Ocrelizumab and Malignancies

Clinical Trials (Controlled Treatment Period)[1,2]

- During the clinical trials (controlled treatment period) of ocrelizumab in MS, malignancy was reported in 4 patients in the IFN β-1a/placebo arms and 15 patients in the ocrelizumab arms. Of the 15 patients in the ocrelizumab arms:
  - Breast cancer was reported in 6 female patients (there were no reports of breast cancer in the comparator arms)
  - NMSC was reported in 4 patients
  - The remaining 5 malignancies in patients treated with ocrelizumab were single cases: renal cancer, anaplastic large-cell cancer, pancreatic neoplasm, endometrial cancer, and malignant melanoma

Clinical Trials (Ocrelizumab All-Exposure Population)[3]

- As of January 2019, the age- and sex-standardized incidence rate of malignancies (excluding NMSC*) per 100 PY in the ocrelizumab all-exposure population (detailed in Figure 1 footnote) remained stable over time, with the confidence intervals overlapping and within epidemiological references (**Figure 1A**)
- The age-standardized incidence rate of female breast cancer remained stable over time, with the confidence intervals overlapping and within epidemiological references (**Figure 1B**)
- Yearly incidence rates of all malignancies and female breast cancer fluctuate and do not suggest a time-dependent exposure effect (**Table 1**)

Figure 1: Standardized incidence rates per 100 PY over time of all malignancies (A) and female breast cancer (B)[a]
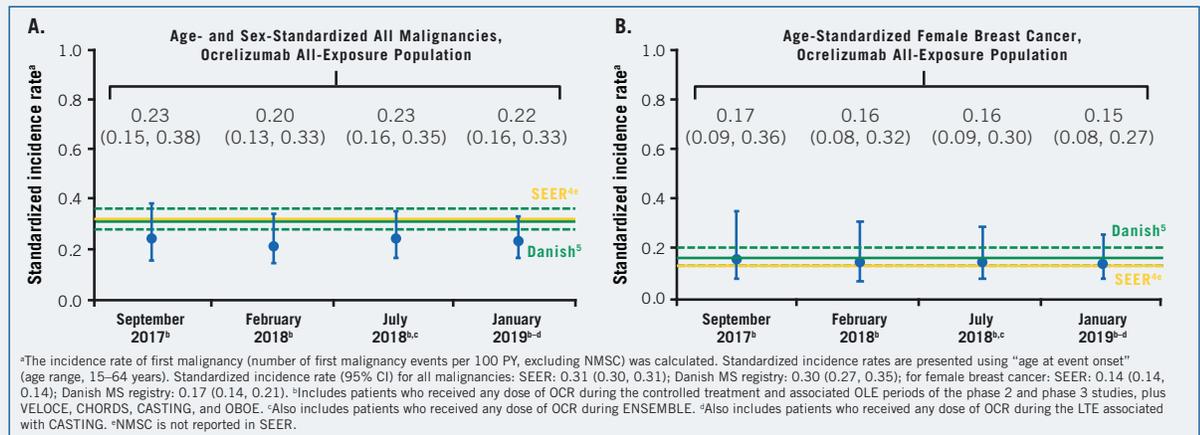

[a]The incidence rate of first malignancy (number of first malignancy events per 100 PY, excluding NMSC) was calculated. Standardized incidence rates are presented using "age at event onset" (age range, 15–64 years). Standardized incidence rate (95% CI) for all malignancies: SEER: 0.31 (0.30, 0.31); Danish MS registry: 0.30 (0.27, 0.35); for female breast cancer: SEER: 0.14 (0.14, 0.14); Danish MS registry: 0.17 (0.14, 0.21). [b]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the phase 2 and phase 3 studies, plus VELOCE, CHORDS, CASTING, and OBOE. [c]Also includes patients who received any dose of OCR during ENSEMBLE. [d]Also includes patients who received any dose of OCR during the LTE associated with CASTING. [e]NMSC is not reported in SEER.

Table 1: Yearly incidence rates of all malignancies (A) and female breast cancer (B) in the ocrelizumab all-exposure population[a]

A. All Malignancies				B. Female Breast Cancer			
All-Exposure Population	PY	No. of AEs	AEs per 100 PY (95% CI)	All-Exposure Population	PY	No. of AEs	AEs per 100 PY (95% CI)
Year 1 (N=4611)	4357	12	0.28 (0.14, 0.48)	Year 1 (N=2939)	2782	1	0.04 (0, 0.20)
Year 2 (N=3870)	3290	15	0.46 (0.26, 0.75)	Year 2 (N=2474)	2078	7	0.34 (0.14, 0.69)
Year 3 (N=2234)	2048	14	0.68 (0.37, 1.15)	Year 3 (N=1369)	1241	5	0.40 (0.13, 0.94)
Year 4 (N=1835)	1696	10	0.59 (0.28, 1.08)	Year 4 (N=1106)	1021	2	0.20 (0.02, 0.71)
Year 5 (N=1542)	1267	7	0.55 (0.22, 1.14)	Year 5 (N=921)	749	1	0.13 (0, 0.74)
Year 6 (N=1106)	991	6	0.61 (0.22, 1.32)	Year 6 (N=643)	575	0	0 (0, 0.64)

Investigator text for AEs was encoded using MedDRA version 21.1. Breast cancer is identified using AEs falling into the standard MedDRA query 'Malignant tumors (narrow)' or 'Breast malignant tumors (narrow)'. For patients with malignancies, PYs are calculated from first treatment to onset of first malignancy event. [a]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the phase 2 and phase 3 studies, plus VELOCE, CHORDS, CASTING (and associated LTE), OBOE, and ENSEMBLE (as of January 2019).

- The incidence rates of malignancies are derived from varied sources, and intended to provide context. Confounding factors that may influence incidence rates have not been accounted for, and therefore, no direct comparisons should be made. Such factors may include, but are not limited to, type of MS, disease duration, risk factors, geographical region, population size, drug exposure, comorbid conditions, treatment history, and duration of follow-up

Post-Marketing Experience[6]

- As of July 31, 2019, 76,554 female patients with RMS and PPMS had started ocrelizumab globally outside of clinical trials,[†] corresponding to an exposure of 74,039 PY
  - A total of 95 cases reporting breast cancer were received, resulting in a crude incidence rate (95% CI) of 0.128 (0.105, 0.160)

Footnotes:
*NMSC data have been excluded from these analyses as they are classified as a non-serious event and excluded from databases like SEER. [†]There are well-recognized limitations that should be considered when interpreting spontaneous post-marketing safety reports, including events that may not be causally related to drug exposure; in the real-world setting, events are frequently confounded by factors such as multiple drug use and the presence of pre-existing comorbidities; reporting bias may exist for more significant outcomes, which may result in an overrepresentation of the more serious outcomes; and reporting rates can be stimulated by external factors, such as press reports.

The causes of malignancies are recorded as reported to the company; while the company follows up on all reports to identify the cause, an exact diagnosis is not always possible. Some of the investigations remain ongoing and, therefore, the information may be subject to change.

Abbreviations:
AE=adverse event; CI=confidence interval; IFN=interferon; LTE=long-term extension; MedDRA=Medical Dictionary for Regulatory Activities; MS=multiple sclerosis; NMSC=non-melanoma skin cancer; OCR=ocrelizumab; OLE=open-label extension; PPMS=primary progressive MS; PY=patient-years; RMS=relapsing MS; SEER=Surveillance, Epidemiology, and End Results Program.

References:
1. Hauser SL, et al. *N Engl J Med.* 2017;376:221–234; 2. Montalban X, et al. *N Engl J Med.* 2017;376:209–220;
3. Hauser SL, et al. Presented at ECTRIMS 2019 (P648); 4. https://seer.cancer.gov/about/overview.html. Accessed February 14, 2020;
5. Nørgaard M, et al. *Mult Scler Relat Disord.* 2019;28:81–85; 6. Genentech data on file.

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