# Ocrelizumab and Malignancies

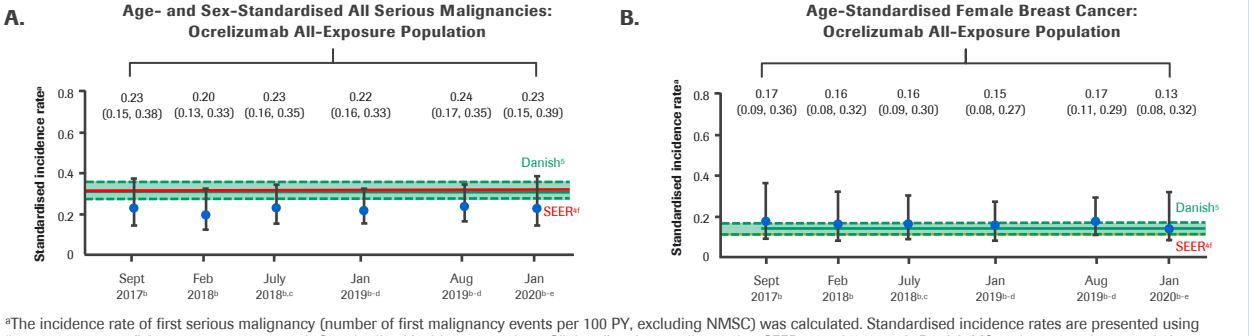
## Clinical Trials (Controlled Treatment Period)[1,2]

- During the pivotal phase 3 clinical trials (controlled treatment period) of ocrelizumab in MS, malignancy was reported in 4 patients in the interferon-beta 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]

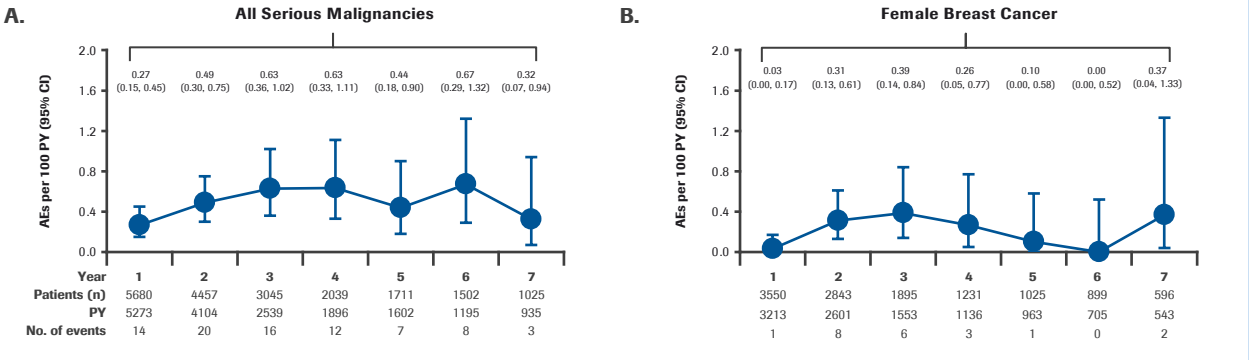
- As of January 2020, the age- and sex-standardised incidence rate of all serious malignancies (excluding NMSC*) per 100 PY in the ocrelizumab all-exposure population (detailed in Figure 1 footnote) remained stable over time and within epidemiological references (Figure 1A)
- The age-standardised incidence rate of female breast cancer remained stable over time and within epidemiological references (Figure 1B)
- Yearly crude incidence rates of all serious malignancies, including NMSC, and female breast cancer in the ocrelizumab all-exposure population remained stable over time (Figure 2)

**Figure 1: Standardised Incidence Rates per 100 PY Over Time of All Serious Malignancies (A) and Female Breast Cancer (B)[a]**




[a]The incidence rate of first serious malignancy (number of first malignancy events per 100 PY, excluding NMSC) was calculated. Standardised incidence rates are presented using "age at event onset" (age range: 15–64 years). Standardised incidence rate (95% CI) for all serious 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 described in ENSEMBLE. [d]Also includes patients described in LIBERTO. [e]Also includes patients described in CONSONANCE. [f]NMSC is not reported in SEER.

**Figure 2: Yearly Incidence Rates of All Serious Malignancies (A) and Female Breast Cancer (B) in the Ocrelizumab All-Exposure Population[a]**




Investigator text for AEs was encoded using MedDRA version 22.1. Breast cancer is identified using AEs falling into the standard MedDRA query 'Malignant tumours (narrow)' or 'Breast malignant tumours (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, OBOE, ENSEMBLE, LIBERTO, and CONSONANCE, including patients originally randomised to comparator who switched to open-label ocrelizumab treatment (as of January 2020).

- The incidence rates of serious 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 29 February 2020, 57,267 female patients with RMS and PPMS had started ocrelizumab in the United States outside of clinical trials,[†] corresponding to an exposure of 79,423 PY
  - A total of 98 cases reporting breast cancer were received, resulting in a crude incidence rate of 0.123, and an age-standardised incident rate (95% CI) of 0.524 (0.425, 0.638)

## Prescribing Information

Indications vary in different countries. The local prescribing information from your country is the primary source of information on the known and potential risks associated with ocrelizumab.

**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-recognised 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; 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;376:210–220; 3. Hauser SL, et al. Presented at MSVirtual2020 (8th Joint ACTRIMS-ECTRIMS Congress) (P0389); 4. SEER. https://seer.cancer.gov/about/overview.html. Accessed 21 September 2020; 5. Nørgaard M, et al. Mult Scler Relat Disord 2019;28:81–85; 6. Roche data on file.

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