



LUND UNIVERSITY  
Faculty of Medicine

---

# LUP

*Lund University Publications*

Institutional Repository of Lund University

---

This is an author produced version of a paper published in Multiple Sclerosis (Houndmills, Basingstoke, England). This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the published paper:  
Magnhild Sandberg Wollheim, Gabrielle Kornmann,  
Dorina Bischof, Margaretha Stam Moraga,  
Brian Hennessy, Enrica Alteri

"The risk of malignancy is not increased in patients with multiple sclerosis treated with subcutaneous interferon beta-1a: analysis of data from clinical trial and post-marketing surveillance settings."

Multiple Sclerosis (Houndmills, Basingstoke, England)  
2011 17(4), 431 - 440

<http://dx.doi.org/10.1177/1352458511403642>

Access to the published version may require journal subscription.

Published with permission from: SAGE Publications

**The risk of malignancy is not increased in patients with multiple sclerosis treated with subcutaneous interferon beta-1a: analysis of data from clinical trial and post-marketing surveillance settings**

Magnhild Sandberg-Wollheim,<sup>1</sup> Gabrielle Kornmann,<sup>2</sup> Dorina Bischof,<sup>2</sup> Margaretha Stam Moraga,<sup>2</sup> Brian Hennessy,<sup>2</sup> Enrica Alteri<sup>2</sup>

<sup>1</sup>Department of Neurology, University Hospital, University of Lund, Sweden

<sup>2</sup>Merck Serono S.A. – Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany

Corresponding author:

Magnhild Sandberg-Wollheim

Department of Neurology, University Hospital, University of Lund, 22185, Lund, Sweden

tel: +46 46 17 12 82

fax: +46 46 177940

e-mail: [magnhild.sandberg\\_wollheim@med.lu.se](mailto:magnhild.sandberg_wollheim@med.lu.se)

## **Abstract**

**Background:** Risks that are potentially associated with long-term therapies should be assessed.

**Objective:** The present analyses were performed to determine the risk of malignancy in patients with MS receiving subcutaneous (sc) interferon (IFN) beta-1a, using pooled safety data from key clinical trials and data from the Merck Serono Global Drug Safety database.

**Methods:** The standard Medical Dictionary for Regulatory Activities query “malignancies” was used to retrieve relevant cases from each data set. The *incidence* of malignancies per 1000 patient-years was calculated using the pooled safety data from clinical trials. The *reporting rates* of malignancy types were calculated for the post-marketing setting based on sales volume. Malignancies were grouped by organ localization and classified as medically confirmed or not medically confirmed according to the source of each report. The number of reported cases of each type was compared with the expected number in the general population.

**Results:** Analysis of pooled safety data from 12 key clinical trials did not show an increased incidence of malignancy per 1000 patient-years with sc IFN beta-1a (4.0; 95% confidence interval [CI]: 2.9–5.5) compared with placebo (6.4; 95% CI: 3.3–11.2). Analysis of the database shows that among the medically confirmed cases, reported to expected ratios ranged from 1:6 to 1:18 for solid tumours and from 1:2 to 1:9 for lymphohaematopoietic tumours.

**Conclusion:** Safety data from both clinical trial and post-marketing settings suggest that treatment with sc IFN beta-1a does not increase the risk of malignancy in patients with MS.

**Key words (6–8):** multiple sclerosis, subcutaneous interferon beta-1a, malignancy, safety, database, long-term

## Introduction

MS requires long-term treatment with immunomodulating or immunosuppressive agents. Therefore, it is important to assess potential risks that may be related to the continuous use of these therapies over the long term [1]. Agents currently licensed for the treatment of MS include the immunomodulators interferon (IFN) beta and glatiramer acetate, which are generally considered first-line therapies for relapsing forms of MS. By contrast, the currently available immunosuppressive agents, natalizumab and mitoxantrone, are usually used to treat patients with aggressive forms of MS [2, 3]. The use of IFN beta in MS is supported by safety and efficacy data from large, randomized clinical trials [4-7]. However, none of these trials were statistically powered to assess rare adverse events such as malignancy.

The background risk of malignancy in patients with MS has been evaluated in population-based cohort studies [8-16]. Most of these studies indicate that the risk of any type of malignancy does not differ substantially between patients with MS and the general population. However, one Swedish study [12] found a slightly reduced overall risk of malignancy in patients with MS, particularly for lymphomas and digestive, respiratory, ovarian and prostate cancers relative to the general population. By contrast, a slightly increased risk was reported for other types of malignancy in patients with MS, such as for urinary tract and brain tumours. None of these findings were statistically significant. In addition, it was not possible to determine whether the differing risks for malignancy between patients with MS and the general population reported in the Swedish study were due to disease-related factors or behavioural differences between the two groups. Also, the elevated risk of brain tumours may possibly have been due to surveillance bias resulting from frequent monitoring of patients with MS using MRI.

Two published studies have assessed the risk of malignancy in patients with MS receiving immunomodulatory drugs [17, 18]. The first study [17] compared the risk in patients with MS

in Israel with that in the general Israeli population and additionally analysed the relative risk of malignancy associated with treatment versus non-treatment using a time-dependent Cox model. It reported no significantly elevated risks of malignancy in patients treated with immunomodulatory drugs. However, this study did not precisely define the patient population or how the MS clinic population may have differed from the general Israeli population, making the elimination of possible confounding factors difficult. Further, it did not report whether data from deceased patients were included in the analysis, or comprehensively define the duration of follow-up. The second study [18], which compared the incidence of cancer in patients with MS in France with the general French population, also concluded that there was no heightened malignancy risk associated with immunomodulatory therapy. However, it is possible that this study may have been compromised by incomplete registration of cancer cases in the clinical database used, which could have led to inaccuracy in the estimated incidence of malignancy. Further, the analysis did not adjust for confounding risk factors.

The assessment of the risk of malignancy using clinical trial data is limited by the relatively small sample sizes, short duration of follow-up and restricted study population.

Spontaneously reported adverse events in the post-marketing setting present a greater dataset obtained from real-life clinical practice; however, their assessment is also limited – the true incidence of malignancy cannot be calculated due to potential under-reporting and uncertainty of the denominator. In an attempt to overcome the limitations of each of these approaches, the present analysis aimed to evaluate the risk of malignancy in patients with MS receiving subcutaneous (sc) IFN beta-1a treatment by assessing both pooled data from key clinical trials and data from the Merck Serono Global Drug Safety database.

## Methods

The data sources for the two analyses are shown in Figure 1. Data on serious adverse events recorded in the 12 key clinical trials are also captured in the Global Drug Safety database, and were therefore included in both analyses. However, the number of such cases was relatively small. Other subsets of data were analysed separately as shown.

For both data sources, data were retrieved using the Medical Dictionary for Regulatory Activities (MedDRA) standard query 20000090 for “malignancies”. This query comprises four sub-queries, covering more than 1500 preferred terms relating to different aspects of the evaluation of malignancy. The data are coded in MedDRA version 12.1.

### Data sets analysed

#### *Pooled data from key clinical trials of sc IFN beta-1a*

Safety data collected during Merck Serono-sponsored Phase III trials on sc IFN beta-1a in the indication of MS, with locked data available at the time of analysis (n=12), were pooled for the evaluation (Table 1). Five of these 12 key trials included placebo-controlled periods of between 1 and 3 years, while another two used active comparator groups. The remaining five trials evaluated sc IFN beta-1a alone in open-label designs. The safety data set consisted of data from all patients who had been treated with sc IFN beta-1a, placebo or active comparators. Results regarding active comparators are not presented. As these studies employed differing study designs, the data were grouped into three cohorts, as shown in Table 2, to allow comprehensive analysis: Cohort A comprised data up to the first 2 years of all studies; Cohort B was limited to data collected during the first 2 years of the placebo-controlled studies only; and Cohort C comprised data from all sc IFN beta-1a or placebo patients in all studies for the full duration of treatment.

Incidence rates of malignancies per 1000 patient-years were calculated for each treatment group in each cohort. The design of some of the trials included in Cohort C allowed patients to switch from one treatment arm to another. In such cases, the patient was counted twice – once for treatment, once for placebo. For calculations of treatment exposure in these specific cases, the time the patient spent in each treatment arm was considered separately. Any events were linked to the treatment the patient was receiving at the time of the event onset, and calculations of overall incidence rates took into account individual patient exposure.

*Data from the Global Drug Safety database*

Subcutaneous IFN beta-1a (Rebif<sup>®</sup>) is manufactured and marketed by Merck Serono S.A., Geneva, Switzerland (a division of Merck KGaA, Darmstadt, Germany). In compliance with international regulations, all individual case safety reports (ICSRs) received in the post-marketing setting are recorded in the Global Drug Safety database. In addition, the database records all ICSRs from clinical trials that have been classified as serious events. It should be noted that only 1.7% of all events reported in the database originate from clinical trials; the remaining 98.3% relate to the spontaneous reporting in the post-marketing setting.

The ICSRs included in this analysis were received between 1 February 1998 and 3 November 2009. These ICSRs comprised information gathered from healthcare professionals, health authorities, patients, published case reports and clinical trial reports. The ICSRs included in this analysis were limited to those from patients who had been exposed to sc IFN beta-1a (at any dose). Although the database gathers data on patients receiving placebo in clinical trials, reports from these patients are excluded from the Global Drug Safety analyses. Selected ICSRs were categorized according to their origin as follows: reports were classified as ‘medically confirmed’ (MC) if the ICSR was received from a healthcare professional, health authority, literature case report or clinical trial; or ‘not medically confirmed’ (NMC) if the ICSR was received from a patient or relative, either

spontaneously or when solicited, i.e. provided in response to a call out to patients from the company support network. When a patient or relative reported a serious event, medical confirmation was then sought from the treating physician. However, if upon follow-up the physician considered the event as unrelated to sc IFN beta-1a, the ICSR remained categorized as NMC.

Retrieved ICSRs were grouped by the body system or location of the malignancy. They were then counted to obtain the number of reported (observed) cases. Since the reporting rate was the endpoint of the analysis, if a patient presented with two or more malignancies that had no obvious pathophysiological link between them, each malignancy was counted as a separate event in the appropriate category. For example, for one patient diagnosed with Hodgkin's lymphoma and lung cancer, two malignancy events were counted.

The exposure of patients to sc IFN beta-1a in the post-marketing setting was estimated according to sales volume; however, this estimation was based on several assumptions and thus cannot provide a precise denominator. Additionally, spontaneous reporting may under-report the incidence of adverse events. Therefore the analyses presented refer to the reporting rate rather than incidence. For each malignancy type examined as part of the Global Drug Safety database analysis, the number of reported cases was compared with the number of expected cases in the general population. The expected figures for all malignancy types except leukaemia subtypes were based on the incidence rates in 'more developed regions' as defined and reported in the 2002 GLOBOCAN report [19]. The GLOBOCAN subdivision 'more developed regions' was selected as it was considered to best represent a suitable comparator population, representative of regions where patients with MS may be treated with sc IFN beta-1a. Since GLOBOCAN does not provide detailed statistics for leukaemia subtypes, for cases of acute and chronic myeloid leukaemia and acute and



chronic lymphocytic leukaemia, expected numbers were based on the 2002–2006 USA Surveillance Epidemiology and End Results (SEER) Cancer Statistics review [20].

The majority (88%) of the NMC malignancies identified in the Global Drug Safety database originated from the USA, where a support programme is available to all patients starting or continuing sc IFN beta-1a. All patients who participate in the programme are contacted regularly by certified MS nurses, either by telephone or in person (depending on individual patient need), and if an adverse event is reported, it is captured and incorporated into the Global Drug Safety Database. Most reports of NMC cases were thus considered to be 'solicited'. For this reason, the expected figures for comparison with NMC cases were based on general population data for the USA only.

The reported to expected (R:E) ratio, with 95% CIs, for each type of malignancy was calculated using the methods for standardized morbidity ratio calculations [21]. Benign tumours were excluded from the analysis. Non-melanoma skin cancers were also excluded from the analysis, as these cancers are incompletely reported and thus incidence figures are not available from cancer registries. Cases in which sc IFN beta-1a had been used in an oncology indication in clinical trials were also excluded to avoid confounding the analysis by indication bias.

## **Results**

### *Pooled data from key clinical trials of sc IFN beta-1a*

Data for a total of 3746 patients treated with sc IFN beta-1a were included in this analysis. The mean (range) patient exposure to sc IFN beta-1a was 29.6 (0.0–96.0) months; 1096 patients had more than 3 years of exposure and 568 had more than 5 years. Furthermore, the mean (range) duration per patient of safety follow-up was 33.5 (0.0–98.0) months, with 1257 and 737 patients having more than 3 and 5 years' safety follow-up, respectively.

Analysis of data from the first 2 years of placebo-controlled studies (Cohort B) revealed that there was a lower incidence of malignancies per 1000 patient-years in patients who had received sc IFN beta-1a (2.5; 95% CI: 0.9–5.4) compared with those who had received placebo (6.3; 95% CI: 2.9–11.9) (Table 3), although this was not statistically significant. This trend for lower malignancy incidence in patients treated with sc IFN beta-1a was also observed for Cohorts A and C, although the difference was smaller in these two cohorts than in Cohort B (Table 3). Figure 2 shows the incidence per 1000 patient-years over time, which indicates that the incidence of malignancies did not increase with the length of follow-up.

*Data from the global drug safety database in the post-marketing setting*

As of 3 November 2009, the cumulative patient exposure to sc IFN beta-1a was estimated at 720,123 patient-years, based on sales volume. The exposure to sc IFN beta-1a in clinical trials is negligible in comparison and therefore was not taken into account.

A total of 741 ICSRs reporting malignant events were retrieved from the Global Drug Safety database. The following reports were excluded from the analysis: two non-cancer cases (erroneously identified by the database query); 13 benign nodules; 53 non-serious neoplasms; 35 cases of non-melanoma skin cancer and 11 cases in which sc IFN beta-1a had been used in clinical trials for an oncology indication. Twenty-seven patients experienced two types of malignancies and their reports were therefore counted twice as explained above.

Of the remaining 654 reports, 193 were MC, including 39 events originating from clinical trials of sc IFN beta-1a in patients with MS. The R:E ratios ranged from 1:18.38 to 1:6.07 for solid tumours (Table 4). The overall ratio for lymphohaematopoietic tumours was 1:3.83, with sub-category ratios (such as for non-Hodgkin's Lymphoma and leukaemia subtypes) ranging between 1:1.53 and 1:8.85.

A total of 461 NMC malignancies were identified, including 56 (12%) reports from outside the USA. Of these, 405 (88%) NMC malignancies were solicited reports from a patient support call centre in the USA (Table 5).

In all MC malignancy categories and most of the NMC malignancy categories the reported numbers were lower than the expected numbers. As shown in Table 5, the R:E ratios were around 1 for NMC reports of brain, thyroid and lymphohaematopoietic malignancies. These three types of malignancies are discussed in details below.

#### *Central nervous system malignancies*

In total, 18 events were reported in the category 'brain and nervous system', excluding one non-USA NMC case (Tables 4 and 5). All events were located in the brain. The R:E ratio was 1:9.38 for MC and 1:0.77 for NMC cases. Most of these cases (15/18; 83%) occurred within 2 years of sc IFN beta-1a treatment initiation. Only two cases were reported after a treatment period longer than 2 years; one additional case had an unknown latency period. In four of 18 cases, brain tumours had already been present before initiation of sc IFN beta-1a therapy. Four further cases were associated with potential confounding factors. These were identified as: 'benign brain lesion prior to sc IFN beta-1a treatment'; 'unspecified brain lesion prior to sc IFN beta-1a treatment'; 'human immunodeficiency virus (HIV)' and 'history of melanoma'.

#### *Thyroid malignancies*

A total of 30 cases of thyroid cancer were reported, excluding one non-USA NMC case (Tables 4 and 5). The R:E ratio was 1:7.97 for MC cases and 1:0.78 for NMC cases. Of these malignancies, only 4/30 (13.3%) occurred after more than 2 years' exposure to sc IFN beta-1a.

### *Lymphohaematopoietic malignancies*

A total of 74 lymphohaematopoietic malignancies were reported. The R:E ratio was 1:3.83 for MC cases and 1:1.80 for NMC cases. More than half (43/74; 58.1%) of these malignancies were reported less than 2 years after the start of sc IFN beta-1a therapy. Twenty patients (27%) had potential confounding factors, including previous treatment with agents carrying an increased risk of haematopoietic malignancy, such as azathioprine or mitoxantrone [22].

## **Discussion**

Results from these analyses do not suggest an association between sc IFN beta-1a treatment and occurrence of malignancy in patients with MS. However, while reported rates were lower than expected rates, R:E ratios in the brain, thyroid and lymphohaematopoietic categories were higher than those in other categories. Therefore risks relating to these types of malignancies warrant further examination.

It should be noted that there is potential for surveillance bias regarding brain malignancies in patients with MS, as these patients undergo regular MRI scans for the assessment of MS disease progression. As a result, tumours are more likely to be detected in patients with MS than in the general population. In addition, for almost half of brain malignancy events assessed in this analysis (8/18; 44%), relevant confounding factors, such as pre-existing tumours and HIV were known to be present.

The comparatively high number of thyroid cancer cases reported in this analysis could also be explained by potential surveillance bias. Patients treated with sc IFN beta-1a are closely monitored for thyroid disorders, in accordance with treatment guidelines. Twenty percent of treated patients presented with thyroid nodules before treatment onset and thus may have

been monitored even more closely by their healthcare professionals. Eighty-four percent of the thyroid malignancies were reported in female patients, which is in line with the sex distribution of thyroid cancer (more common in females than males with a ratio of 3:1) [23], and of MS (70% of patients are females). Lastly, at the time of this analysis the most recent records to estimate the expected number of cases that were available dated from 2002, while most reported cases occurred between 2005 and 2009. As the incidence of thyroid cancer is increasing over time (according to the USA cancer registries), this may have also have led to an over-estimation of the R:E ratio for thyroid neoplasms [24].

The R:E ratio for solid tumours was much lower for MC events compared with NMC events. However, the ratios are comparable between MC and NMC events for lymphohaematopoietic malignancies. One possible explanation for this difference is that healthcare professionals may monitor patients more closely for haematopoietic neoplasms due to a perceived link between these types of malignancies and the pharmacological mechanisms of immunomodulatory therapies. Haematological tests are performed regularly on treated patients with MS in order to monitor blood cell counts, which may also increase the likelihood of early detection of haematopoietic neoplasms, relative to the general population. Additionally, in most of the MC cases of acute myeloid leukaemia, the patients had previously been treated with immunosuppressive therapy. Chronic use of such therapies may be associated with a heightened long-term risk of malignancy [25]. It is known that other agents used in the treatment of cancer carry a risk of secondary, therapy-related leukaemias, which increases by up to 1% per year from 2 years after treatment initiation [26]. Most brain, thyroid and lymphohaematopoietic malignancies in our analysis were reported within 2 years of initiation of sc IFN beta-1a treatment. Therefore a causal relationship between these malignancies and IFN beta-1a treatment was deemed unlikely.

The analyses reported here are subject to limitations. When comparing the number of malignancies reported in patients exposed to sc IFN beta-1a with those expected in the general population, it should be noted that adverse events may be under-reported in the post-marketing setting. In general, the under-reporting of drug-associated adverse events to market authorization holders has been estimated to be 94% for all events and between 80–85% for serious events only [27]. In the case of the drug safety database analysis, the true incidence of malignancies cannot be calculated from spontaneously reported events due to uncertainty of the size of both the numerator and denominator. However, due to the comprehensive patient support programme for patients receiving sc IFN beta-1a in the USA, the reported figures in these analyses are likely to be close to the actual occurrences of malignancies. Hence, these data are considered to be highly relevant, although medical details for individual cases may be incomplete.

Analysis of pooled clinical trial data is also limited by the inclusion of short-term clinical trials with relatively small sample size, and by the short duration of the placebo-controlled phases of some of the studies. It is recognized that malignancies can occur after long latency periods. It should be noted that in the analysis of pooled clinical trial data, the rate of incidence of malignancies did not increase during 6 or more years of follow-up. Indeed, the upper limit of CI for incidence rate is lower at 6 years and beyond than that at 0–1 years. However, the trial data analysis did not include assessment of the risk of malignancy following discontinuation of treatment.

In conclusion, these analyses evaluated the risk of malignancy in patients with MS treated with sc IFN beta-1a during the clinical development programme, and in the post-marketing setting. Overall, the data do not indicate any increased risk of malignancy in these patients. These findings confirm and extend those of previous studies examining sc IFN beta-1a in patients with MS. However, while there was no clear association between sc IFN beta-1a

therapy and brain, thyroid or lymphohaematopoietic malignancies, these topics remain an area for close pharmacovigilance surveillance.

### **Acknowledgements**

The authors thank Steve Smith of Caudex Medical, Oxford, UK (supported by Merck Serono S.A. – Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany) for assistance in preparing the initial draft of the manuscript, collating the comments of authors and other named contributors, and assembling tables and figures; and Joanne Tang (Caudex Medical, supported by Merck Serono S.A. – Geneva, Switzerland), for assistance in editing for English, formatting manuscript to meet journal guidelines, and coordinating submission requirements.

### **Funding**

This work was supported by Merck Serono S.A. – Geneva, Switzerland (an affiliate of Merck KGaA, Darmstadt, Germany).

### **Conflicts of interests**

MS-W has received honoraria from Serono Symposia International Foundation and sanofi-aventis (lectures); from Merck Serono (lectures, work in data safety monitoring boards DSMB); from Genentech (DSMB); from Elan (advisory board); from the Swedish bank SEB Enskilda (lectures); from Bayer Health Care (contribution of articles to Swedish health website). She has also received honoraria for serving on the board of directors of Active Biotech in Lund, Sweden, and as external reviewer of a PhD thesis at the University of Copenhagen. GK, DB, MSM, BH and EA are employees of Merck Serono S.A. – Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.

## References

1. **Kingwell E, Tremlett H.** Interferons and multiple sclerosis: is it plausible that beta-IFN treatment could influence the risk of cancer among MS patients? *Expert Rev Neurother* 2009; **9**: 1263-5.
2. **European Medicines Agency.** *Tysabri summary of product characteristics.*  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000603/human\\_med\\_001119.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000603/human_med_001119.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125). Accessed 14 Oct 2010.
3. **Food and Drug Administration.** *Novantrone prescribing information.*  
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=NOVANTRONE>. Accessed 14 Oct 2010.
4. **PRISMS (Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group.** Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998; **352**: 1498-504.
5. **Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM et al.** Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996; **39**: 285-94.
6. **The IFNB Multiple Sclerosis Study Group.** Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; **43**: 655-61.
7. **Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP et al.** Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. *Neurology* 1995; **45**: 1268-76.
8. **Moller H, Kneller RW, Boice JD Jr, Olsen JH.** Cancer incidence following hospitalization for multiple sclerosis in Denmark. *Acta Neurol Scand* 1991; **84**: 214-20.



9. **Midgard R, Glattre E, Gronning M, Riise T, Edland A, Nyland H.** Multiple sclerosis and cancer in Norway. A retrospective cohort study. *Acta Neurol Scand* 1996; **93**: 411-5.
10. **Wynn DR, Kurland LT, O'Fallon WM, Rodriguez M.** A reappraisal of the epidemiology of multiple sclerosis in Olmsted County, Minnesota. *Neurology* 1990; **40**: 780-6.
11. **Sumelahti ML, Pukkala E, Hakama M.** Cancer incidence in multiple sclerosis: a 35-year follow-up. *Neuroepidemiology* 2004; **23**: 224-7.
12. **Bahmanyar S, Montgomery SM, Hillert J, Ekbom A, Olsson T.** Cancer risk among patients with multiple sclerosis and their parents. *Neurology* 2009; **72**: 1170-7.
13. **Nielsen NM, Rostgaard K, Rasmussen S, Koch-Henriksen N, Storm HH, Melbye M et al.** Cancer risk among patients with multiple sclerosis: a population-based register study. *Int J Cancer* 2006; **118**: 979-84.
14. **Hjalgrim H, Rasmussen S, Rostgaard K, Nielsen NM, Koch-Henriksen N, Munksgaard L et al.** Familial clustering of Hodgkin lymphoma and multiple sclerosis. *J Natl Cancer Inst* 2004; **96**: 780-4.
15. **Goldacre MJ, Seagroatt V, Yeates D, Acheson ED.** Skin cancer in people with multiple sclerosis: a record linkage study. *J Epidemiol Community Health* 2004; **58**: 142-4.
16. **Fois AF, Wotton CJ, Yeates D, Turner MR, Goldacre MJ.** Cancer in patients with motor neuron disease, multiple sclerosis, and Parkinson's disease: record-linkage studies. *J Neurol Neurosurg Psychiatry* 2010; **81**: 215-21.
17. **Achiron A, Barak Y, Gail M, Mandel M, Pee D, Ayyagari R et al.** Cancer incidence in multiple sclerosis and effects of immunomodulatory treatments. *Breast Cancer Res Treat* 2005; **89**: 265-70.
18. **Lebrun C, Debouverie M, Vermersch P, Clavelou P, Rumbach L, de Seze J et al.** Cancer risk and impact of disease-modifying treatments in patients with multiple sclerosis. *Mult Scler* 2008; **14**: 399-405.

19. **Ferlay J, Bray F, Pisani P, Parkin D.** *GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide*, IACR CancerBase, No 5, version 2.0. IARC Press, 2004.
20. **Surveillance, Epidemiology, and End Results (SEER).** *Cancer statistics review, National Cancer Institute 2002-2006*. <http://www.seer.cancer.gov>. Accessed 28 Aug 2007.
21. **Breslow NE, Day NE.** Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ* 1980; **32**: 5-338.
22. **Ellis R, Boggild M.** Therapy-related acute leukaemia with mitoxantrone: what is the risk and can we minimise it? *Mult Scler* 2009; **15**: 505-8.
23. **Lentsch EJ, Gillespie M, Goddard JC, Wilhoit C, Rumboldt Z, Hoda RS et al.** *Thyroid, papillary carcinoma, early*. <http://emedicine.medscape.com/article/849000-overview>. Accessed 22 Jan 2010.
24. **National Cancer Institute.** [http://seer.cancer.gov/csr/1975\\_2006/browse\\_csr.php?section=26&page=sect\\_26\\_table\\_04.html](http://seer.cancer.gov/csr/1975_2006/browse_csr.php?section=26&page=sect_26_table_04.html). Accessed 17 Nov 2009.
25. **Penn I.** Malignancies associated with immunosuppressive or cytotoxic therapy. *Surgery* 1978; **83**: 492-502.
26. **Pedersen-Bjergaard J, Rowley JD.** The balanced and the unbalanced chromosome aberrations of acute myeloid leukemia may develop in different ways and may contribute differently to malignant transformation. *Blood* 1994; **83**: 2780-6.
27. **Hazell L, Shakir SA.** Under-reporting of adverse drug reactions: a systematic review. *Drug Saf* 2006; **29**: 385-96.

**Table 1** Key clinical trials included in the pooled analysis

<p><b>6789 PRISMS</b></p> <p>2-year, randomized, multicentre, double-blind, placebo-controlled study (sc IFN beta-1a 22 mcg or 44 mcg tiw vs placebo); 4-year extension</p>	<p><b>6613 Study</b></p> <p>1-year, randomized, multicentre, open-label study with 6 months untreated lead-in followed by 6 months of treatment (sc IFN beta-1a 11 mcg or 33 mcg tiw; no placebo or comparator)</p>
<p><b>6954 SPECTRIMS</b></p> <p>3-year, randomized, multicentre, double-blind, placebo-controlled study (sc IFN beta-1a 22 mcg or 44 mcg tiw vs placebo); 3-year extension</p>	<p><b>25632 Rebif® New Formulation safety and immunogenicity study</b></p> <p>96-week, nonrandomized, multicentre, open-label, historically controlled, single-group assignment study (sc IFN beta-1a 44 mcg tiw; no placebo or comparator)</p>
<p><b>6976 Nordic SPMS</b></p> <p>3-year, randomized, multicentre, double-blind, placebo-controlled study (sc IFN beta-1a 22 mcg qw vs placebo); 2-year extension</p>	<p><b>8000 Extension 6613</b></p> <p>18-month, open-label, multicentre extension of trial 6613 (sc IFN beta-1a 11 mcg or 33 mcg tiw; no placebo or comparator)</p>
<p><b>7480 ETOMS</b></p> <p>2-year, randomized, multicentre, double-blind, placebo-controlled study (sc IFN beta-1a 22 mcg qw vs placebo); 2-year extension</p>	<p><b>24810 Safety and immunogenicity study</b></p> <p>48-week, nonrandomized, open-label, multicentre, single-group assignment study (sc IFN beta-1a 44 mcg tiw; no placebo or comparator)</p>

<p><b>7999 OWIMS</b></p> <p>48-week, randomized, multicentre, double-blind, placebo-controlled study (sc IFN beta-1a 22 mcg or 44 mcg qw vs placebo); 2-year extension</p>	<p><b>22930 Long-term follow-up of study 6789 (PRISMS)</b></p> <p>Open-label, multicentre study with single visit between year 8 and 9 of original treatment in PRISMS (patient may be receiving any commercial treatment or be off treatment at LTFU visit)</p>
<p><b>21125 EVIDENCE</b></p> <p>48-week, randomized, multicentre, open-label, assessor-blinded, parallel-group study (sc IFN beta-1a 44 mcg tiw vs im IFN beta-1a 30 mcg qw); extension (up to 45 weeks post-transition)</p>	<p><b>24735 REGARD</b></p> <p>96-week, randomized, multicentre, open-label, parallel-group study (sc IFN beta-1a 44 mcg tiw vs sc glatiramer acetate 20 mg qd)</p>

ETOMS, Early Treatment Of Multiple Sclerosis; EVIDENCE, Evidence of Interferon Dose-response: European North American Comparative Efficacy; IFN, interferon; im, intramuscular; LTFU, long-term follow-up; OWIMS, Once Weekly Interferon for Multiple Sclerosis; PRISMS, Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis; qd, daily; qw, weekly; REGARD, Rebif<sup>®</sup> versus Glatiramer Acetate in Relapsing Multiple Sclerosis Disease; sc, subcutaneous; SPECTRIMS, Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon beta-1a in Multiple Sclerosis; SPMS, secondary progressive multiple sclerosis; tiw, three times weekly.

**Table 2** Analysis cohorts for pooled clinical trial data

Cohort	Description	Studies included
A	First 2 years of study treatment (placebo or sc IFN beta-1a) <sup>a</sup>	Studies 6613/8000, 24735, 25632, and 24810 <sup>b</sup> Studies 6789/22930, 7480, and 21125 <sup>c</sup> Study 7999 <sup>d</sup> Studies 6954 and 6976 <sup>e</sup>
B	As for Cohort A, except this cohort only included the placebo-controlled studies	Studies 6789, 6954, 6976, 7480, and 7999
C	All patients for the full duration of their treatment	All studies

<sup>a</sup>All studies but two (24810 and 21125) lasted at least 2 years (or 96 weeks). Patients were tabulated under the treatment they received first in the study.

<sup>b</sup>All data for patients receiving sc IFN beta-1a or placebo are included.

<sup>c</sup>All data during the placebo-controlled or comparative phases are included.

<sup>d</sup>All data for the placebo subjects are included. All data for the sc IFN beta-1a arm during the first 2 years are included.

<sup>e</sup>For both the placebo and sc IFN beta-1a groups, any data collected during the first 2 years are included.

IFN, interferon; sc, subcutaneous.

**Table 3** Incidence of neoplasms<sup>a</sup> in clinical trials of sc IFN beta-1a

<b>Cohort</b>	<b>Treatment</b>	<b>Number of patients</b>	<b>Total exposure to treatment (patient-years)</b>	<b>Number of patients with events</b>	<b>Incidence per 1000 patient-years (95% confidence interval)</b>
A	Placebo	824	1425.42	9	6.3 (2.9–11.9)
(First 2 years of study treatment)	sc IFN beta-1a (all doses)	2829	4419.09	18	4.1 (2.4–6.4)
B	Placebo	824	1425.42	9	6.3 (2.9–11.9)
(First 2 years of study treatment, placebo-controlled trials only)	sc IFN beta-1a (all doses)	1319	2432.24	6	2.5 (0.9–5.4)
C	Placebo	824	1867.50	12	6.4 (3.3–11.2)
(All patients for full treatment duration)	sc IFN beta-1a (all doses)	3746	10377.32	42	4.0 (2.9–5.5)

<sup>a</sup>Including non-melanoma skin cancer.

IFN, interferon; sc, subcutaneous.

**Table 4** Analysis of the Global Drug Safety database – medically confirmed

malignancies: reported versus expected cases

	Reported (R) cases, N	Expected (E) cases, N	Ratio, R:E	Ratio R:E (95% confidence interval)
All categories (except NMSC)	193 <sup>a</sup>	2154.59	1:11.16	0.090 (0.077–0.103)
Lung	14	218.12	1:15.58	0.064 (0.035–0.108)
Breast	34	522.64	1:15.37	0.065 (0.045–0.091)
Colorectal	12	220.58	1:18.38	0.054 (0.028–0.095)
Thyroid	5	39.87	1:7.97	0.125 (0.041–0.293)
Cervix uteri	5	79.63	1:15.93	0.063 (0.020–0.147)
Corpus uteri <sup>b</sup>	10	97.21	1:9.72	0.103 (0.049–0.189)
Ovary	10	72.66	1:7.27	0.138 (0.066–0.253)
Melanoma of skin	13	78.95	1:6.07	0.165 (0.088–0.282)
Brain, nervous system <sup>c</sup>	4	37.72	1:9.43	0.106 (0.029–0.272)
Bladder	6	56.30	1:9.38	0.107 (0.039–0.232)
All lymphohaematopoietic <sup>d</sup>	38	145.41	1:3.83	0.261 (0.185–0.359)
Non-Hodgkin's lymphoma	7	61.95	1:8.85	0.113 (0.045–0.233)
Hodgkin's disease	3	18.28	1:6.09	0.164 (0.034–0.480)
Multiple myeloma	4	18.61	1:4.65	0.215 (0.059–0.550)
Leukaemia <sup>e</sup> (total including NOS)	21	46.57	1:2.22	0.451 (0.279–0.689)
AML	11	16.84	1:1.53	0.653 (0.326–1.169)
CML	4	7.89	1:1.97	0.507 (0.138–1.298)
ALL	0	5.29	–	0.000 (0.000–0.697)
CLL	3	14.54	1:4.85	0.206 (0.043–0.603)

<sup>a</sup>45 cases were not classified in the groups here because they occurred infrequently.<sup>b</sup>2 cases of hysterectomy with no documented reason for intervention were classified under 'corpus uteri'.



<sup>c</sup>Meningiomas are not included in the 'brain, nervous system' category.

<sup>d</sup>Includes all leukaemias, multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma and myelodysplastic syndromes (3 cases; data not shown).

<sup>e</sup>Includes CML, CLL, AML, ALL and unspecified leukaemia.

ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphoid leukaemia; CML, chronic myeloid leukaemia; NMSC, non-melanoma skin cancer; NOS, not otherwise specified.

**Table 5** Analysis of the Global Drug Safety database – serious, non-medically confirmed malignancies in the USA population: reported versus expected cases

	Reported (R) cases, N	Expected (E) cases, N	Ratio, R:E	Ratio R:E (95% confidence interval)
All categories (except NMSC)	405	775.42	1:1.91	0.522 (0.473–0.576)
Lung	49	86.50	1:1.76	0.566 (0.419–0.749)
Breast	101	202.09	1:2.00	0.500 (0.407–0.607)
Colorectal	27	70.86	1:2.62	0.381 (0.251–0.554)
Thyroid	25	19.42	1:0.78	1.287 (0.833–1.900)
Cervix uteri	7	15.80	1:2.26	0.443 (0.178–0.913)
Corpus uteri	17	45.03	1:2.65	0.378 (0.220–0.604)
Ovary	20	19.71	1:0.99	1.015 (0.620–1.567)
Melanoma of skin	15	37.84	1:2.52	0.396 (0.222–0.654)
Brain, nervous system <sup>a</sup>	14	10.72	1:0.77	1.306 (0.714–2.191)
Bladder	7	20.65	1:2.95	0.339 (0.136–0.698)
All lymphohaematopoietic <sup>b</sup>	32	57.45	1:1.80	0.557 (0.381–0.786)
Non-Hodgkin's lymphoma	15	28.20	1:1.88	0.532 (0.298–0.877)
Hodgkin's disease	1	6.83	1:6.83	0.146 (0.004–0.816)
Multiple myeloma	4	6.96	1:1.74	0.575 (0.157–1.471)
Leukaemia <sup>c</sup> (total including NOS)	11	15.47	1:1.41	0.711 (0.355–1.273)
AML	6	4.69	1:0.78	1.279 (0.469–2.785)
CML	0	2.20	–	0.000 (0.000–1.677)
ALL	1	1.47	1:1.47	0.680 (0.017–3.790)
CLL	2	4.05	1:2.02	0.494 (0.060–1.784)

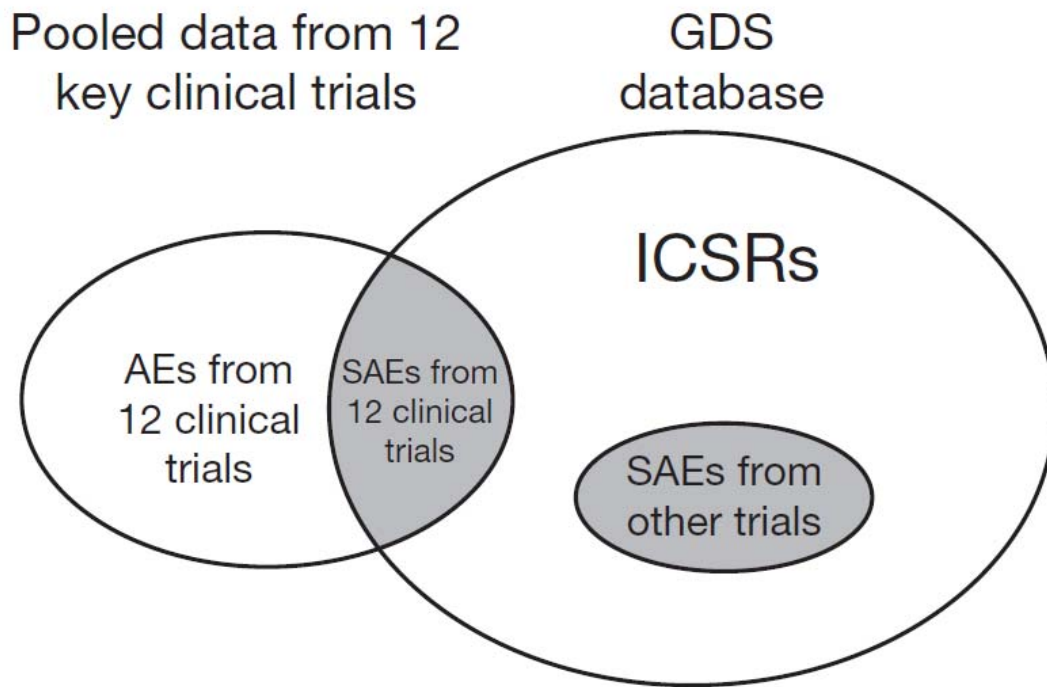
<sup>a</sup>Meningioma, pituitary tumours and MRI findings (reported as such) with no confirmation of malignancy were not included; all events reported as 'brain tumour' with no further details were included.

<sup>b</sup>Includes all leukaemias, multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma and myelodysplastic syndromes (1 case; data not shown).

<sup>c</sup>Includes CML, CLL, AML, ALL and unspecified leukaemia.

ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphoid leukaemia; CML, chronic myeloid leukaemia; NMSC, non-melanoma skin cancer; NOS, not otherwise specified.

**Figure 1** Datasets used for the analyses of risk of malignancy in patients with MS receiving sc IFN beta-1a treatment – pooled data from the 12 key clinical trials and safety data from the GDS database. AE, adverse event; GDS, global drug safety; ICSR, individual case study report; SAE, serious adverse event.



**Figure 2** Analysis of pooled clinical trial data: incidence of malignancy over time in patients treated with subcutaneous interferon beta-1a.

