Supplementary Table 1 Studies evaluating the effect of disease modifying therapies on cancer risk and cervical cancer risk

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| **Authors** | **Type of study** | | **Location** | | **Participants** | | **Index Period** | | **DMTs** | | **Results**  **Risk/Incidence/n= of overall cancer** | | **Results**  **Risk/Incidence/n(%) of Cervical abnormalities** | | **Interpretation** | |
| **Analysis of grouped immunosuppression** | | | | | | | | | | | | | | | | |
| Lebrun et al., 2008(1) | Descriptive study | | France | | 7418 MS patients  5182 women | | 1995 – 2006 | | IM: interferons beta 1a, 1b and GA  IS: AZA, CTX, mitoxantrone and MTX | | **Risk**  IM only  RR 0.8 (95% CI 0.32 – 2.02, p = 0.6357)  IS only  RR 1.96 (0.84-4.61, 0.121)  IM + IS  RR 0.54 (0.15-1.91, 0.3375)  Duration of exposure to IS increased risk  IS/year RR 1.08 (95% CI 1.01-1.16, p = 0.0035) | | **n (%)**  Gynaecological cancer (ovarian, cervix, uterine)  IM only  5 (0.22%)  IS only  3 (0.41%)  IM + IS  2 (0.44%)  (P = 0.75) | | Treatment with IM, IS only and IM + IS exposure did not increase overall cancer risk.  Risk of cancer increased with increasing duration of IS exposure.  Risk of gynaecological cancer not increased in patients treated with IM or IS. | |
| Dugué et al., 2015(2) | Cohort study | | Denmark | | 14403 MS patients | | 1977-2010 | | Antimetabolites (MTX, AZA)  Systemic corticosteroids  Other immunosuppressants | | NR | | **Risk**  Treatment vs non-treatment  HR = 1.0 (95% CI 0.8–1.2)  Antimetabolites  HR 1.1 (95% CI 0.9-1.5)  Corticosteroids HR 0.9 (95% CI 0.7-1.2)  Other IS  HR 0.5 (95% CI 0.2-1.7) | | Treatment did not increase cervical cancer risk. | |
| Ragonese et al.,2017(3) | Cohort study | | Italy | | 531 MS patients | | 1994 - 2011 | | IS: MTX, AZA, CTX | | **Risk**  Cancer  IS treatment  Adjusted HR: 11.05; CI 1.67–73.3; p =0.013 | | No cervical abnormality reported | | Increased risk of cancer in patients exposed to IS therapy. | |
| Moisset et al., 2017(4) | Case-control study | | France | | 1107 MS patients  1568 controls | | 2014-2015 | | IM: Interferonβ, GA, DMF  IS: FTY, NTZ, Mitoxantrone, MTX, AZA  CTX, MMF, Teriflunomide, RIX | | **Risk**  Multivariate analysis  Risk of cancer with IM DMT use  OR 1.22 (95% CI 0.632.35; p=0.55)  Risk of cancer with IS DMT use  OR 0.82 (95% CI 0.33–2.06; p=0.67)  Risk of cancer with IS & IM DMT use  OR 0.78 95% CI 0.331.80; p=0.55) | | **n (%)**  Gynaecological cancers  MS  13 (1.17%)  Controls  28 (2.93%) | | DMT use (immunomodulators immunosuppressants) did not increase the risk of cancer. | |
| D’Amico et al., 2019(5) | Observational study | | Spain | | 1180 MS patients | | 2003-2013 | | IM: Interferonβ, GA  IS: MTZ, Mitoxantrone, FTY, AZA, NTZ | | **Risk**  Cancer  No DMT  RR = 1.03 (CI 95% 0.56–1.41)  No DMT-switch  RR = 1.17 CI 95% (1.02–2.34)  One DMT switch  RR = 1.99 (CI 95% 1.14–3.45)    >/=2 DMT switch  3.38 (CI95% 1.83–6.22) in. | | No cervical abnormality reported | | Higher cancer risk in MS patients switching more than two DMTs. | |
| Gil‑Bernal et al., 2021(6) | Retrospective observational study | | Spain | | 250 MS patients  232 on DMT | | 1981-2019 | | Interferonβ  GA  Teriflunomide  DMF  NTZ  FTY  Alemtuzumab | | **Risk**  Time of Interferonβ use  HR= 0.923 (95% CI 0.873–0.977, p = 0.006)  Time of DMF use  HR = 0.725 (95% CI 0.507-1.036, p = 0.077)  Time of FTY use  HR = 1.219 (95% CI 0.979 – 1.517, p = 0.133) | | No cervical abnormality reported | | Interferonβ and DMF use were protective against neoplasm development. | |
| Mariottini et al., 2022(7) | Case-control study | | Italy | | 661 pwMS (68% exposed to DMTs) | | 2002 - 2018 | | GA  Interferonβ-1A  Interferonβ--1B  DMF  Teriflunomide  FTY  NTZ  Alemtuzumab  Cladribine  Ocrelizumab  Rituximab  Mitoxantrone  AZA  CYP | | **Incidence**  incidence of malignancy  MS cohort: 3.9/ 1000 py (95% CI 3.75–4.15)  Control cohort: 4.1/ 1000py (95% CI 3.76 –4.42) person-years  **SMR**  MS cohort: 2.0/1000 py (95% CI 1.58–2.37)  Control cohort: 2.0 / 1000 py (95% CI 1.58–2.37) | | **n (%)**  Gynaecological cancer  MS  5 (22%)  **Controls**  12 (5%) | | Incidence of cancer and mortality did not differ between pwMS and the general population.  Higher incidence of gynaecological cancer seen in the MS population compared with controls. | |
| **Low efficacy therapies: Interferons and Glatiramer acetate** | | | | | | | | | | | | | | | | |
| Kappos et al., 2006(8)  BENEFIT  NCT00185211 | Phase 3 Placebo-controlled trial | | International multicentre | | 292 Interferonβ-1b  176 Placebo | | 2002-2008 | | Interferonβ-1b | | No cancer reported | | No cervical abnormality reported | |  | |
| O’Connor et al., 2009(9)  BEYOND  NCT00099502 | Phase 3 randomised control trial | | International multicentre | | 1796 Interferonβ-1b  448 GA | | 2003-2005 | | Interferonβ-1b  GA | | No cancer reported | | No cervical abnormality reported | |  | |
| Reder et al., 2010(10) | Cross-sectional observation study | | North America | | 328 Interferonβ-1b | | 1988-2005 | | Interferonβ-1b | | No cancer reported | | No cervical abnormality reported | |  | |
| Bloomgren et al., 2012(11) | Observational study | | North America | | 402,250 patients | | 1996-2011 | | Interferonβ-1a | | Overall cancer incidence NR. Sub analyses performed for individual cancer types did not show increased cancer risk. | | **Incidence**  Cervical cancer  Cumulative reporting rate 0.83 per 100 000 p/years (95% CI 0.4–1.5)  **Risk**  Cervical cancer  Interferonβ-1a vs general population  OR 0.11 (95% CI 0.01 -0.79, p = 0.002)  Interferonβ-1a vs MS Interferonβ-1a non-users  OR 0.22 (95% CI 0.03–1.74, p= 0.082)  Interferonβ-1a vs untreated MS  OR 0.20 (95% CI 0.02–0.71, p = 0.88) | | No significant difference in malignancy prevalence in intramuscular IFNβ-1a users.  Reduced risk of cervical cancer seen in patients treated with Interferonβ-1a compared with the general population.  No difference in risk of cervical cancer seen in MS patients treated with Interferonβ-1a. | |
| Wolinsky et al., 2015(12)  GLACIER  NCT01874145 | Phase 3 Randomised, Parallel-Arm Study | | International multicentre | | 209 GA | | 2013-2014 | | GA | | No cancer reported | | No cervical abnormality reported | |  | |
| **Moderate- or High-Efficacy Therapies** | | | | | | | | | | | | | | | | |
| **Dimethyl-Fumarate** | | | | | | | | | | | | | | | | |
| Gold et al., 2012(13)  DEFINE  NCT00420212 | | Phase 3 randomised, placebo-controlled trial | | International multicentre | | 556 DMF  408 Placebo | | 2007-2011 | | DMF | | **n (%)**  DMF  2 (<1%)  Placebo  2 (<1%) | | **n (%)**  DMF  1(<1%)  Placebo  0 | | No increased risk of malignancy associated with DMF. |
| Gomez-Moreno et al., 2021(14) | | Non-interventionalist, prospective post-marketing study | | Spain | | 886 DMF | | 2014-2019 | | DMF | | **n=**  DMF  7 | | **n=**  LSIL  1 | | No increased risk of malignancy associated with DMF. |
| **Inhibition of Lymphocyte Migration: Natalizumab and Sphingosine-1-Phosphate Receptor Antagonists** | | | | | | | | | | | | | | | | |
| **Natalizumab** | | | | | | | | | | | | | | | | |
| Polman et al., 2006(15)  AFFIRM  NCT00027300 | Phase 3 randomised, placebo-controlled trial | | International multicentre | | 942 MS patients  627 NTZ  315 Placebo | | 2001-2004 | | NTZ | | **n (%)**  NTZ  5 (<1%)  Placebo  1 (<1%) | | **n (%)**  Cervical abnormality  NTZ  NR (<1%)  Placebo  NR (0%)  (p=0.999)  Cervical carcinoma in situ  NTZ  1  Placebo  0 | | Rates of cervical abnormalities were not increased in patients treated with NTZ. | |
| Rolfes et al., 2013(16) | Case report | | Netherlands | | 4 | | <2013 | | NTZ | | NR | | **n =**  Pre-cancer (CIN 2 & 3)  NTZ  4 | | Four cases of cervical pre-cancer reported in association with NTZ. | |
| Durrieu et al., 2018(17) | Case report | | France | | 1 | | 2016 | | NTZ | | NR | | **n =**  Pre-cancer (CIN 3)  NTZ  1 | | One case of cervical pre-cancer seen in association with NTZ. | |
| Wan et al., 2019(18) | Case Report | | Australia | | 1 | | 2007-2009 | | NTZ | | NR | | **n =**  Cervical cancer  NTZ  1 | | Rapid progression LSIL to squamous cell carcinoma of the cervix within 2 years. | |
| Alping et al., 2020(19) | Cohort study | | Sweden | | 6136 MS, 37,801 non-MS controls  1,670 NTZ | | 2011-2017 | | RIX, FTY, NTZ | | **Incidence**  NTZ  IR(/10 000py) = 26.0 (95% CI 15.1–41.6)  Controls  IR 31.0 (95% CI, 27.8–34.4)  **Risk**  NTZ vs controls  HR = 1.01 (95% CI 0.57–1.77) | | **Incidence**  Pre-cancer (CIN 3)  IR (/10 000py) 31.3 (95% CI 17.5-51.6)  **Risk**  HR 1.29 (95% CI 0.71-2.34) | | No difference in risk of invasive cancer between NTZ, and the general population.  No difference in risk of cervical cancer between NTZ, and the general population. | |
| **Fingolimod** | | | | | | | | | | | | | | | | |
| Kappos et al., 2010(20)  FREEDOMS  NCT00289978 | Phase 3 placebo-controlled trial | | International multicentre | | 1033 MS patients  854 FTY 418 Placebo | | 2006-2007 | | FTY | | **n =**  FTY  8  Placebo  10 | | **n =**  Cervical cancer  FTY  0  Placebo  1 | | Incidence of overall cancer and cervical cancer not increased in patients treated with FTY. | |
| Cohen et al., 2010(21)  TRANSFORMS  NCT00340834 | Phase 3  double-blind, parallel group trial | | International multicentre | | 1153 MS patients  857 FTY  435 Interferon Beta-1a | | 2006-2007 | | FTY | | **n =**  FTY  12  Interferon-beta-1a  1 | | No cervical abnormality reported | |  | |
| Calabresi et al., 2014(22)  FREDOMS II  NCT00355134 | Phase 3 placebo-controlled trial | | International multicentre | | 1083 MS patients  728 FTY 355 Placebo. | | 2006-2009 | | FTY | | **n =**  FTY  27  Placebo  8 | | No cervical abnormality reported | |  | |
| Lublin et al., 2016(23)  INFORMS  NCT00731692 | Phase 3 placebo-controlled trial | | International multicentre | | 823 PPMS patients  336 FTY  487 Placebo | | 2008-2011 | | FTY | | **n =**  FTY  26  Placebo  12 | | No cervical abnormality reported | |  | |
| Cohen et al., 2019(24)  LONGTERMS  NCT01201356 | Phase 3b, extension study. | | International multicentre | | 4086 MS patients FTY | | 2010-2017 | | FTY | | **n (%)**  Benign, malignant, and unspecified neoplasms  NR (2.6) | | **Incidence (n=):**  Cervical abnormality  IR 0.04  (7)  **n =**  Cervical cancer  1 | |  | |
| Mhanna et al., 2020(25) | Case series | | France | | 16 MS patients, 11women | | 2019 | | FTY | | NR | | **n (%)**  Cervical abnormalities  9 (56.2%)  (5 LSIL, 4 HSIL) | | Nine cases of cervical abnormalities seen in association with FTY. | |
| Alping et al., 2020(19) | Cohort study | | Sweden | | 6136 patients with MS, 37,801 non-MS controls  1,620 FTY | | 2011-2017 | | RIX, FTY, NTZ | | **Incidence**  FTY  IR (/10 000py) = 44.0 (95% CI 29.2–63.5)  Controls  IR 31.0 (95% CI 27.8–34.4)  **Risk**  FTY vs controls  HR = 1.53 (95% CI = 0.98–2.38) | | **Incidence**  FTY  Cervical abnormality  CIN 3  IR (/10 000py) 39.1 (95% CI 22.8–62.6)  **Risk**  Cervical abnormality  HR 1.63 (95% CI 0.94-2.82) | | No difference in risk of cervical cancer FTY compared with the general population. | |
| **Siponimod** | | | | | | | | | | | | | | | | |
| Kappos et al., 2018(26)  EXPAND  NCT01665144 | Phase 3 randomised placebo-controlled trial | | International multicentre | | 1651 SPMS, 1099 Siponimod, 546 Placebo | | 2013-2015 | | Siponimod | | **n =**  Siponimod  28  Placebo  17 | | No cervical abnormality reported | |  | |
| **Inhibitors of DNA Synthesis: Teriflunomide and Cladribine** | | | | | | | | | | | | | | | | |
| **Teriflunomide** | | | | | | | | | | | | | | | | |
| O’Connor et al., 2011(27)  TEMSO  NCT00134563 | Phase 3 randomised, placebo-controlled trial | | International multicentre | | 1088 MS patients  725 TER  363 Placebo | | 2004-2008 | | TER | | **n =**  TER  1  Placebo  3 | | **n =**  Cervical cancer  TER  1  Placebo  1 | |  | |
| Miller et al., 2014(28)  TOPIC  NCT00622700 | Phase 3  randomised, placebo-controlled trial | | International multicentre | | 618 MS patients  421 TER  197 Placebo | | 2008-2012 | | TER | | No cancer reported | | No cervical abnormality reported | |  | |
| Confavreux et al., 2014(29)  TOWER  NCT00751881 | Phase 3 randomised, placebo-controlled trial | | International multicentre | | 1169 MS patients    780 TER  385 Placebo | | 2008-2011 | | TER | | **n =**  TER  1 | | No cervical abnormality reported | |  | |
| O’Connor et al, 2016(30)  TEMSO Extension  NCT00803049 | Phase 3 extension study | | International multicentre | | 742 TER | | 2008-2013 | | TER | | **Incidence (n)**  0.01 (10) vs general MS population in Sweden 0.11 | | **n =**  Cervical cancer  TER  1 | | Overall incidence cancer comparable to the general MS population in Sweden | |
| **Cladribine** | | | | | | | | | | | | | | | | |
| Giovannoni et al., 2010(31)  CLARITY  NCT00213135 | Phase 3 ramdomised, placebo-controlled trial | | International multicentre | | 1326 RRMS  884 Cladribine  453 Placebo | | 2005-2007 | | Cladribine | | **n (%)**  Cladribine  10 (1.1%)  Placebo  0 (0%) | | **n =**  Cladribine  1 cervical carcinoma in situ  Placebo  0 | |  | |
| Leist et al., 2014(32)  ORACLE-MS  NCT00725985 | Phase 3, ramdomised, placebo-controlled trial | | International multicentre | | 616 patients  410 Cladribine  206 Placebo | | 2008 – 2010 | | Cladribine | | **n =**  Benign, malignant and unspecified neoplasms  Cladribine  4  Placebo  6 | | No cervical abnormality reported | |  | |
| Giovannoni et al., 2018(33)  CLARITY Extension  NCT00641537 | Phase 3b extension study | | International multicentre | | 867  884 Cladribine 453 Placebo | | 2008-2011 | | Cladribine | | **n (%)**  11 (1.4%) | | No cervical abnormality reported | |  | |
| **Monoclonal antibodies: Rituximab, Ocrelizumab and Alemtuzumab** | | | | | | | | | | | | | | | | |
| **Rituximab** | | | | | | | | | | | | | | | | |
| Alping et al., 2020(19) | Cohort study | | Sweden | | 6136 patients with MS, 37,801 non-MS controls  4187 RIX | | 2011-2017 | | RIX, FTY, NTZ | | **Incidence**  RIX  IR (/10 000py) = 34.4 (95% CI 23.7–48.3)  Controls  IR 31.0 (95% CI 27.8–34.4)  **Risk**  RIX vs controls  HR = 0.85, 95% CI = 0.54–1.32) | | **Incidence**  RIX  Cervical abnormalities  CIN 3  IR (/10 000py) 22.3 (95% CI 12.5–36.8)  **Risk**  Cervical abnormalities  HR 1.15 (95% CI 0.66-2.02) | | No difference in risk of cervical cancer between RIX, and the general population. | |
| **Ocrelizumab** | | | | | | | | | | | | | | | | |
| Montablan et al., 2017(34)  ORTORIO | Phase 3 andomised, placebo-controlled trial | | International multicentre | | 732 PPMS patients  488 OCR  244 Placebo | | 2011-2012 | | OCR | | **n (%)**  OCR  11 (2.3%)  Placebo  2 (0.8%) | | **n (%)**  OCR  0 (0%)  Placebo  1 (0.4%) | |  | |
| Hauser et al., 2017(35)  OPERA I  NCT01247324 | Phase 3 randomised trial | | International multicentre | | 821 MS patients  410 OCR  411 Interferon beta | | 2011 – 2013 | | OCR | | **n (%)**  OCR  1 (0.7%)  Interferon beta  1 (0.2%) | | No cervical abnormality reported | |  | |
| Hauser et al., 2017(35)  OPERA II  NCT014123 | Phase 3 randomised trial | | International multicentre | | 835 patients  417 OCR  418 Interferon beta | | 2011- 2013 | | OCR | | **n (%)**  OCR  1 (0.2%)  Interferon beta  1 (0.2%) | | No cervical abnormality reported | | No difference in risk of cervical cancer between OCR and interferon. | |
| Wolinsky et al., 2020(36)  ORTORIO Extension  NCT01194570 | Open-labelled extension study of ORTORIO | | International multicentre | | 527 PPMS patients  367 OCR  160 Placebo | | 2011 – 2019 | | OCR | | **Incidence**  All exposure population  0·91/100py (95% CI 0·61–1·32)  OCR  0.93/100py (95% CI 0·52–1·54)  Placebo  0.27 /100py (95% CI 0·03–0·99) | | No cervical abnormality reported | |  | |
| Hauser et al., 2021(37) | Pooled safety analysis of 11 phase 2 and 3 trials, phase 3b clinical trials | | International multicentre | | 5,680 OCR | | 2008-2020 | | OCR | | **Incidence**  0.46 / 100py (95% CI 0.37–0.57) | | **n =**  1 (cervical carcinoma stage II) | |  | |
| **Alemtuzumab** | | | | | | | | | | | | | | | | |
| Coles et al., 2008(38)  CAMMS223  NCT00050778 | Phase 2 randomised, blinded trial | | International multicentre | | 334 patients  216 Alemtuzumab  118  Interferon 1beta | | 2002-2004 | | Alemtuzumab | | **Incidence (n=)**  Alemtuzumab  0.0044 per person year  (3)  Interferon 1 beta  0.0036 per person year  (1) | | **n =**  Alemtuzumab  1  Interferon-1beta  No | |  | |
| Cohen et al, 2012(39)  CARE MS/ CAMMS323  NCT00530348 | Phase 3 randomised controlled trial | | International multicentre | | 376 Alemtuzumab  187 Interferon beta 1a | | 2007-2009 | | Alemtuzumab | | **n (%)**  Alemtuzumab  (1%)  Interferon beta1a  0 (0%) | | No cervical abnormality reported | |  | |
| Coles et al., 2012(40)  CARE-MS II  CAMMS324  NCT00548405 | Phase 3 randomised controlled trial | | International multicentre | | 596 Alemtuzumab  202 Interferon beta 1a | | 2007-2009 | | Alemtuzumab | | **n =**  Alemtuzumab  5  Interferon beta 1a  2 | | No cervical abnormality reported | |  | |
| Coles et al., 2017(41)  CARE-MS II Extension  NCT00930553 | Extension study of  CARE-MS II | | International multicentre | | 435 Alemtuzumab | | 2009-2014 | | Alemtuzumab | | **Incidence (n=)**  Post-treatment:  EAIR 0.2/ 100 py  (4) | | No cervical abnormality reported | |  | |
| Steingo et al et al., 2020(42)  CAMMS223 Extension  NCT00930553 | Extension study of CAMMS223 | | International multicentre | | 60 Alemtuzumab | | 2002 – 2014 | | Alemtuzumab | | **Incidence (n=)**  EAIR 0.3 /100 py  (2) | | No cervical abnormality reported | |  | |
| **Ofatumumab** | | | | | | | | | | | | | | | | |
| Hauser et al., 2020(43)  ASCLEPIOS I  NCT02792218 | Phase 3 randomised-controlled trial | | International multicentre | | 465 Ofatumumab  462 TER | | 2016-2018 | | Ofatumumab  TER | | **n (%)**  Ofatumumab  1 (0.6%)  TER  3 (0.6%) | | **n =**  Ofatumumab  0  TER  1 | |  | |
| Hauser et al., 2020(43)  ASCLEPIOS II  NCT02792231 | Phase 3 randomised-controlled trial | | International multicentre | | 5481 Ofatumumab  474 TER | | 2016-2018 | | Ofatumumab  TER | | **n (%)**  Ofatumumab  1 (0.4%)  TER  1 (0.2%) | | No cervical abnormality reported | |  | |

Abbreviations: AHR: adjusted hazard ratio, AZA: azathioprine, CI: confidence interval, CIN: cervical intraepithelial neoplasia, CTX: cyclophosphamide, DMF: dimethyl fumerate, DMT: disease modifying therapy, EAIR: exposure-adjusted incidence rate, FTY: fingolimod, GA: glatiramer acetate, HSIL: high grade squamous intraepithelial lesion, HR: hazard ratio, IM: immunomodulatory, IR: incidence rate, IRR: incidence rate ratio, LSIL: low grade squamous intraepithelial lesion, IS: immunosuppressive, IVIG: intravenous immunoglobulin, MMF: mycophenolate mofetil, MS: multiple sclerosis, MTX: methotrexate, NR: not reported, OCR: ocrelizumab, OR: odds ratio, py: person years, RIX: rituximab, RR: relative risk, SIR: Standardised incidence ratio, SMR: Standardised mortality ratio, TER: teriflunomide.

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