

that have been reported to Centocor for any patient who participated in a completed Centocor-sponsored study of Remicade and non-LPD malignancies reported during 3 years of long-term safety follow-up, is presented in [Table 1](#).

Patients with Crohn's Disease

During the long-term safety follow-up period in patients with CD, 1 non-melanoma skin cancer (Remicade-treated patient) and 7 other malignancies were reported (5 in Remicade-treated patients and 2 in patients who received placebo). Among the five Remicade-treated patients who had malignancies, the following types of cancer were reported: papillary thyroid carcinoma (1 patient), prostate cancer (1 patient), skin cancer (1 patient), adenocarcinoma of the colon (1 patient) and signet cell colon carcinoma (Dukes C1, 1 patient). Among placebo-treated patients who had malignancies, the following types of cancer were reported: one spindle cell and one clear-cell, renal carcinoma.

Patients with Rheumatoid Arthritis

Seven Remicade-treated patients with RA had non-LPD malignancies reported during the 3-year follow-up period. The non-LPD malignancies for these 6 patients, who were reported in previous marketing applications, include the following types of cancer: malignant lung neoplasm (1 patient), Clark's level II superficial spreading melanoma (1 patient), basal cell carcinoma of the skin of the lower left leg (1 patient), melanoma (1 patient), prostate cancer (1 patient), ovarian cancer (1 patient), and multiple myeloma (1 patient).

In addition, non-LPD malignancies were reported in 2 placebo-treated patients during the 3-year follow-up period. One patient had malignant melanoma and uterine cancer, and the other colon cancer.

Table 1 Summary of subjects with 1 or more non- lymphoproliferative disease malignancies who participated in Centocor-sponsored Remicade clinical studies^a

	CD Studies		RA Studies		All Studies	
	Placebo	Remicade	Placebo	Remicade	Placebo	Remicade
During study						
Non-melanoma skin cancers	0	2	1 ^b	5 ^c	1 ^b	7 ^c
Other malignancies	0	3	0	5 ^c	0	8 ^c
Long-term follow-up (up to 3 yrs after treatment)						
Non-melanoma skin cancers	0	1	0	1	0	2
Other malignancies	2	5	2 ^b	6	4 ^b	11
Total non- lymphoproliferative disease malignancies						
Total non-melanoma skin cancers	0	3	1 ^b	6 ^c	1 ^b	9 ^c
Total other malignancies	2	8	2 ^b	11 ^c	4 ^b	19 ^c
Total non- lymphoproliferative disease malignancies	2	11	2^b	16^c	4^b	27^c

^a Includes malignancies in Datasets 1,2,3, and during 3 years of long-term follow-up.

^b Subject C0168T22-27005 had both nonmelanoma skin cancer and a melanoma (counted under “other malignancy”); this subject is counted once in the Total malignancies row.

^c Subject C0168T22-27008 had both nonmelanoma skin cancer and a melanoma (counted under “other malignancy”); this subject is counted once in the Total malignancies row.

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Appendix A Calculation of Standard Incidence Ratios

Calculation of SIRs

Calculation of Expected Number of Cancer Cases

The expected number of cancer cases in the general US population, according to the NIH SEER database, is the number of cases expected in a cohort of individuals that is similar (with respect to age, gender, and duration of follow-up) to those patients enrolled in Remicade clinical trials. Centocor uses the 1999 SEER database (Surveillance, Epidemiology and End Results), adjusted for age, gender and race.

The SEER database summarizes cancer data by race, gender and age groups (in 5 year groups, e.g., 30-34 years of age). The SEER rate of malignancy is calculated as the number of cancer cases reported in an age-race-gender group, divided by the number of people represented in the database in that age-race-gender group.

The expected number of cancer cases in the general US population in each age-race-gender group is calculated as the SEER rate of malignancy, multiplied by the number of patient years of follow-up in that age-race-gender category from the Remicade database. The expected number of cancer cases provided in Centocor ISS tables is the sum of all expected numbers of cancer cases for all age-race-gender groups.

Calculation of Standardized Incidence Ratio (SIR) and Confidence Interval

The Standard Incidence Ratio (SIR) is calculated as

$$SIR = \frac{\text{observed cases}}{\text{age - gender - race adjusted incidence in the general US population from SEER}}$$

An exact 95% confidence interval for the SIR is calculated based on Poisson distribution. The two confidence limits are computed as

$$CI_L: \quad SIR \times \lambda_L / D \text{ where } \lambda_L \text{ is the solution of } \sum_{i=D}^{\infty} \frac{e^{-\lambda_L} \lambda_L^i}{i!} = 0.025$$

$$\text{and } CI_U: \quad SIR \times \lambda_U / D \text{ where } \lambda_U \text{ is the solution of } \sum_{i=0}^D \frac{e^{-\lambda_U} \lambda_U^i}{i!} = 0.025$$

and D=number of observed cases.

References:

Sahai, H and Khurshid, A (1996). *Statistics in Epidemiology. Methods, Techniques, and Applications*. CRC Press. Boca Raton.

Software, PAMCOMP (Ref: <http://medweb.unimuenster.de/institute/epi/pamcomp/pamcomp.html>)

Dirk Taeger, Yi Sun, Ulrich Keil, Kurt Straif. A Standalone Windows Application for Computing Exact Person-Years, Standardized Mortality Ratios and Confidence Intervals in Epidemiological Studies, *Epidemiology* 2000; 11: 607-608.