects from the ongoing trial and from the long-term follow-up cohorts regardless of genotype (data not shown). The applicant subsequently proposed to analyze safety data in the program based on different cohorts (e.g. health volunteer cohort, B cohort- the only controlled safety data). The Division also agreed with the approach (meeting minutes to the type B meeting, 2018)
Mention of the review of historical data – not clear whether it was used for decision making	**5**	0	26.3 (5)	23.5 (4)	FDA: for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestationalage births in women exposed to treatment during pregnancy compared to an unexposed control population.

Minor edits including removing drug and study names.