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 patients5182 women  | 1995 – 2006 | IM: interferons beta 1a, 1b and GAIS: AZA, CTX, mitoxantrone and MTX | **Risk**IM onlyRR 0.8 (95% CI 0.32 – 2.02, p = 0.6357)IS only RR 1.96 (0.84-4.61, 0.121) IM + ISRR 0.54 (0.15-1.91, 0.3375)Duration of exposure to IS increased riskIS/year RR 1.08 (95% CI 1.01-1.16, p = 0.0035) | **n (%)**Gynaecological cancer (ovarian, cervix, uterine) IM only5 (0.22%)IS only3 (0.41%)IM + IS2 (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-treatmentHR = 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 ISHR 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 treatmentAdjusted 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, DMFIS: FTY, NTZ, Mitoxantrone, MTX, AZA CTX, MMF, Teriflunomide, RIX | **Risk**Multivariate analysisRisk 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 MS13 (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, GAIS: 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 switch3.38 (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 patients232 on DMT  | 1981-2019 | InterferonβGA Teriflunomide DMFNTZFTYAlemtuzumab  | **Risk** Time of Interferonβ useHR= 0.923 (95% CI 0.873–0.977, p = 0.006)Time of DMF useHR = 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 | GAInterferonβ-1AInterferonβ--1BDMFTeriflunomide FTY NTZAlemtuzumabCladribineOcrelizumabRituximab Mitoxantrone AZA CYP  | **Incidence** incidence of malignancyMS 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-1b176 Placebo  | 2002-2008  | Interferonβ-1b | No cancer reported  | No cervical abnormality reported  |  |
| O’Connor et al., 2009(9) BEYONDNCT00099502 | Phase 3 randomised control trial  | International multicentre | 1796 Interferonβ-1b448 GA | 2003-2005  | Interferonβ-1bGA | 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 populationOR 0.11 (95% CI 0.01 -0.79, p = 0.002)Interferonβ-1a vs MS Interferonβ-1a non-usersOR 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) GLACIERNCT01874145 | 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)DEFINENCT00420212 | Phase 3 randomised, placebo-controlled trial | International multicentre | 556 DMF 408 Placebo | 2007-2011 | DMF  | **n (%)**DMF2 (<1%)Placebo 2 (<1%) | **n (%)**DMF1(<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=**DMF7 | **n=**LSIL1 | 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 patients627 NTZ315 Placebo  | 2001-2004 | NTZ | **n (%)**NTZ 5 (<1%)Placebo 1 (<1%) | **n (%)**Cervical abnormality NTZNR (<1%) PlaceboNR (0%)(p=0.999)Cervical carcinoma in situNTZ1Placebo 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)NTZ1 | 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**NTZIR(/10 000py) = 26.0 (95% CI 15.1–41.6)ControlsIR 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)FREEDOMSNCT00289978 | Phase 3 placebo-controlled trial  | International multicentre | 1033 MS patients 854 FTY 418 Placebo | 2006-2007 | FTY | **n =**FTY 8 Placebo10  | **n =**Cervical cancer FTY 0 Placebo1  | Incidence of overall cancer and cervical cancer not increased in patients treated with FTY. |
| Cohen et al., 2010(21) TRANSFORMSNCT00340834 | Phase 3 double-blind, parallel group trial  | International multicentre | 1153 MS patients857 FTY 435 Interferon Beta-1a  | 2006-2007 | FTY  | **n =**FTY 12 Interferon-beta-1a1  | No cervical abnormality reported |  |
| Calabresi et al., 2014(22) FREDOMS IINCT00355134 | Phase 3 placebo-controlled trial  | International multicentre | 1083 MS patients728 FTY 355 Placebo. | 2006-2009 | FTY  | **n =**FTY 27 Placebo 8  | No cervical abnormality reported |  |
| Lublin et al., 2016(23)INFORMSNCT00731692 | Phase 3 placebo-controlled trial  | International multicentre | 823 PPMS patients336 FTY 487 Placebo  | 2008-2011 | FTY  | **n =**FTY 26 Placebo 12  | No cervical abnormality reported |  |
| Cohen et al., 2019(24) LONGTERMSNCT01201356 | Phase 3b, extension study. | International multicentre | 4086 MS patients FTY  | 2010-2017 | FTY  | **n (%)**Benign, malignant, and unspecified neoplasmsNR (2.6)   | **Incidence (n=):**Cervical abnormalityIR 0.04 (7)**n =** Cervical cancer1  |  |
| 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**FTYIR (/10 000py) = 44.0 (95% CI 29.2–63.5)ControlsIR 31.0 (95% CI 27.8–34.4) **Risk**FTY vs controls HR = 1.53 (95% CI = 0.98–2.38) | **Incidence**FTY Cervical abnormalityCIN 3IR (/10 000py) 39.1 (95% CI 22.8–62.6)**Risk**Cervical abnormalityHR 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)EXPANDNCT01665144  | 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 TER363 Placebo  | 2004-2008 | TER  | **n =** TER 1 Placebo 3  | **n =** Cervical cancer TER 1 Placebo 1  |  |
| Miller et al., 2014(28)TOPIC NCT00622700 | Phase 3randomised, placebo-controlled trial  | International multicentre | 618 MS patients421 TER 197 Placebo  | 2008-2012 | TER | No cancer reported  | No cervical abnormality reported |  |
| Confavreux et al., 2014(29)TOWERNCT00751881 | Phase 3 randomised, placebo-controlled trial | International multicentre | 1169 MS patients 780 TER385 Placebo   | 2008-2011 | TER | **n =** TER1  | 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 TER1  | 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 RRMS884 Cladribine 453 Placebo   | 2005-2007 | Cladribine  | **n (%)**Cladribine 10 (1.1%)Placebo 0 (0%)  | **n =** Cladribine 1 cervical carcinoma in situPlacebo 0 |  |
| Leist et al., 2014(32) ORACLE-MS NCT00725985 | Phase 3, ramdomised, placebo-controlled trial | International multicentre | 616 patients410 Cladribine 206 Placebo  | 2008 – 2010 | Cladribine  | **n =**Benign, malignant and unspecified neoplasmsCladribine 4 Placebo6 | No cervical abnormality reported |  |
| Giovannoni et al., 2018(33)CLARITY ExtensionNCT00641537 | Phase 3b extension study | International multicentre | 867884 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)ControlsIR 31.0 (95% CI 27.8–34.4) **Risk**RIX vs controls HR = 0.85, 95% CI = 0.54–1.32) | **Incidence**RIXCervical 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%) Placebo2 (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 OCR411 Interferon beta  | 2011 – 2013 | OCR | **n (%)**OCR1 (0.7%) Interferon beta1 (0.2%)  | No cervical abnormality reported |  |
| Hauser et al., 2017(35)OPERA IINCT014123 | Phase 3 randomised trial  | International multicentre | 835 patients 417 OCR418 Interferon beta | 2011- 2013 | OCR | **n (%)**OCR 1 (0.2%) Interferon beta1 (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 OCR160 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) CAMMS223NCT00050778  | Phase 2 randomised, blinded trial  | International multicentre  | 334 patients216 Alemtuzumab 118Interferon 1beta  | 2002-2004 | Alemtuzumab | **Incidence (n=)**Alemtuzumab0.0044 per person year (3)Interferon 1 beta0.0036 per person year(1) | **n =** Alemtuzumab 1 Interferon-1beta No  |  |
| Cohen et al, 2012(39) CARE MS/ CAMMS323NCT00530348 | Phase 3 randomised controlled trial | International multicentre | 376 Alemtuzumab 187 Interferon beta 1a  | 2007-2009 | Alemtuzumab  | **n (%)**Alemtuzumab (1%) Interferon beta1a0 (0%)  | No cervical abnormality reported |  |
| Coles et al., 2012(40)CARE-MS IICAMMS324NCT00548405 | Phase 3 randomised controlled trial | International multicentre  | 596 Alemtuzumab202 Interferon beta 1a  | 2007-2009 | Alemtuzumab | **n =**Alemtuzumab 5 Interferon beta 1a2  | No cervical abnormality reported |  |
| Coles et al., 2017(41)CARE-MS II Extension NCT00930553 | Extension study ofCARE-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 Ofatumumab462 TER | 2016-2018 | OfatumumabTER | **n (%)**Ofatumumab 1 (0.6%) TER3 (0.6%)  | **n =** Ofatumumab 0TER 1  |  |
| Hauser et al., 2020(43)ASCLEPIOS IINCT02792231 | Phase 3 randomised-controlled trial | International multicentre | 5481 Ofatumumab474 TER  | 2016-2018 | Ofatumumab TER | **n (%)**Ofatumumab 1 (0.4%) TER1 (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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