**Supplementary Table 1.** Cancer data from Summary of Product Characteristics (as of 2 June 2024)

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| **Drug** | **Contraindications to therapy**  **in cancer** | **Contraindications to immunosuppressive/anti-cancer therapy** | **Mutagenic effect** | **Carcinogenicity** | **Occurrence of cancer**  **during treatment** |
| Beta interferons | Cancer disease is not listed as a contraindication | No information on combination of immunosuppressants/anti-cancer drugs | *In vitro* genotoxicity studies (Ames test) showed no mutagenic effect. Results of cell transformation assays did not indicate potential for cancer | Carcinogenicity studies on INF in animals have not been conducted | No cases of cancer have been reported in clinical trials |
| Glatiramer acetate | Cancer disease is not listed as a contraindication | No information on combination of immunosuppressants/anti-cancer drugs | *In vitro* data showed no genotoxicity.  No animal studies have been performed | *In vitro* studies showed no evidence of carcinogenicity.  No studies on animals have been conducted | No cases of cancer have been reported in clinical trials |
| Dimethyl fumarate | Cancer disease is not listed as a contraindication | Use of this medicine in combination with anti-cancer or immunosuppressive drugs has not been studied. *Caution should be exercised when using them concomitantly* | *In vitro* results with a mammalian cell chromosomal aberration test (Ames test) showed no mutagenic effect. *In vivo* micronucleus assay in rats showed no potential for malignancy | *Incidence ofrenal tubular cell carcinoma was increased in mice*at a dose corresponding to recommended human dose.  *Incidence ofrenal tubular cell carcinoma and testicular Leydig cell adenomas increased* at a dose 2 times higher than recommended in humans.  *Incidence of squamous cell papilloma and cancer in forestomach was increased in mice* at recommended human dose and *in rats* below this dose | No detailed information |
| Teriflunomide | Cancer disease is not listed as a contraindication | Concomitant use with *anti-cancer drugs has not been evaluated* | No *in vitro* mutagenic or *in vivo* clastogenic effects. Minor metabolite TFMA (4-trifluoromethylaniline) caused mutagenicity and clastogenic effects *in vitro* but not *in vivo* | No evidence of carcinogenicity was observed in rats or mice | Clinical trials have not demonstrated an increased risk of cancer |
| Fingolimod | Active malignancies | Anti-cancer, immunomodulatory, or immunosuppressive drugs *should not be used concomitantly* due to risk of additive effects on immune system | Animal studies have not shown mutagenicity or clastogenicity | *No evidence of carcinogenicity* was foundin a 2-year study in *rats* at a dose equivalent to c.50 times exposure in humans.  *In a 2-year study in mice, an increase in incidence of malignant lymphomas was found* at doses c.6 times higher than recommended in humans | Benign, malignant and unspecified neoplasms:  *Common:*basal cell carcinoma  Uncommon: melanoma  *Rare:* lymphoma, squamous cell carcinoma  *Very rare:* Kaposi’s sarcoma  *Not known*: Merkel cell carcinoma |
| Ozanimod | Active malignancies | *Anti-cancer, immunomodulatory, or immunosuppressive drugs should not be administered concomitantly* because of risk of additive effects on immune system | Ozanimod and its major active metabolites in humans were not genotoxic *in vitro* or *in vivo* | No tumours were found in a 2-year biological test *on rats.*  In a 6-month study *in mice*, a dose-related increase in incidence of haemangiosarcoma was found  Occurrence of haemangiosarcoma in mice may be species-specific and not predictive in humans | Half of cancer cases reported in phase III trials included skin malignancies other than melanoma, with most common skin cancer being basal cell carcinoma |
| Ponesimod | Active malignancies | Caution should be exercised when immunosuppressants and anti-cancer drugs are administered concomitantly because of risk of additive immunological effects during such therapy and weeks after its completion | No genotoxic potential was revealed *in vitro*or*in vivo* | In a 2-year study*, no neoplastic lesions were observed* in rats at highest dose tested, which was 18.7 times higher than in humans.  *An increased incidence of sarcoma and haemangioma* was observed in mice onhigh drug doses | In a clinical trial, a case of melanoma and two cases of basal cell carcinoma were found (0.4%) compared to one case of basal cell carcinoma (0.2%) in patients on teriflunomide |
| Siponimod | Active malignancies | Not assessed in combination with anti-cancer, immunomodulatory, or immunosuppressive drugs. Caution should be exercised when these drugs are used concomitantly because of risk of their additive effect on immune system, as well as in weeks after treatment completion | No genotoxicity *in vitro* or *in vivo* | In mice, it caused lymphomas, haemangiomas and haemangiosarcomas, *while in male rats,* follicular adenomas and thyroid cancers were reported. This was considered mice-specific or attributed to metabolic adaptive changes in liver in rats; their significance for humans is unclear | Skin cancers: cases of basal cell carcinoma and other skin cancers, including squamous cell carcinoma, have been reported.  Benign, malignant and unspecified neoplasms (including cysts and polyps):  *Common:* Pigmented nevi, basal cell carcinoma.  *Uncommon:* Squamous cell carcinoma |
| Natalizumab | Confirmed active malignancies except for patients with basal cell carcinoma | Safety in combination with immunosuppressants and anti-cancer drugs *has not been established*  Concomitant use *may increase the risk of infections, including opportunistic infections*. Therefore, itis contraindicated | No clastogenic or mutagenic effects were observed in Ames test or human chromosome aberration test. Drug had no *in vitro* effect on proliferation assays of tumour α-4 integrin positive cells or cellular toxicity tests *in vitro* | In mice, increased growth and metastasis of melanoma cells and tumours in lymphoblastic leukaemia have not been demonstrated | Malignancies:  After two years of treatment, there were no differences in incidence or type of malignancies between patients on natalizumab and placebo. However, patients using drug for a long time should be followed-up |
| Ocrelizumab | Active malignancies | Concomitant use of other immunosuppressive therapies is not recommended | No mutagenic studies have been performed | Carcinogenicity studies have not been performed | *Malignancies:*  Clinical trials found an increased number of malignancies (including breast cancer). Incidence was within the range predicted for MS patients |
| Ofatumumab | Active malignancy | Risk of additive effects on immune system should be considered when combined with immunosuppressive agents | No mutagenic studies have been performed | Carcinogenicity studies have not been performed | No information about cancer occurrence during treatment |
| Alemtuzumab | *Caution should beexercised* in patients with pre-existing and/or active malignancy | No information about concomitant use with anti-cancer drugs | No studies have been conducted to evaluate mutagenic potential | No studies have been conducted to assess carcinogenic potential | Benign, malignant and unspecified neoplasms (including cysts and polyps):  *Common*: skin papilloma  It is not known if there is an increased risk of thyroid cancer. However, autoimmune thyroid disease may be a risk factor for thyroid cancers |
| Cladribine | Active malignancy | Treatment is contraindicated in immunocompromised patients, including those on immunosuppressive or myelosuppressive therapy | No induction of gene mutations in bacteria or mammalian cells.  It has a clastogenic effect. It damages chromosomes in mammalian cells *in vitro* at concentrations 17 times higher than those used in humans. In mice, *in vivo*, clastogenicity was detected at lowest dose. Genotoxicity was demonstrated in *a study in mice*, which was confirmed by a micronucleus test at a dose 16 times higher than recommended in humans | Long-term data from studies in mice (each dose up to 25 times human dose) and monkeys (subcutaneous injections) does not support a significant increase in risk of carcinogenicity in humans. No cases of cancer were observed in monkeys | Malignancies:  In clinical trials, malignancies were observed more frequently in patients treated with cladribine compared to placebo.  In clinical trials and during long-term follow-up of patients treated with cladribine oral dose of 3.5 mg/kg, malignancies were observed more frequently in patients treated with cladribine (0.29/100 patient-years) compared to patients treated with a placebo (0.15/ 100 patient-years) |

**Supplementary Table 2.** New DMT – phase III clinical trials – registration studies

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| **Drug** | **Phase III study** | **Indication** | **Comparator** | **Time of the study**  **(weeks)** | **Study groups**  **N** | **Cancer study group**  **n (%)** | **Cancer control group**  **n (%)** |
| **Dimethyl fumarate** | **DEFINE [35]**  **CONFIRM [36]** | RRMS  RRMS | Placebo  (n=480)  Placebo (n=363)  Glatiramer acetate  (n=350) | 96  96 | Dimethyl Fumarate 240mg (twice daily)  (n=410)  Dimethyl fumarate 240mg (three times daily)  (n=416)  Dimethyl fumarate 240mg (twice daily)  (n=359)  Dimethyl fumarate 240mg (three times daily)  (n=345) | **Cancers n=2** (<1.0%): basal cell carcinoma n=1  bladder cancer n=1  **Cancers n=2** (<1.0%):  breast cancer n=1  cervical cancer n=1  **Cancers n=0**  **Cancers n=0** | Cancers n=2 (<1.0%):  breast cancer n=1,  basal cell carcinoma n=1  Placebo:  Cancers n=1 (0.2%):  breast cancer n=1  Glatiramer acetate:  Cancers n=4 (1.1%): cervical cancer n=1, endometrial cancer n=1, basal cell carcinoma n=1, thyroid cancer n=1 |
| **Teriflunomide** | **TEMSO [40]**  **TOWER** | RRMS | Placebo  (n=363)  Placebo  (n=389) | 108  132 | Teriflunomide 7mg (n=366)  Teriflunomide 14mg (n=359)  Teriflunomide 7mg (n=408)  Teriflunomide 14mg (n=372) | **Cancers n=0**  **Cancers n=1**(0.2%):  cervical cancer in situ n=1  **Cancers n=0**  **Cancer n=1** (0.2%): thyroid cancer n=1 | Cancers n=3 (0.8%):  breast cancer n=1,  cervical cancer n=1, thyroid cancer n=1  Cancers n=0 |
| **Fingolimod** | **FREEDOMS [44]**  **TRANSFORMS [45]** | RRMS | Placebo  (n=481)  INF beta 1a  (n=435) | 96  48 | Fingolimod 1.25mg (n=429)  Fingolimod 0.5mg (n=425)  Fingolimod 1.25mg (n=426)  Fingolimod 0.5mg (n=431) | **Cancers n=4** (0.93%):  basal cell carcinoma n=1, breast cancer n=1, melanoma n=1, squamous cell carcinoma n=1  **Cancers n=4** (0.94%): basal cell carcinoma n=4  **Cancers n=4** (0.93%):  basal cell carcinoma n=2, breast cancer n=2  **Cancers n=8** (1.8%):  basal cell carcinoma n=3, melanoma n=3,  breast cancer n=2 | Cancers n=10 (2.4%):  basal cell carcinoma n=3, breast cancer n=3, melanoma n=1, cervical cancer n=1, endometrial cancer n=1, prostate cancer n=1  Cancers n=2 (0.45%): basal cell carcinoma n=1, squamous cell carcinoma n=1 |
| **Ponesimod** | **OPTIMUM [56]** | RRMS | Teriflunomide 14mg  (n=566) | 108 | Ponesimod 20mg  (n=567) | **Cancers n=6** (1.0%):  skin cancer n=5: basal cell carcinoma n=4, melanoma n=1;  another malignancy not related to the skin n=1 | Cancers n=3 (0.5%):  skin cancers n=1: basal cell carcinoma |
| **Ozanimod** | **RADIANCE [59]**  **SUNBEAM [60]** | RRMS  RRMS | INF beta 1a  (n=441)  INF beta 1a  (n=448) | 96  48 | Ozanimod 1mg  (n=434)  Ozanimod 0.5mg (n=439)  Ozanimod 1mg  (n=447)  Ozanimod 0.5mg (n=451) | **Cancers n=4** (0.9%):  breast cancer n=2, basal cell carcinoma n=1, squamous cell carcinoma n=1  **Cancers n=3** (0.7%): melanoma in situ n=1, medulloblastoma n=1, basal cell carcinoma n=1  **Cancers n=1** (0.2%): testicular cancer n=1  **Cancers n=2** (0.4%): breast cancer n=1, basal cell carcinoma n=1 | Cancers n=2 (0.5%): leukemia n=1, basal cell carcinoma n=1  Cancers n=0 |
| **Siponimod** | **EXPAND [63]** | SPMS | Placebo  (n=546) | 42 | Siponimod 2mg  (n=1,099) | **Cancers n=14**  skin cancers =14 (1.0%), including basal cell carcinoma =11 | Skin cancer n=6 (1.0%) |
| **Natalizumab** | **AFFIRM [66]** | RRMS | Placebo  (n=315) | 120 | Natalizumab 300mg  (n = 627) | **Cancers n=5** (0.8%): breast cancer n=3, cervical cancer n=1, melanoma n=1. | Cancers n=1 (0.3%): basal cell carcinoma n=1 |
| **Ocrelizumab** | **OPERA I [75]**  **OPERA II**  **ORATORIO [77]** | RRMS  RRMS  PPMS | INF beta 1a  (n=411)  INF beta 1a  (n=418)  Placebo (n=244) | 96  96  120 | Ocrelizumab 600mg  (n=410)  Ocrelizumab  600mg  (n=417)  Ocrelizumab 600mg  (n=488) | **Cancers n=3** (0.7%):  breast cancer n=2,  kidney cancer n=1  **Cancers n=1** (0.2%): melanoma n=1  **Cancers n=11** (2.3%): breast cancer n=4, basal cell carcinoma n=3, lymphoma n=1, endometrial cancer n=1, histiocytoma n=1, pancreatic cancer n=1 | Cancers n=1(0.2%):  Lymphoma n=1  Cancers n=1: squamous cell carcinoma n=1  Cancers n=2 (0.8%): basal cell carcinoma n=1, cervical cancer n=1 |
| **Ofatumumab** | **ASCLEPIUS [81]**  **ASCLEPIUS II** | RRMS | Teriflunomide 14mg  (n=462)  Teriflunomide 14mg  (n=474) | 120 | Ofatumumab 20mg (n=465)  Ofatumumab 20mg(n=481) | **Cancers n=3** (0.6%)  **Cancers n=2** (0.4%)  **Total number of cancers (Ofatumumab): n=5:**  basal cell carcinoma=2, melanoma n=1, breast cancer n=1, lymphoma n=1 | Cancers n=3 (0.6%)  Cancers n=1 (0.2%)  Total number of cancers (placebo) n=4: basal cell carcinoma n=2, cervical cancer n=1, fibrosarcoma n=1 |
| **Alemtuzumab** | **CARE MS –I [83]**  **CARE MS II [84]** | RRMS | INF beta 1a (n=187)  INF beta 1a (n=202) | 96 | Alemtuzumab 24mg (n=376)  Alemtuzumab 12 mg (n=426)  Alemtuzumab 24 mg (n=170) | **Cancers n=2** (1.0%): thyroid cancer n=2  **Cancers n=2** (0.4%): basal cell carcinoma n=1, thyroid cancer n=1  **Cancers n=2** (1.1%):  vulvar cancer n=1  colorectal cancer n=1 | Cancers n=0  Cancers n=2 (0.9%): basal cell carcinoma n=1, leukemia n=1 |
| **Cladribine** | **CLARITY [93]** | **RRMS** | Placebo (n=437) | 96 | Cladribine 3.5mg/kg  (n=433)  Cladribine 5.25mg/kg  (n=456) | **Neoplasms n=6** (1.4%)  **Neoplasms n=4** (0.9%)  Uterine leiomyoma n=5, cervical in situ carcinoma n=1, melanoma n=1, ovarian carcinoma n=1, pancreatic carcinoma n=1,  myelodysplastic syndrome n=1. | Cancers n**=0** |