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Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.
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Safety of Ocrelizumab in Multiple Sclerosis: Updated Analysis in Patients With Relapsing and Primary Progressive Multiple Sclerosis

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Phase II (NCT00676715); OPERA I (NCT01247324); OPERA II (NCT01412333); ORATORIO (NCT01194570); VELOCE (NCT02545868); CHORDS (NCT02637856); CASTING (NCT02861014); OBOE (NCT02688985); ENSEMBLE (NCT03085810); LIBERTO (NCT03599245); CONSONANCE (NCT03523858)

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X Montalban has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, Genzyme, Immunic, Medday, Merck, Mylan, Nervgen, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF, and NMSS.

C Chognot is an employee of F. Hoffmann-La Roche Ltd.

L Craveiro is an employee of F. Hoffmann-La Roche Ltd.

A Pradhan is an employee of Genentech, Inc.

K Prajapati has received consulting fees from F. Hoffmann-La Roche Ltd for statistical assistance, and is an employee of IQVIA Solutions Inc.

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Background and objectives

- The safety and efficacy of OCR in patients with MS have been characterized in Phase II and Phase III clinical trials[1–3]
- OCR reduced disease activity and disability progression in patients with RMS vs IFN β-1a[2] and PPMS vs placebo[3]
- In the Phase III trials, the most common AEs associated with OCR included IRRs, respiratory tract infections, and UTIs[2–5]

Objective: To report ongoing safety evaluations from OCR clinical trials and associated OLE periods up to January 2020 and selected post-marketing data

AE, adverse event; IFN, interferon; IRR, infusion-related reaction; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; UTI, urinary tract infection. Please scan the QR code to access slide footnotes and references.

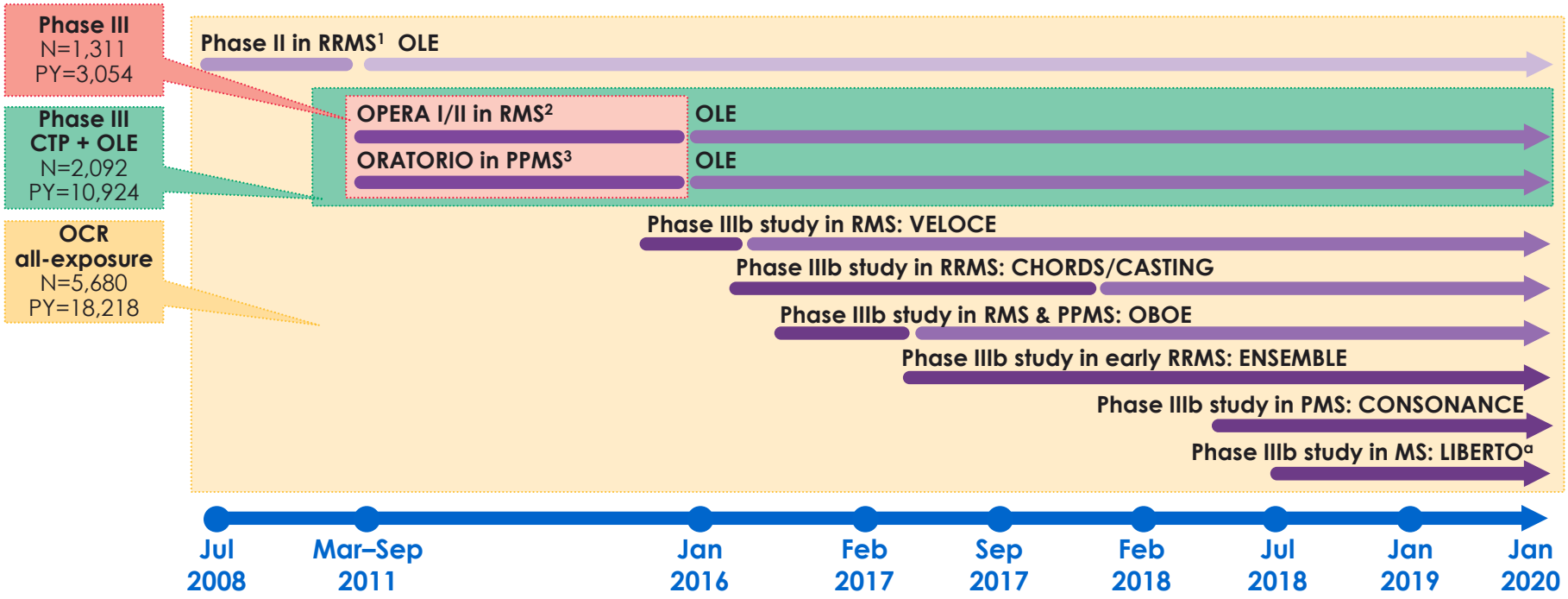
Methods

- Safety analyses are based on integrated data for all patients who received OCR in the following MS clinical trials:
  - **OPERA OLE**: The Phase III OPERA I (NCT01247324) and OPERA II (NCT01412333) clinical trials, and OLE periods[a]
  - **ORATORIO OLE**: The Phase III ORATORIO (NCT01194570) clinical trial and OLE period[a]
  - **OCR all-exposure**: The Phase II (NCT00676715) and Phase III MS clinical trials and associated OLE periods, plus the Phase IIIb trials VELOCE (NCT02545868), CHORDS (NCT02637856), CASTING (NCT02861014), OBOE (NCT02688985), ENSEMBLE (NCT03085810); LIBERTO (NCT03599245), and CONSONANCE (NCT03523858)
- The number of post-marketing OCR-treated patients is based on the estimated number of vials sold and US claims data
- AEs are classified according to MedDRA and the rates of AEs are expressed per 100 PY

[a]Upon completion of the CTP, patients were eligible to receive OCR in OLEs. In ORATORIO, following completion of the DBP, patients could enter the OLE, via an ECP.
AE, adverse event; CTP, controlled-treatment period; DBP, double-blind period; ECP, extended-controlled period; MedDRA, Medical Dictionary for Regulatory Activities; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PY, patient years.

Overview of Phase II/III/IIIb studies and patient exposure

- As of January 2020, 5,680 patients with MS had received OCR across multiple clinical trials (amounting to 18,218 patient-years of exposure)



- As of July 2020, over 170,000 patients with MS have started OCR globally in the post-marketing setting

CTP, controlled-treatment period; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PMS; progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis. Please scan the QR code to access additional slide footnotes.

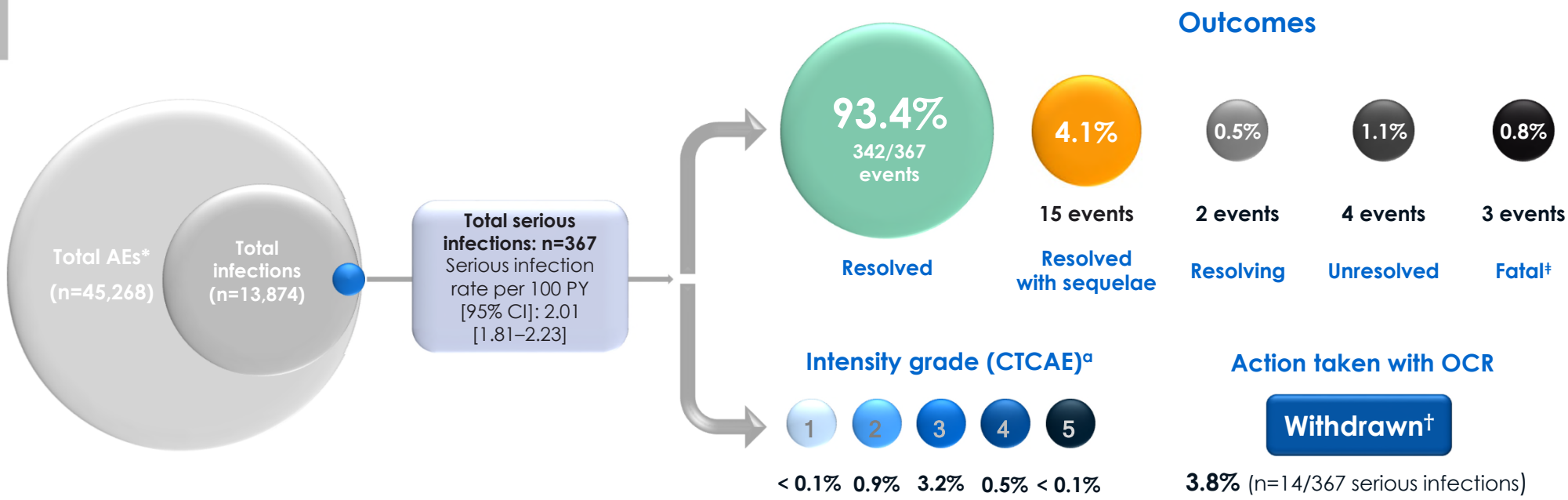
Over 7 years, the safety profile of OCR remained consistent

Adverse event Rate per 100 PY (95% CI)	CTP[a]				CTP/OLE[b]		
	OPERA		ORATORIO		OPERA	ORATORIO	OCR all-exposure population[c]
	IFN β-1a	OCR	Placebo	OCR	OCR	OCR	
Total no. of patients	826	825	239	486	1,448	644	5,680
Total PY	1,399	1,448	729	1,606	7,862	3,562	18,218
Any AEs	**296** (287–305)	**290** (281–299)	**259** (247–271)	**252** (244–260)	**206** (203–209)	**237** (232–242)	**248** (246–251)
AEs leading to discontinuation	**3.93** (2.96–5.12)	**2.35** (1.63–3.28)	**1.10** (0.47–2.16)	**1.25** (0.76–1.92)	**1.25** (1.01–1.52)	**1.07** (0.76–1.46)	**1.06** (0.92–1.22)
Serious AEs	**6.3** (5.1–7.8)	**5.4** (4.3–6.7)	**12.1** (9.7–14.9)	**10.2** (8.7–11.8)	**5.9** (5.4–6.5)	**12.9** (11.8–14.2)	**7.3** (7.0–7.7)
Infections and infestations	**67.8** (63.5–72.2)	**84.5** (79.9–89.4)	**72.5** (66.5–79.0)	**70.8** (66.8–75.0)	**72.2** (70.3–74.1)	**74.2** (71.4–77.1)	**76.2** (74.9–77.4)
Serious infections[d]	**1.79** (1.16–2.64)	**0.83** (0.43–1.45)	**3.02** (1.89–4.57)	**2.74** (1.99–3.68)	**1.32** (1.08–1.60)	**4.41** (3.75–5.15)	**2.01[e]** (1.81–2.23)
IRRs	**7.9** (6.5–9.5)	**34.9** (31.9–38.1)	**20.3** (17.2–23.8)	**31.0** (28.3–33.9)	**14.3** (13.5–15.1)	**20.3** (18.9–21.9)	**25.9** (25.1–26.6)
Malignancies[f,g]	**0.14** (0.02–0.52)	**0.28** (0.08–0.71)	**0.27** (0.03–0.99)	**0.93** (0.52–1.54)	**0.36** (0.24–0.52)	**1.00** (0.70–1.39)	**0.46** (0.37–0.57)
Deaths	**0.14** (0.02–0.52)	**0.07** (0–0.38)	**0.41** (0.08–1.20)	**0.25** (0.07–0.64)	**0.05** (0.01–0.13)	**0.39** (0.21–0.66)	**0.14** (0.09–0.21)

- The **rate of AEs and SAEs** in **OPERA OLE**, **ORATORIO OLE**, and the **OCR all-exposure population** remained consistent with the rates observed during the CTP of the Phase III trials
  - IRRs, upper respiratory tract infections, and UTIs remained the most common AEs; infections remained the most reported SAE
- The rate of AEs leading to treatment discontinuation remained low over time and with additional exposure, and was not driven by serious infections

AE, adverse event; CTP, controlled-treatment period; IFN, interferon; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PY, patient years; SAE, serious adverse event; SOC, system organ class; UTI, urinary tract infection. Please scan the QR code to access additional slide footnotes.

Intensity and outcomes of serious infections in the OCR all-exposure population (Total exposure 18,218 PY)

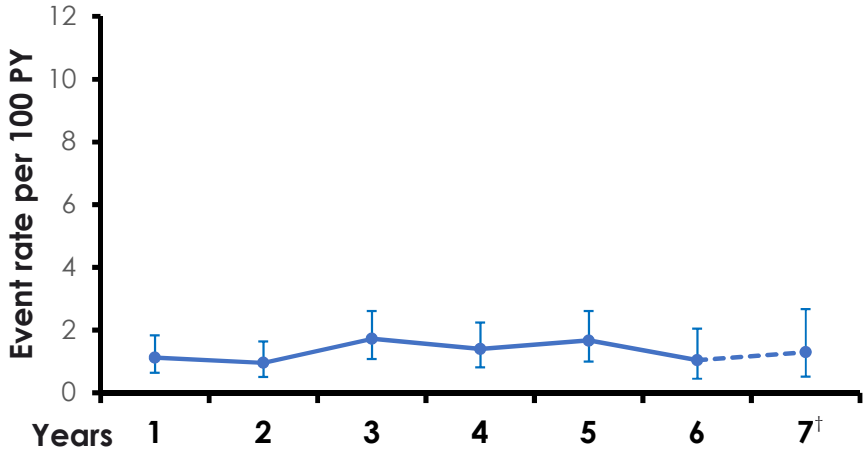


- In the OCR all-exposure population, the **rate of serious infections** remained low[b] and was consistent with rates of infection-related hospitalizations reported in a real-world MS cohort[c]
- The most common serious infections were **pneumonia**, **UTIs,** and **cellulitis**; the majority of the serious infections **resolved** without discontinuing OCR treatment.
- The majority of **serious infections** were of Grade 3 intensity or below, **resolved without sequelae**, **most (57.7%)** resolved within ≤2 weeks and **were not treatment limiting**

*Figure not drawn to scale. †Serious infections leading to withdrawal included sepsis (n=2), septic shock (n=2), acute hepatitis C (n=1), anal abscess (n=1), bronchitis (n=1), *Clostridium Difficile* colitis (n=1), Herpes Zoster (n=1), infection (n=1), large intestine infection (n=1), mastoiditis (n=1), pneumonia (n=1), viral infection (n=1). ‡Fatal serious infections included urosepsis (n=1) and pneumonia (n=2). AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MS, multiple sclerosis; OCR, ocrelizumab; PY, patient-years; UTI, urinary tract infection

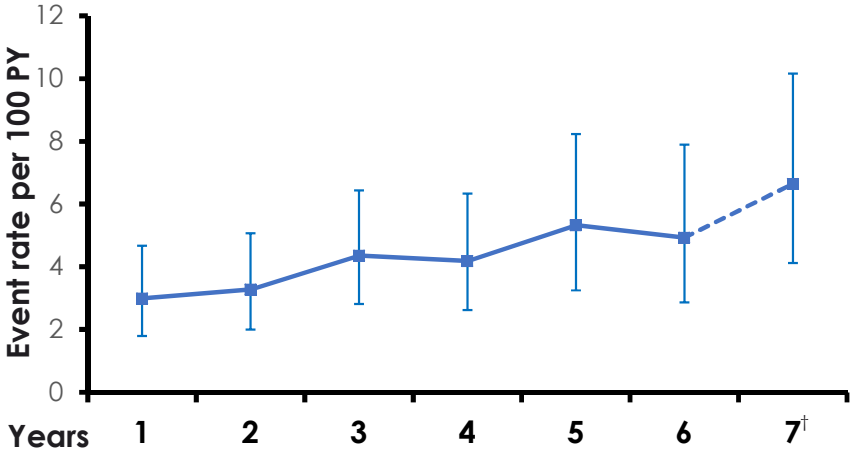
Yearly rate of serious infections over 7 years: RMS and PPMS populations

RMS (OPERA I/II)



	1	2	3	4	5	6	7†
Exposure (PY)	1,422	1,360	1,277	1,216	1,139	770	541
Event rate (per 100 PY)	1.125	0.956	1.723	1.398	1.668	1.039	1.295

PPMS (ORATORIO)



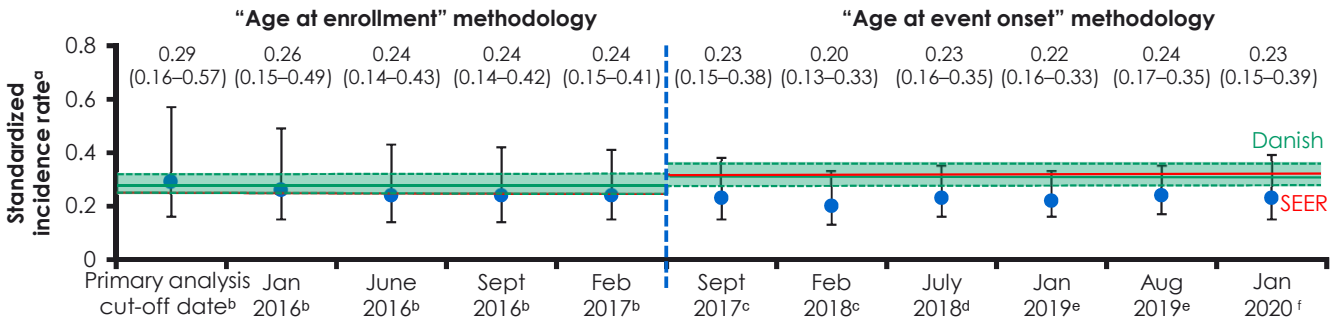
	1	2	3	4	5	6	7†
Exposure (PY)	635	610	573	525	375	345	316
Event rate (per 100 PY)	2.993	3.280	4.365	4.188	5.328	4.933	6.648

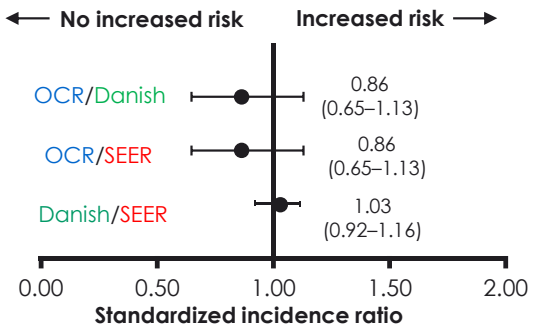
- No new or particular patterns of serious infections were identified by year in either the RMS or PPMS OCR-treated patients
- In the PPMS population, the rate of serious infections remained higher than in the RMS population
- The most frequently reported serious infections overall were consistent with the frequently reported serious infections reported for each year

†The exposure in PY during Year 7 is limited for meaningful interpretation, so these data are presented in the plots with dotted lines. MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis. Please scan the QR code to access additional slide footnotes and references.

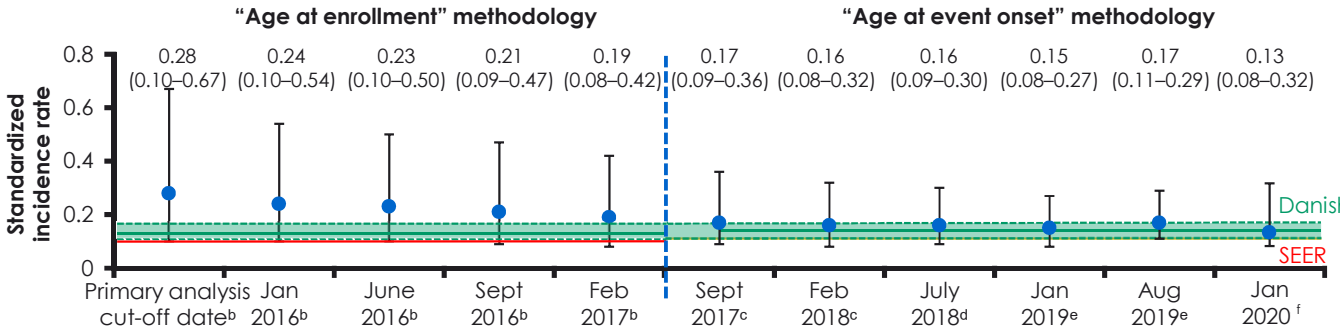
Cumulative standardised incidence rates of all malignancies and female breast cancer remained stable over time and within the range reported in registries

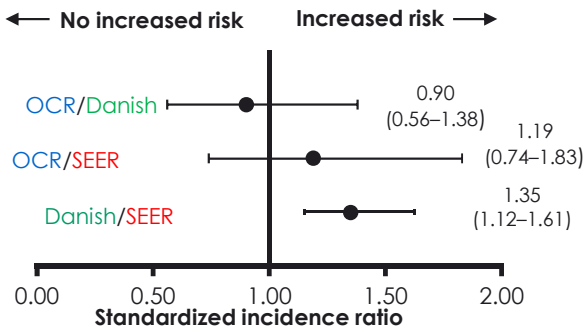
All malignancies: Age- and sex-standardized





Female breast cancer: Age-standardized





- The **cumulative standardized incidence rates of all malignancies and female breast cancer** in OCR-treated patients remained stable over time, and within the range reported in epidemiologic data[1,2]
- **Yearly crude incidence rates of all malignancies**, including NMSC, and female breast cancer in the OCR-all exposure population remained stable over time (data available in supplemental materials)[g]

Please scan the QR code to access additional slide footnotes and references. NMSC, nonmelanoma skin cancer; OCR, ocrelizumab; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio.

Conclusions

- The **reported rates of AEs** in OPERA OLE, ORATORIO OLE and the ocrelizumab all-exposure population and post-marketing settings continue to be generally consistent with those seen during the CTP of the Phase III trials (RMS/PMS populations)
- In the ocrelizumab all-exposure population, the **rate of serious infections** remained low and generally consistent with the rates of infection-related hospitalisations reported in real-world MS cohorts
- The types of infections were also similar to frequent infections observed in MS patients in general, and the majority of serious infections were of Grade 3 intensity or below, resolved without sequelae, within <2 weeks and were not treatment limiting
- The **rate of malignancies and female breast cancer** in ocrelizumab-treated patients remained within the range reported in epidemiological data
- Based on the limited data available to date (presented earlier this year[1]), there is currently no evidence to suggest a more severe course of COVID-19 in ocrelizumab-treated patients with MS (updated data to be presented at this congress during the late-breaking session [Sept. 26 10:45-12:15 EDT. Oral presentation #2110[†]])

Long-term follow-up and **post-marketing requirement studies** will monitor **patient safety over time** in patients with MS receiving ocrelizumab, including identified and potential risks

[†]Session number: SS02.05 . AE, adverse event; COVID-19, coronavirus disease 2019; CTP, controlled-treatment period; MS, multiple sclerosis; OLE, open-label extension; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis. 1. Hughes R, *et al. Mult Scler Relat Disord* 2020. doi: https://doi.org/10.1016/j.msard.2020.102192.

Supplemental materials

- Additional methods
- Overview of study designs
- Treatment exposure
- AEs leading to treatment discontinuation
- Potential serious opportunistic infections, including PML
- Standardized incidence rates of all malignancies and female breast cancer
- Yearly crude incidence rates of all malignancies and female breast cancer
- Presentation footnotes

AE, adverse event; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.

Methods: Malignancies

- Age- and sex-standardized incidence rates of all malignancies (excluding NMSC), and age-standardized incidence rates of female breast cancer were compared with rates from real-world epidemiologic sources, both MS-specific (Danish MS Registry)[1] and for the general population (National Cancer Institute [NCI] SEER database)[2]
- The standardized incidence ratio, calculated as observed/expected number of events, was determined for all malignancies (excluding NMSC) and female breast cancer, using SEER and Danish MS Registry as reference populations

MS, multiple sclerosis; NMSC, non-melanoma skin cancer; SEER, Surveillance, Epidemiology, and End Results.

1. Nørgaard M, *et al. Mult Scler Relat Disord* 2019;28:81–85. 2. National Institutes of Health (NIH). Available at https://seer.cancer.gov.

Overview of study designs

Study name	Population (start date)	Naïve/pre-treated (%)[a]	Design	Treatment	Number of patients	Overall PY (Jan 2020)	Duration of main study	Entering OLE?[b]	Objective of study	Primary endpoint	Current status
Phase II (NCT00676715)	RRMS (2008)	Naïve and pre-treated (41.3%)	Controlled	OCR 2,000 mg every 6M[c,d]	55	1,223	96 weeks	Yes	Evaluate the efficacy and safety of two dose regimens of OCR	Total number of Gd-enhancing T1 lesions observed on brain MRI scans at Week 12, 16, 20, and 24	Active, not recruiting
				OCR 600 mg every 6M[e]	55						
				Placebo every 6M[f]	54						
				IFN β-1a 30 µg once weekly[f]	54						
OPERA I (NCT01247324)	RMS (2011)	Naïve and pre-treated (27.4%)	Controlled	OCR 600 mg every 6M[e]	410	4,052	96 weeks	Yes	Evaluate the efficacy and safety of OCR in comparison with IFN β-1a	ARR at Week 96	Active, not recruiting
				IFN β-1a 44 µg three times weekly	411						
OPERA II (NCT01412333)	RMS (2011)	Naïve and pre-treated (25.9%)	Controlled	OCR 600 mg every 6M[e]	417	3,810	96 weeks	Yes	Evaluate the efficacy and safety of OCR in comparison with IFN β-1a	ARR at Week 96	Active, not recruiting
				IFN β-1a 44 µg three times weekly	418						
ORATORIO (NCT01194570)	PPMS (2011)	Naïve and pre-treated (11.6%)	Controlled	OCR 600 mg every 6M[g]	488	3,562	120 weeks	Yes	Evaluate the efficacy and safety of OCR in comparison with placebo	Percentage of patients with CDP sustained for at least 12 weeks	Active, not recruiting
				Placebo every 6M	244						

6M, 6 months; ARR, annualized relapse rate; CDP, confirmed disability progression; Gd, gadolinium; IFN, interferon; OCR, ocrelizumab; OLE, open-label extension; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis. Please scan the QR code to access additional slide footnotes and references.

Overview of study designs (cont.)

Study name	Population (start date)	Naïve/pre-treated (%)[a]	Design	Treatment	Number of patients	Overall PY (Jan 2020)	Duration of main study	Entering OLE?[b]	Objective of study	Primary endpoint	Current status
VELOCE (NCT02545868)	RMS (2015)	Naïve and pre-treated (41.2%)	Controlled	OCR 2,000 mg every 6M[e]	68	346	24 weeks	Yes	Evaluate the immune response to vaccines after administration of OCR	Percentage of patients with a positive response 8-weeks post-tetanus vaccine	Active, not recruiting
				IFN β-1a or no DMT	34						
CHORDS (NCT02637856)	RRMS (2016)	Pre-treated (100%)	Single arm	OCR 600 mg every 6M[e]	611	1,116	96 weeks	No[h]	Evaluate the efficacy and safety of OCR in patients with a suboptimal response to a DMT in the USA/Canada	Percentage of patients free from any protocol-defined event during 96-week period, including occurrence of at least one of the following: a protocol-defined relapse, a T1 Gd-enhancing lesion, a new and/or enlarging T2 lesion, or CDP at 24 weeks	Completed
CASTING (NCT02861014)	RRMS (2016)	Pre-treated (100%)	Single arm	OCR 600 mg every 6M[e]	681	508	96 weeks	Yes	Evaluate the efficacy and safety of OCR in patients with a suboptimal response to a DMT in Europe	Percentage of patients with NEDA (as per protocol-defined events) during 96-week period	Active, not recruiting

6M, 6 months; CDP, confirmed disability progression; DMT, disease-modifying therapy; Gd, gadolinium; IFN, interferon; NEDA, no evidence of disease activity; OCR, ocrelizumab; OLE, open-label extension; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

Overview of study designs (cont.)

Study name	Population (start date)	Naïve/pre-treated (%)[a]	Design	Treatment	Number of patients	Overall PY (Jan 2020)	Duration of main study	Entering OLE?[b]	Objective of study	Primary endpoint	Current status
OBOE (NCT02688985)	RMS (2016) PPMS (2016)	Naïve and pre-treated (37.5%)	Single arm	OCR 600 mg every 6M[e] OCR 600 mg every 6M[g]	88 16	290	52 weeks	Yes	Explore the mechanism of action of OCR and B-cell biology	Change in NfL levels in the CSF from baseline to post-treatment with OCR; change in the number of CD19+ B cells and CD3+ T cells in the CSF from baseline to post-treatment with OCR	Active, not recruiting
ENSEMBLE (NCT03085810)	Early-stage RRMS (2017)	Naive	Single arm	OCR 600 mg every 6M[e]	1,233[j]	1,700	192 weeks	Yes	Evaluate the efficacy and safety of OCR	A set of endpoints addressing different facets of MS: clinical assessments conducted every 24 weeks; MRI conducted at Week 8 (re-baselining), 24, 48, 96, 144, and 192	Active, not recruiting
LIBERTO (NCT03599245)	MS (2018)	Naïve and pre-treated (100%)	Single arm	OCR 600 mg every 6M[e]	1,500[j]	1,155	144 weeks	Yes	Long-term extension study to CASTING and ENSEMBLE to evaluate the efficacy and safety of OCR	Effectiveness of OCR in patients with MS assessed by progression of disease up to 2 years	Active, not recruiting

6M, 6 months; OCR, ocrelizumab; OLE, open-label extension; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

Overview of study designs (cont.)

Study name	Population (start date)	Naïve/pre-treated (%)[a]	Design	Treatment	Number of patients	Overall PY (Jan 2020)	Duration of main study	Entering OLE?[b]	Objective of study	Primary endpoint	Current status
CONSONANCE (NCT03523858)	PMS (2018)	Pre-treated	Single arm	OCR 600 mg every 6M[j]	633	457	192 weeks	Yes	Open-label study to evaluate effectiveness and safety of OCR in patients with PMS	Percentage of patients with NEP and NEPAD from baseline to Week 96, Week 96 to Week 192, and baseline to Week 192	Active, not recruiting

6M, 6 months; NEP, no evidence of progression; NEPAD, no evidence of progression and no active disease; OCR, ocrelizumab; OLE, open-label extension; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; PY, patient years.

Treatment exposure

- In the OCR all-exposure population, over 50% of patients (3,232) received ≥5 doses

	Phase III CTP + OLE (N=2,092)[a]		
	OPERA CTP/OLE (N=1,448)[a]	ORATORIO CTP/OLE (N=644)[a]	OCR all-exposure (N=5,680)[b]
Age at start of treatment, median (range), years	38.0 (18–58)	47.0 (20–59)	38.0 (18–66)
Total patient years	7,862	3,562	18,218
Number of doses, n (%)[c]	**Number of patients**	**Number of patients**	**Number of patients**
≥1	1,448 (100)	644 (100)	5,680 (100)
≥2	1,382 (95.4)	621 (96.4)	5,480 (96.5)
≥3	1,346 (93.0)	608 (94.4)	4,695 (82.7)
≥4	1,314 (90.7)	590 (91.6)	4,131 (72.7)
≥5	1,263 (87.2)	570 (88.5)	3,232 (56.9)
≥6	1,232 (85.1)	550 (85.4)	2,496 (43.9)
≥7	1,200 (82.9)	531 (82.5)	2,209 (38.9)
≥8	1,181 (81.6)	510 (79.2)	1,877 (33.0)
≥9	1,159 (80.0)	477 (74.1)	1,761 (31.0)
≥10	1,135 (78.4)	362 (56.2)	1,593 (28.0)
Number of doses, mean (SD)	11.9 (4.7)	11.8 (5.3)	7.2 (5.2)
Number of doses, median	13.0	12.0	5.0
Total cumulative dose, mg			
Mean (SD)	7,144 (2,823)	5,662 (2,621)	4,150 (2,952)
Median	7,800	6,600	3,000
Range	9–10,800	19–9,600	9–14,600

CTP, controlled-treatment period; OCR, ocrelizumab; OLE, open-label extension.
Please scan the QR code to access additional slide footnotes and references.

IRRs, neoplasms, and infections were the most common AEs leading to discontinuation in the OCR all-exposure population[a]

MedDRA SOC MedDRA preferred term	Number of patients
Overall total number of patients	**181**
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	**40**
Invasive ductal breast carcinoma	8
Breast cancer	5
Malignant melanoma	4
Papillary thyroid cancer	2
Prostate cancer	2
Adenocarcinoma of colon	1
Anaplastic large-cell lymphoma	1
Basal cell carcinoma	1
Carcinoma in situ of penis	1
Cervix carcinoma stage II	1
Chondrosarcoma	1
Endometrial adenocarcinoma	1
Endometrial cancer	1
Hypergammaglobulinemia benign monoclonal	1
Invasive breast carcinoma	1
Lobular breast carcinoma in situ	1
Lung neoplasm malignant	1
Malignant fibrous histiocytoma	1
Metastatic malignant melanoma	1
Nodular melanoma	1
Pancreatic carcinoma metastatic	1
Renal cell carcinoma	1
Squamous cell carcinoma	1
Transitional cell carcinoma	1

MedDRA SOC MedDRA preferred term	Number of patients
Injury, poisoning, and procedural complications	**35**
Infusion-related reaction	33
Lumbar vertebral fracture	1
Subdural hematoma	1
Infections and infestations	**27**
Urinary tract infection	4
Herpes zoster	2
Infection[b]	2
Sepsis	2
Septic shock	1
Acute hepatitis C	1
Anal abscess	1
Bacterial vaginosis	1
Bronchitis	1
Cellulitis	1
Clostridium difficile colitis	1
Coccidioidomycosis	1
Large intestine infection	1
Latent tuberculosis	1
Mastoiditis	1
Esophageal candidiasis	1
Periodontitis	1
Pneumonia	1
Pulmonary tuberculoma	1
Viral infection	1

IRRs, neoplasms, and infections were the most common AEs leading to discontinuation in the OCR all-exposure population[a] (cont.)

MedDRA SOC MedDRA preferred term	Number of patients
Psychiatric disorders	**13**
Depression	3
Anxiety	2
Completed suicide	2
Delusion	1
Depressive symptom	1
Hallucination	1
Mental disorder	1
Suicidal ideation	1
Suicide attempt	1
Skin and subcutaneous tissue disorders	**12**
Rash	2
Alopecia	1
Asteatosis	1
Decubitus ulcer	1
Dermatitis allergic	1
Dermatitis bullous	1
Erythema nodosum	1
Guttate psoriasis	1
Interstitial granulomatous dermatitis	1
Pruritis allergic	1
Skin lesion	1
Gastrointestinal disorders	**8**
Crohn's disease	4
Colitis	1
Colitis ulcerative	1
Diarrhea	1
Enterocolitis	1

MedDRA SOC MedDRA preferred term	Number of patients
General disorders and administration site conditions	**7**
Fatigue	2
Asthenia	1
Chest pain	1
Chills	1
Influenza-like illness	1
Pyrexia	1
Nervous system disorders	**6**
Multiple sclerosis relapse	2
Headache	1
Optic neuritis	1
Secondary progressive multiple sclerosis	1
Speech disorder	1
Investigations	**9**
Neutrophil count decreased	2
B lymphocyte count decreased	1
Blood creatine increased	1
Blood immunoglobulin G decreased	1
CD4 lymphocytes decreased	1
Electrocardiogram QT prolonged	1
Gamma-glutamyltransferase increased	1
Transaminases increased	1
Musculoskeletal and connective tissue disorders	**5**
Arthralgia	1
Osteonecrosis	1
Pain in extremity	1
Psoriatic arthropathy	1
Seronegative arthritis	1

IRRs, neoplasms, and infections were the most common AEs leading to discontinuation in the OCR all-exposure population[a] (cont.)

MedDRA SOC MedDRA preferred term	Number of patients
Hepatobiliary disorders	**3**
Hepatitis	1
Hepatitis fulminant	1
Portal vein thrombosis	1
Metabolism and nutrition disorders	**3**
Diabetes mellitus inadequate control	1
Hypoproteinemia	1
Lactic acidosis	1
Blood and lymphatic system disorders	**3**
Lymphocytosis	1
Lymphopenia	1
Neutropenia	1
Cardiac disorders	**2**
Aortic valve incompetence	1
Congestive cardiomyopathy	1

MedDRA SOC MedDRA preferred term	Number of patients
Immune system disorders	**3**
Hemophagocytic lymphohistiocytosis	1
Hypersensitivity	1
Hypogammaglobulinemia	1
Reproductive system and breast disorders	**2**
Cervical dysplasia	1
Metrorrhagia	1
Respiratory, thoracic, and mediastinal disorders	**2**
Dysphonia	1
Sinus congestion	1
Eye disorders	**1**
Vitreous floaters	1

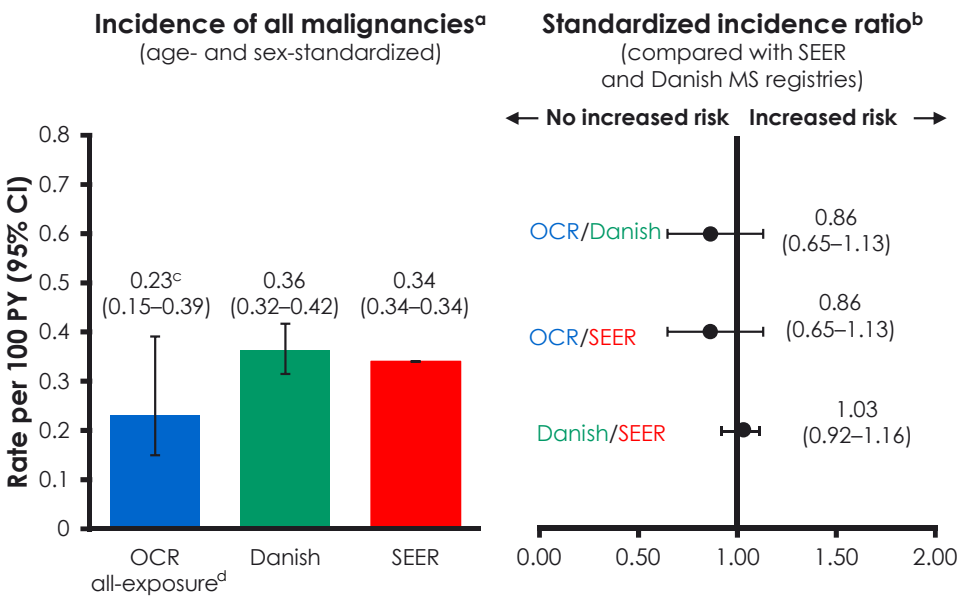
Potential serious opportunistic infections

- As of January 2020, the incidence of potential SOIs in the OCR all-exposure population was low, at a rate of 0.08 per 100 PY (95% CI 0.04–0.13)
  - The rates remained stable year-on-year compared with the rates observed during the CTP (0.09 per 100 PY; 95% CI 0.02–0.23)
  - Herpes was the unique cluster of potentially SOIs in the OCR all-exposure population, but the rates were very low (0.03 per 100 PY; 95% CI 0.01–0.07)
  - No cases of hepatitis B virus infection reactivation, fever of unknown origin, cryptococcosis, aspergillosis, listeriosis, toxoplasmosis, or cytomegalovirus infection were reported in the OCR all-exposure population
- As of March 31, 2020, no cases of PML were reported in the context of clinical trials
  - Nine confirmed cases of PML were reported outside the clinical trial setting
    - Eight cases reported by the treating physicians as "carry-over" cases from previous treatment with either natalizumab (n=7) or fingolimod (n=1)
    - One case where the patient was treated with OCR for 2 years, without history of a previous DMT, but with contributing risk factors for PML, notably old age (78 years) and Grade 1 lymphopenia
    - A fatal outcome was reported in two cases

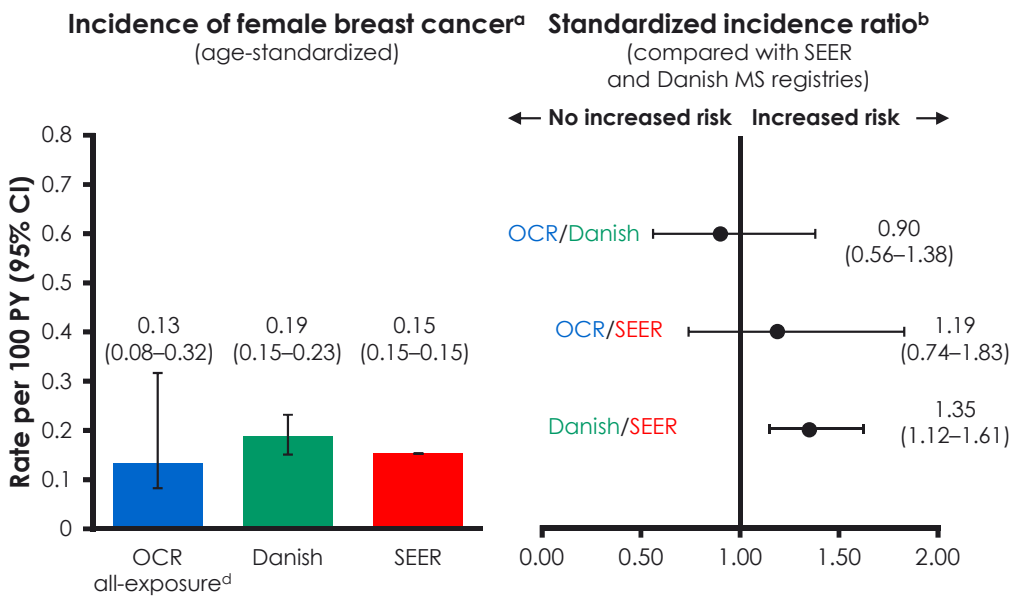
CTP, controlled-treatment period; DMT, disease-modifying therapy; OCR, ocrelizumab; PML, progressive multifocal leukoencephalopathy; PY, patient years; SOI, serious opportunistic infection.

Over 7 years, the standardized incidence rates of all malignancies and female breast cancer remained within the range reported in registries

Incidence of all malignancies
Age- and sex-standardized



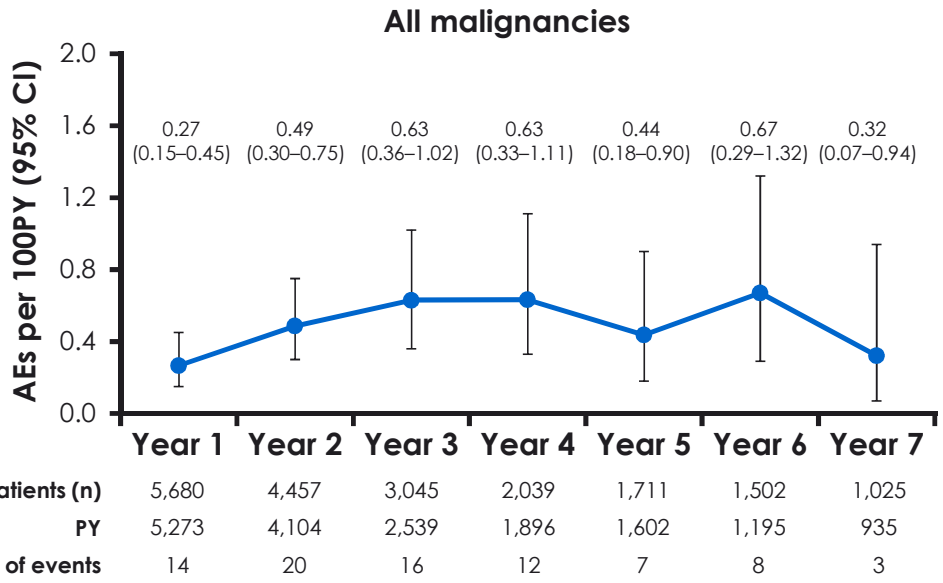
Incidence of female breast cancer
Age-standardized



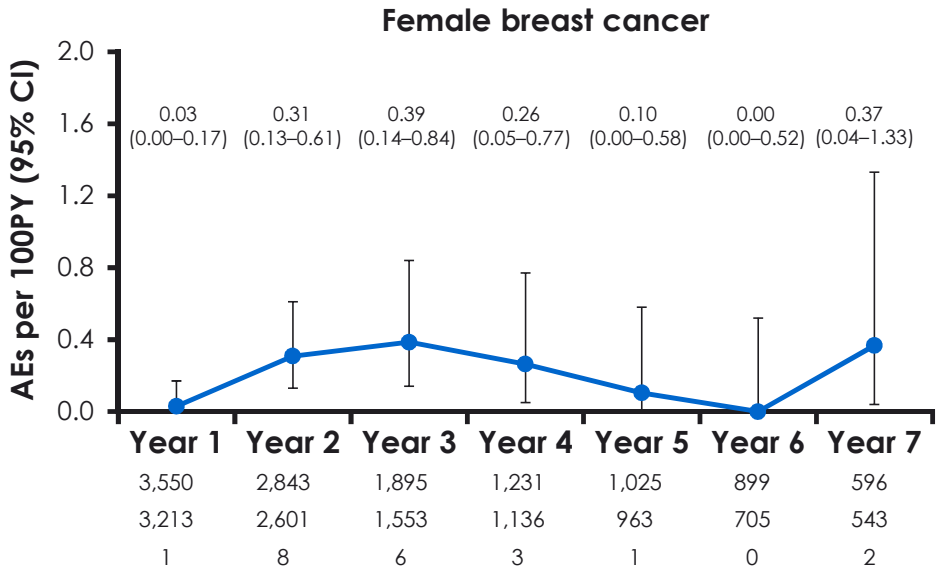
- The **rate of all malignancies and female breast cancer** in OCR-treated patients remained stable compared with the rates observed in the CTP of the Phase III trials, and within the range reported in epidemiologic data[1,2]

CTP, controlled-treatment period; IFN, interferon; MS, multiple sclerosis; OCR, ocrelizumab; PY, patient years; SEER, Surveillance, Epidemiology, and End Results.

Over 7 years, no significant year-on-year variation was observed in the incidence rates of all malignancies and female breast cancer



	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Patients (n)	5,680	4,457	3,045	2,039	1,711	1,502	1,025
PY	5,273	4,104	2,539	1,896	1,602	1,195	935
No. of events	14	20	16	12	7	8	3



	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
	3,550	2,843	1,895	1,231	1,025	899	596
	3,213	2,601	1,553	1,136	963	705	543
	1	8	6	3	1	0	2

- Yearly crude incidence rates of all malignancies, including NMSC, and female breast cancer in the OCR all-exposure population remained stable over time[a]
  - There were three events of all malignancies at Year 7 (n=1,025; 935 PY) and two at Year 8 (n=646; 391 PY)
  - There were two events of female breast cancer at Year 7 (n=596; 543 PY)

AE, adverse event; CTP, controlled-treatment period; IFN, interferon; NMSC, non-melanoma skin cancer; OCR, ocrelizumab; OLE, open-label extension; PY, patient years.

Supplemental materials: Presentation footnotes

Slide 3

AE, adverse event; IFN, interferon; IRR, infusion-related reaction; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; UTI, urinary tract infection.

1. Kappos L, *et al*. *Lancet* 2011;378:1779–1787. 2. Hauser SL, *et al*. *N Engl J Med* 2017;376:221–234. 3. Montalban X, *et al*. *N Engl J Med* 2017;376:209–220.
4. Genentech. Ocrevus (Ocrelizumab) [Full Prescribing Information] [online]. Available at: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed 18 August 2020. 5. European Medicines Agency. Ocrevus [Summary of Product Characteristics] [online]. Available at: https://www.ema.europa.eu/en/documents/product-information/ocrevus-epar-product-information_en.pdf. Accessed 18 August 2020.

Slide 5

[a]LIBERTO is the long-term extension study to CASTING and ENSEMBLE.

CTP, controlled-treatment period; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PMS; progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

1. Kappos L, *et al. Lancet* 2011;378:1779–1787;
2. Hauser SL, et al *N Engl J Med* 2017;376:221–234; 3. Montalban X, *et al. N Engl J Med* 2017;376:209–220.

Slide 6

AEs were classified according to MedDRA versions 18.0, 18.1, and 22.1. Multiple occurrences of the same AE in one patient are counted multiple times, except for malignancies.

[a]Data as of April–July 2015; [b]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase III studies, including patients originally randomized to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of January 2020); [c]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO and CONSONANCE, including patients originally randomized to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of January 2020); [d]Serious infections are defined using AEs falling into the MedDRA SOC Infections and infestations, and using 'Is the event non-serious or serious?' from the AE case report form; [e]Rates of infection-related hospitalizations (1.88 per 100 PY; 95% CI 1.77–2.01) in the British Columbia registry[1] are shown for epidemiological reference. [f]Malignancies are identified using AEs falling into the standard MedDRA query 'Malignant tumors (narrow)'; [g]For malignancies, incidence rates are reported and exposure in PY was calculated from first treatment to onset of first malignancy.

AE, adverse event; CTP, controlled-treatment period; IFN, interferon; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PY, patient years; SAE, serious adverse event; SOC, system organ class; UTI, urinary tract infection.

1. Wijnands JMA, *et al. J Neurol Neurosurg Psychiatry* 2018;89:1050–1056.

Supplemental materials: Presentation footnotes

Slide 7

Data cut-off: January 2020.

Yearly rates of serious infections in the OCR all-exposure population, which includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, and CONSONANCE (N=5,680; PY=18,218).

[a]Grade 1 (mild): asymptomatic or mild symptoms/clinical or diagnostic observation only/ intervention not indicated; Grade 2 (moderate): minimal, local or non-invasive intervention indicated/ limiting age appropriate instrumental ADL[d]; Grade 3 (severe): severe or medically insignificant but not immediately life-threatening/ hospitalization or prolongation of hospitalization indicated/ disabling/ limiting self-care ADL[e]; Grade 4 (life-threatening): life-threatening consequences/ urgent intervention required; Grade 5 (death): death related to AE (not applicable for all AEs); [b]2.01 (1.81–2.23) per 100 PY; 95% CI 2.30–4.75; [c]Rates of infection-related hospitalizations (1.88 per 100 PY; 95% CI 1.77–2.01) in the British Columbia registry[1] are shown for epidemiological reference; [d]Instrumental ADL referring to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.; [e]self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

ADL, activities of daily living; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; CTP, controlled treatment period; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PY, patient-years; UTI, urinary tract infection.

1. Wijnands JMA, *et al. J Neurol Neurosurg Psychiatry* 2018;89:1050–1056.

Slide 8

Data cut-off: January 2020.

RMS and PPMS populations: Yearly rates of serious infections in patients with RMS or PPMS treated with OCR during the CTP and associated OLE periods of the Phase III trials (OPERA 1, OPERA 2, and ORATORIO) for a period of up to 7 years. It includes patients randomized to OCR and patients who received PBO or IFN β-1a during the CTPs, but subsequently switched to OCR at the beginning of the OLE periods (N=2,092; 10,924 PY).

CTP, controlled-treatment period; IFN, interferon; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis.

Supplemental materials: Presentation footnotes

Slide 9

Data cut-off: January 2020. The incidence rate of first malignancy (number of first malignancy events per 100 PY) was calculated. Standardized incidence rates of malignancies were calculated using the age of the patient at study baseline ("age at enrollment"; age range: 15–59 years) up to February 2017; from September 2017 onwards, rates were calculated based on the age of the patient at the onset of malignancy ("age at event onset"; age range: 15–64 years). The "age at event onset" is a more accurate method which reflects the fact that patients become older throughout the course of the studies. Data from different methodologies separated by a dashed line.

[a]NMSC is not reported in SEER; [b]Includes patients who received any dose of OCR during the controlled treatment, ECP, and associated OLE periods of the Phase II and Phase III studies, including patients originally randomized to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment; [c]Includes patients described in [b] plus VELOCE, CHORDS, CASTING and OBOE; [d]Includes patients described in [c] plus ENSEMBLE; [e]Includes patients described in [d] plus LIBERTO. [f]Includes patients described in [d] plus CONSONANCE; [g]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, and CONSONANCE, including patients originally randomized to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment.

NMSC, nonmelanoma skin cancer; OCR, ocrelizumab; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio.

Slide 10

[†]Session number: SS02.05 . AE, adverse event; COVID-19, coronavirus disease 2019; CTP, controlled-treatment period; MS, multiple sclerosis; OLE, open-label extension; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis. 1. Hughes R, *et al. Mult Scler Relat Disord* 2020. doi: https://doi.org/10.1016/j.msard.2020.102192.

Supplemental slides 3–6 (overview of study designs)

[a]Percentage refers to the number of pre-treated patients; [b]Patients in the OLE received 600 mg OCR every 6M; [c]The first OCR dose was given as 2 x 1,000-mg infusions with 14-day interval; [d]At Week 24, OCR 2,000 mg was reduced to 1,000 mg; [e]The first OCR dose was given as 2 x 300-mg infusions with 14-day interval; [f]At Week 24, patients in the placebo and IFN β-1a groups received OCR 600 mg[c]; [g]All doses of OCR were given as 2 x 300-mg infusions; [h]Optional infusion at Week 96 (dose 5; not included in safety analysis); eligible patients could participate in the CHORDS extension substudy, when they received a 600-mg infusion of OCR over a reduced infusion time of approximately 2 hours; [i]Estimated enrollment; [j]An initial dose of 2 x 300-mg infusions separated by 14 days (on Days 1 and 15), and then 600 mg at every subsequent dose every 24 weeks for the remainder of the study treatment period (approximately 192 weeks).

6M, 6 months; ARR, annualized relapse rate; CDP, confirmed disability progression; Gd, gadolinium; IFN, interferon; NEP, no evidence of progression; NEPAD, no evidence of progression and no active disease; OCR, ocrelizumab; OLE, open-label extension; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

Supplemental slide 7 (treatment exposure)

Data cut-off: January 2020. Doses were administered every 6 months.

[a]Includes patients who received any dose of OCR during the CTP-associated OLE periods of the Phase III studies, including patients originally randomized to comparator (IFN β-1a or PBO) who switched to open-label OCR treatment; [b]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, and CONSONANCE, including patients originally randomized to comparator (IFN β-1a or PBO) who switched to open-label OCR treatment; [c]If a patient received any infusion in one dose, it was counted as one dose.

CTP, controlled-treatment period; IFN, interferon; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo.

Supplemental materials: Presentation footnotes

Supplemental slide 8 (AEs leading to discontinuation)
Investigator text for AEs was encoded using MedDRA version 22.1. Multiple occurrences of the same AE in one patient will be counted multiple times.
[a]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies, including patients originally randomized to comparator (IFN β-1a or PBO) who switched to open-label OCR treatment, plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, CONSONANCE, and LIBERTO. [b]Reported terms: Infection-suspicion, WBC count 18.4 x 10^9/L, and Infectious syndrome of unknown cause.
AE, adverse event; CTP, controlled-treatment period; IFN, interferon; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; SOC, system organ class; WBC, white blood cell.

Supplemental slide 9 (AEs leading to discontinuation)
Investigator text for AEs was encoded using MedDRA version 22.1. Multiple occurrences of the same AE in one patient will be counted multiple times.
[a]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies, including patients originally randomized to comparator (IFN β-1a or PBO) who switched to open-label OCR treatment, plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, CONSONANCE, and LIBERTO.
AE, adverse event; CTP, controlled-treatment period; IFN, interferon; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; SOC, system organ class.

Supplemental slide 10 (AEs leading to discontinuation)
Investigator text for AEs was encoded using MedDRA version 22.1. Multiple occurrences of the same AE in one patient will be counted multiple times.
[a]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies, including patients originally randomized to comparator (IFN β-1a or PBO) who switched to open-label OCR treatment, plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, CONSONANCE, and LIBERTO.
AE, adverse event; CTP, controlled-treatment period; IFN, interferon; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; SOC, system organ class.

Supplemental materials: Presentation footnotes

Supplemental slide 12 (standardized incidence rates of all malignancies and female breast cancer)
Data cut-off: January 2020. Registry cut-off: SEER database 2016, Danish MS Registry 2015.
OCR all-exposure population: Data represents the follow-up of 5,680 patients covering a period of approximately 7 years (up to January 2020).
[a]The standardized incidence rates were reported to allow comparison with the SEER database and the Danish MS Registry, using the direct standardization method. Standardized incidence rates were derived by applying age-gender specific rates to the 2000 USA standard population, with restriction to the age range of the MS clinical trials (15–59 years); [b]The SIR, calculated as observed/expected number of events, was determined for all malignancies (excluding NMSC) and female breast cancer, using the SEER database and the Danish MS Registry as reference populations; [c]It excludes NMSC for comparison with SEER rates, as NMSC is not reported in SEER; [d]OCR all-exposure population.
CTP, controlled-treatment period; IFN, interferon; MS, multiple sclerosis; NMSC, non-melanoma skin cancer; OCR, ocrelizumab; PY, patient years; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio.
1. National Institutes of Health (NIH). Available at: https://seer.cancer.gov; 2. Nørgaard M, *et al. Mult Scler Relat Disord* 2019;28:81–85.

Supplemental slide 13 (yearly crude incidence rates of all malignancies and female breast cancer)
Data cut-off: January 2020. Studies are ongoing.
[a]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, and CONSONANCE, including patients originally randomized to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment.
AE, adverse event; CTP, controlled-treatment period; IFN, interferon; NMSC, non-melanoma skin cancer; OCR, ocrelizumab; OLE, open-label extension; PY, patient years.