GUIDELINES

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Recommendations of Multiple Sclerosis and Neuroimmunology Section of Polish Neurological Society and Immuno-oncology Section of Polish Society of Oncology on oncological risk in patients with multiple sclerosis undergoing immunomodulatory therapy

Iwona Rościszewska-Żukowska[1], Alina Kułakowska[2], Alicja Kalinowska[3], Halina Bartosik-Psujek[1], Dagmara Mirowska-Guzel[4], Mariusz Stasiołek[5], Beata Zakrzewska-Pniewska[6], Waldemar Brola[7], Sławomir Wawrzyniak[8], Marek Gołębiowski[9], Jacek Mackiewicz[10, 11], Grażyna Kamińska-Winciorek[13], Anna M. Czarnecka[13, 14], Adam Maciejczyk[15, 16], Sebastian Giebel[17], Piotr Rutkowski[13], Bożena Cybulska-Stopa[15, 18], Monika Adamczyk-Sowa[19]

[1]Department of Neurology, Institute of Medical Sciences, Medical College of Rzeszow University, Rzeszow, Poland
[2]Department of Neurology, Medical University of Bialystok, Bialystok, Poland
[3]Department of Neurology, Division of Neurochemistry and Neuropathology, Poznan University of Medical Sciences, Poznan, Poland
[4]Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Warsaw, Poland
[5]Department of Neurology, Medical University of Lodz, Lodz, Poland
[6]Department of Neurology, Medical University of Warsaw, Warsaw, Poland
[7]Department of Neurology, Collegium Medicum, Jan Kochanowski University, Kielce, Poland
[8]Department of Neurology, 10th Military Research Hospital and Polyclinic, Bydgoszcz, Poland
[9]First Department of Clinical Radiology, Medical University of Warsaw, Warsaw, Poland
[10]Department of Medical and Experimental Oncology, University of Medical Sciences, Poznan, Poland
[11]Department of Diagnostics and Cancer Immunology, Greater Poland Cancer Centre, Poznan, Poland
[12]Department of Bone Marrow Transplantation and Haematology-Oncology; Skin Cancer and Melanoma Team, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland
[13]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[14]Department of Experimental Pharmacology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland
[15]Department of Clinical Oncology, Lower Silesian Oncology, Pulmonology and Haematology Centre, Wroclaw, Poland
[16]Department of Oncology, Wroclaw Medical University, Wroclaw, Poland
[17]Department of Bone Marrow Transplantation and Haematology-Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland
[18]Department of Haematology and Oncology, Faculty of Medicine, Wroclaw University of Science and Technology, Wroclaw, Poland
[19]Department of Neurology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Katowice, Poland

Address for correspondence: Iwona Rościszewska-Żukowska, Department of Neurology, Institute of Medical Sciences, Medical College of Rzeszow University, Warzywna 1a St., 35–310 Rzeszów, Poland; e-mail: iwona.rosciszewska@op.pl
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ABSTRACT

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS) that is usually diagnosed between the ages of 20 and 40. Changes in the immune system also observed in cancer may suggest a higher prevalence of cancer in the MS patient population. In recent years, many highly effective immunosuppressive drugs have been introduced into disease-modifying therapy (DMT) which may be associated with a higher risk of cancer development in patients with MS. This paper presents current data on the oncological risk of individual drugs. In addition, it provides recommendations on the management for qualifying for DMT and monitoring the safety of the therapy from anoncological perspective.

Keywords: multiple sclerosis, oncological risk, cancer, immunomodulatory therapy

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Introduction

Multiple sclerosis (MS) is a relatively common inflammatory and neurodegenerative disease of the central nervous system (CNS) that is usually diagnosed between the ages of 20 and 40. Women are affected 2–3 times more often than men [1, 2]. It involves engagement of the immune system, acute inflammatory injury of axons and glia, post-inflammatory gliosis, and neurodegeneration [1]. Relapsing-remitting MS (RRMS) is the most common type of MS, accounting for c.85–90% of cases at onset and affecting especially young people. Its course is characterised by fully or partly reversible episodes (known as relapses) of neurological disability and the differential involvement of motor, sensory, visual, and autonomic systems [3]. The era of disease-modifying therapies (DMTs) began in the 1990s. In the 21st century, many new drugs have been introduced that have improved treatment, not only in terms of effectiveness but also safety. Because most DMTs are immunosuppressive, they may be associated with a higher risk of cancer.

Risk of developing cancer in general population

In Poland, the number of cancer cases has more than doubled in the last two decades. According to the National Cancer Registry, over 146,000 new cancer cases and 99,900 cancer-related deaths were reported in 2020. Malignant neoplasms are the second most common cause of death, and account for over 20% of all deaths [4].

The risk of developing cancer depends on age and sex. In 2020, the number of new cases in young people (i.e. those aged 20–44) in Poland amounted to over 7,000 cases annually in women and over 3,500 in men. In turn, in middle-aged individuals (45–64 years) and people aged 65 and over, the numbers were as follows: over 25,000 cases in women and 21,000 in men, and 40,000 in women and 45,000 in men, respectively [4].

The most prevalent malignancy in women is breast cancer (23.8%), with an increasing incidence, followed by lung cancer (9.9%) and colorectal cancer (8.5%). Endometrial cancer (7.1%) and ovarian cancer (4.1%) are slightly less common. In 2020, the highest mortality was related to lung cancer and breast cancer. In turn, the most prevalent carcinoma in men is prostate cancer (19.6%); followed by lung cancer (15.9%) and colorectal cancer (11.2%). Bladder cancer (6.6%) is less common. The highest mortality is associated with lung cancer [4].

The prevalence of cancer depends on the age structure of the population. In young women (aged 20–44), breast cancer is most prevalent (29% of cases and 29% of deaths due to all cancers), followed by cervical cancer (5% and 9%, respectively), ovarian cancer (5% and 8%, respectively) and colorectal cancer (3% and 9%, respectively). In middle-aged women (aged 45–64), breast cancer is also the most frequently diagnosed carcinoma (31% of cases, 18% of deaths due to all cancers) followed by lung cancer (9% and 20%, respectively), colorectal cancer (8% and 9%, respectively), ovarian cancer (5% and 8% respectively) and endometrial cancer (9% and 3%, respectively) [4]. In young men (aged 20–44), testicular cancer is the most common (26% of cases, 7% of deaths due to all cancers), followed by colorectal cancer (7% and 10%, respectively) and melanoma (7% and 5%, respectively) [4]. In middle-aged men (aged 45–64), the most common cancers are lung cancer (17% of cases, 29% of deaths due to all cancers), prostate cancer (16% and 4%, respectively), and colorectal cancer (13% and 11%, respectively). Bladder cancer (5% and 4%, respectively) and gastric carcinoma (4% and 6%, respectively) are less prevalent [4].

Cancer risk in patients with multiple sclerosis

Early analyses showed a higher risk of cancer among patients with MS, especially brain and urinary tract cancers [5–7]. Recent studies have not confirmed these figures [6, 8, 9], which is in line with a meta-analysis from 2020 that did

not show a higher prevalence of cancer in the population of patients with MS compared to the general population [10].

However, there are still reports suggesting differences in the prevalence of some cancers in patients with MS compared to the general population [7, 11, 12]. Analysis of a Norwegian database (n = 6,949) confirmed a higher cancer incidence in endocrine glands, brain, meninges and respiratory organs [12]. Breast, cervical and gastrointestinal cancers were found to be more common in the MS patient population, especially in women, compared to the control group, which was also demonstrated in a meta-analysis in 2015 [7, 12]. Analysis of a Danish database of MS patients (n = 11,817) showed an increased risk of melanoma [13]. There are reports of a higher incidence of bladder cancer than in the general population, which could be influenced by recurrent urinary tract infections associated with urinary incontinence [7, 14].

The stage of the disease and the phenotype of MS (i.e. clinically isolated syndrome [CIS], relapsing-remitting MS [RRMS], secondary progressive MS [SPMS] or primary progressive MS [PPMS]) do not correlate with a higher risk of cancer development [9]. Many reports have attempted to determine in more detail the risk factors for cancer in the population of patients with MS. However, no clear conclusions can be drawn from them [12, 15, 16]. It is known that age is an important risk factor for the development of cancer. In the population of patients with MS, the risk of carcinoma increases with age. It is higher in individuals over 60 and in patients whose disease occurs later and lasts longer [12, 16].

DMT and cancer risk

Drugs that are effective in inhibiting clinical and radiological activity and disease progression have been registered in the DMT of MS. However, the long-term impact of most of them, especially in terms of adverse effects, is as yet insufficiently understood. Mechanisms of action, including the impact on the immune system, vary between drugs. By inhibiting the immune system, the immunosuppressive effect can cause significant lymphopenia and increase the risk of cancer development, the frequency of infections, or the development of opportunistic infections [17, 18].

Comparing data on the prevalence of cancer in the period before the use of DMT and after its introduction, no clear conclusions can be drawn [12, 13]. To date, data on the safety of DMT does not allow for estimation of the risk, because patients over 55 and those who have had MS for more than 10 years have rarely been enrolled in clinical trials. It has been found that DMT switching could carry a risk of cancer. Patients with a single switch of DMT carry double the risk of developing cancer, and for patients who change therapy two or more times this risk is more than trebled. It has not been demonstrated that the therapy model (i.e. escalation vs. induction) has an impact on the risk of cancer development [16].

Statements of risk of cancer during DMT treatment, and recommendations on the management for DMT and monitoring the safety of the therapy from an oncological perspective, are set out in Table 1.

Beta interferons (IFN-β)

In vitro studies have not found the mutagenic effects of these substances, and no potential carcinogenic effects have been demonstrated. Carcinogenicity studies of IFN-β in animals have not been conducted (Suppl. Tab. 1) [19–22]. No cases of cancer have been reported in clinical registration trials of anyinterferon beta products [23–26].

To date, data on the safety assessment of IFN-β has not shown an increased risk of cancer associated with the use of drugs from this group. Analysis of data from 12 clinical trials on IFN-β 1a s.c. (subcutaneous route) and clinical practice (n = 3,746) did not show a higher incidence of cancer in the group of patients treated with IFN-β compared to the group treated with a placebo [27]. A lack of increased risk of IFN-β 1a i.m. (intramuscular injection) was confirmed in analysis of a very large group of patients from an American population (n = 402,250) [28]. Similarly, in a French study that evaluated patients from 12 MS centres (n = 9,269) treated with IFN-β 1a s.c., IFN-β 1a i.m. and IFN-β 1b, no higher incidence of cancer was noted [29]. No increased cancer risk was demonstrated in a 12-year follow-up of patients treated with IFN-β registered in the British Columbia MS Database (n = 5,146). In this group, a trend toward an increased risk of breast cancer was observed, but with no statistical significance [30].

Glatiramer acetate (GA)

In vitro data has not found genotoxicity or carcinogenicity. No animal studies have been performed (Suppl. Tab. 2) [31]. No cases of cancer have been reported in clinical trials [32].

Most real-world evidence (RWE) studies donot show an increased risk of cancer in patients treated with GA. Based on the data from the British Columbia MS Database, only 2.3% of patients treated with GA were reported to have had cancer. The French study found no association between cancer risk and GA [29, 30]. In a study of patients from an Israeli population, a higher incidence of breast cancer in women was found, depending on the duration of GA therapy. However, the data was not statistically significant [33]. Isolated cases of cutaneous lymphoma and melanoma have been reported in patients exposed to GA [34].

Dimethyl fumarate (DMF)

In vitro genotoxicity studies have not demonstrated the mutagenic effects of DMF. In preclinical studies, mice were found to have an increased prevalence of kidney cancer and

Table 1. Statements and recommendations for DMTs

DMT	Statement	Recommendation
Beta interferons	No increased risk of cancer associated with beta interferon therapy was found	**Recommendation 1** There are no special recommendations related to IFN-β regarding cancer prevention
Glatiramer acetate	There was no evidence of an increased risk of cancer associated with glatiramer acetate therapy	**Recommendation 2** There are no special recommendations for cancer prevention associated with glatiramer acetate therapy
Dimethyl fumarate	No increased risk of cancer associated with dimethyl fumarate therapy has been demonstrated yet. However, this needs to be confirmed in long-term observations	**Recommendation 3** There are no specific recommendations for cancer prevention associated with dimethyl fumarate therapy
Teriflunomide	No increased risk of cancer associated with teriflunomide therapy has been demonstrated yet. However, this needs to be confirmed in long-term observations	**Recommendation 4** There are no special recommendations for cancer prevention associated with teriflunomide therapy

Sphingosine 1-phosphate (S1P) receptor modulators

Recommendation 5

- Patient education in terms of skin observation and self-examination
- Patients are advised to perform regular self-assessment of body, taking into account changes occurring within existing pigmented nevi and appearance of new lesions on skin, especially in areas not associated with exposure to ultraviolet radiation
- Patients are advised to follow rules of safe exposure to sun and to use skin protection against ultraviolet radiation, both natural and artificial (indoor tanning)
- Periodic physical examination and history taking, including a comprehensive skin examination, should be performed
- Periodic dermatology consultation with skin assessment prior to initiation of treatment and during treatment is recommended in accordance with the current SmPC of a given drug (recommended primarily before therapy with fingolimod or siponimod, and to be considered before treatment with ozanimod or ponesimod)
- Phototherapy with UV-B radiation or photochemotherapy with psoralens (PUVA) is contraindicated during treatment
- Use of fingolimod, ozanimod and siponimod is contraindicated in patients with active malignancy. It is recommended to discontinue therapy if active malignancy is diagnosed. (Recommendation 5a, 5c and 5d)
- Use of ponesimod is contraindicated in patients with active malignancy. (Recommendation 5b)
- Caution should be exercised when ponesimod or siponimod is administered concomitantly with anti-cancer drugs, immunomodulatory or immunosuppressive agents due to risk of additive immune effects during such therapy and weeks after its completion (Recommendation 5b, 5d)
- Fingolimod and ozanimod should not be administered concomitantly with anti-cancer drugs, immunomodulatory, or immunosuppressive agents due to risk of additive effects on immune system (Recommendation 5a, 5c)
- It is recommended to perform screening tests for cervical cancer (including a cervical smear every three years in women aged 25–59, or every 1–2 years in women at increased risk, depending on the previous result) and vaccination against human papillomavirus (HPV) in accordance with current standards of care (Recommendation 5a)

DMT	Statement		Recommendation
Fingolimod	An increased risk of cancer associated with fingolimod therapy, especially skin cancers, has been demonstrated		**Recommendation 5a**
Ponesimod	No increased risk of cancer associated with ponesimod has been demonstrated yet. However, long-term observations are warranted In turn, an increased risk of skin malignancies has been found in combination with another S1P receptormodulator (SmPC)		**Recommendation 5b**
Ozanimod	No increased risk of cancer associated with ozanimod has been demonstrated yet. However, further long-term follow-up is necessary An increased risk of skin malignancies has been found in combination with another S1P receptor modulator (SmPC)		**Recommendation 5c**
Siponimod	An increased risk of cancer, especially skin cancers, associated with siponimod has been demonstrated		**Recommendation 5d**
Natalizumab	No increased risk of cancer associated with natalizumab has been demonstrated yet. However, further long-term observations are warranted	Patient education in terms of skin observation and self-examination Patients are advised to regularly self-assess body, taking into account changes within existing pigmented nevi and appearance of new lesions on skin, especially in areas not associated with exposure to ultraviolet radiation Patients are advised to follow rules of safe exposure to sun and to use skin protection against ultraviolet radiation, both natural and artificial (indoor tanning) Periodic physical examination and history taking, including a comprehensive skin examination, should be performed Use of natalizumab is contraindicated in patients with active malignancy, except for basal cell carcinoma (SmPC). Basal cell carcinoma should be removed	**Recommendation 6**

Table 1. cont. Statements and recommendations for DMTs

Ocrelizumab	A higher incidence of cancer, especially breast cancer, was observed in registration trials of ocrelizumab compared to controls RWE observations have not confirmed this yet. Further long-term observations are warranted	Female patients should undergo standard breast cancer screening in accordance with current guidelines: • breast ultrasound every 2 years in women aged 20–30 • ultrasound once a year in women after age 30 • mammography once every 2 years in women over 45 Patients with known risk factors for malignancy and patients who are actively monitored for risk of cancer recurrence should be individually assessed for benefit-risk ratio Use of ocrelizumab in patients with active malignancy is contraindicated	**Recommendation 7**
Ofatumumab	No increased risk of cancer associated with ofatumumab therapy has been demonstrated yet. However, further long-term observations are warranted	Patients with known risk factors for malignancy and patients who are actively monitored for risk of cancer recurrence should be individually assessed for benefit-risk ratio Use of ofatumumab is contraindicated in patients with active malignancy	**Recommendation 8**
Alemtuzumab	No increased risk of cancer associated with alemtuzumab has been demonstrated yet. However, autoimmune thyroid disease alone may be a risk factor for thyroid cancer Further long-term observations are warranted	In cases of autoimmune thyroid disease, patient should be monitored for thyroid cancer also after completion of therapy Caution should be exercised in patients with pre-existing and/or active malignancy	**Recommendation 9**
Cladribine	A higher incidence of cancer was observed in registration studies of cladribine tablets compared to controls However, this has not been confirmed in RWE observations yet. Further long-term observations are warranted	Patients treated with cladribine should be advised to follow Standard Cancer Screening Guidelines (SmPC) Cladribine therapy is contraindicated in cases of active malignancy Individual benefit-risk assessment should be performed in patients with pre-existing malignancies prior to treatment initiation	**Recommendation 10**

Recommendations for eligibility for DMT:

When qualifying a patient with MS for DMT, it is necessary to:

1. Perform an oncological medical interview to check for active and past cancer disease and collect a family history of cancer
2. Inform patient that risk of developing cancer increases with age and thatuse of immunosuppressive therapies may be an additional risk factor for cancer formation
3. Tests should be performed to rule out active malignancy according to standard screening guidelines, depending on risk factors, age and planned DMT
4. Recommend modification of risk factors for the development of cancer (ban on smoking and alcohol abuse, maintenance of normal body weight: BMI < 25)
5. Educate patients in terms of observation and self-examination of skin and breasts
6. Inform patient about need to protect skin from sun exposure using UV filters

Recommendations for monitoring DMT:

When monitoring DMT, recommendations are:

1. Tests for cancer detection:
   a) Performing tests for detection of skin cancers:
      • Educating patients in field of skin observation and self-examination
      • Patients are recommended to regularly self-assessbody, taking into account lesions occurring within existing pigmented nevi and appearance of new lesions on skin, especially in locations not associated with exposure to ultraviolet radiation
      • Patients should be advised to follow rules of safe sun exposure and use skin protection products against ultraviolet radiation – natural and artificial (indoor tanning)
      • Periodic physical examination and history taking, including a comprehensive examination of skin (basal cell carcinoma, melanoma) should be performed. In cases of a suspicious skin lesion, immediate dermatology consultation should be sought
   b) Conducting tests for detection of breast cancer:
      • Educating patients in terms of breast observation and self-examination
      • Regular breast self-examination
      • Breast imaging studies in accordance with current recommendations for general population
   c) Performing tests for detection of cervical cancer in accordance with current recommendations for general population
2. When switching to DMT, an analysis of potential benefit-risk of cancer development should be carried out, considering patient's age, number of previous DMTs, and duration of immunosuppressive treatment

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Table 1. cont. Statements and recommendations for DMTs

Preventive cancer screening – current screening programmes	
Breast Cancer Prevention Programme	In women > 45, mammography once every 2 years
Cervical Cancer Prevention Programme	In women aged 25–64, cytology once every 3 years
	Once a year in women with risk factors (HIV infection, intake of immunosuppressive drugs, and HPV infection of a high-risk type)
Colorectal Cancer Screening Programme	Colonoscopy:
	— In people aged 50–65
	— In people aged 40–49 if a first-degree relative has been diagnosed with colorectal cancer
	— In people aged 25–49with a family history of colorectal cancer unrelated to polyposis
Pilot programme for early detection of lung cancer	Chest computed tomography in former and active smokers > 55

Risk factors for development of cancer disease in a patient treated with DMT: checklist

No.	Risk factors
1.	Patient age > 50
2.	A history of cancer
3.	Oncological history: confirmed oncogenic germline mutations in patient or a family history of cancer in first-degree relative confirmed by genetic consultation
4.	Duration of DMT therapy > 10 years
5.	DMT switching at least twice
6.	Prior immunosuppressive DMT
7.	Current therapy with a drug with a confirmed increased risk of cancer (fingolimod, siponimod, ocrelizumab, cladribine)
8.	Current immunosuppressive therapy (ponesimod, ozanimod, ofatumumab, alemtuzumab)

forestomach cancer. Two times higher exposure than the recommended human dose resulted in a higher incidence of renal cancer and testicular Leydig cell adenoma in rats (Suppl. Tab. 1) [35].

In the DEFINE and CONFIRM registration studies, the prevalence of cancer in patients treated with DMF was not higher than in the placebo group (Suppl. Tab. 2) [36, 37]. In long-term follow-up of patients from the ENDORSE registration trial (median follow-up 8.76 years), a similar number of cancers was recorded in the group treated with DMF from the beginning and the group initially on a placebo (16 cases; 3% vs. 8 cases; 3%). The incidence of cancer in patients treated with DMF was 459 per 100,000 persons per year. This did not differ significantly from the incidence rate in the general population (442 per 100,000 persons per year) [38]. Despite lymphopenia in patients, no higher incidence of cancer was noted in RWE observations. In a Spanish study, the incidence of cancer in patients treated with DMF (n = 886) was low and amounted to 0.9% (n = 8) at a mean follow-up of 39.5 months, with as many as 62% of patients developing cancer (n = 5) over the age of 50 [39].

Teriflunomide (TER)

Thisdrug was not mutagenic *in vitro* or clastogenic *in vivo*. Its metabolite caused mutagenicity and a clastogenic effect *in vitro,*but not *in vivo*. In preclinical studies in rats and mice, no evidence of carcinogenicity of the drug was observed (Suppl. Tab. 1) [40].

The TEMSO and TOWER registration trials did not show an increased risk of cancer in patients treated with TER compared to a placebo group (Suppl. Tab. 2) [41]. In long-term follow-ups (median 13 years) of patients (n = 1,978) from phase II and III clinical trials (i.e. TEMSO, TOWER, TOPIC, TENERE, TERI-PRO, and TAURUS MS I), a total of 19 (0.9%) cases of cancer were reported [42]. In patients on 14 mg TER, no increased risk of cancer was confirmed [43].

Sphingosine 1-phosphate (S1P) receptor modulators: fingolimod, ponesimod, ozanimod, siponimod

Fingolimod (FTY)

In preclinical studies in rats, no evidence of carcinogenicity of FTY was reported. In mice, an increased incidence of lymphomas was demonstrated at the drug dose equivalent of six times the human dose (Suppl. Tab. 1) [44].

According to the Summary of Product Characteristics (SmPC), FTY may induce lymphopenia. It has an immunosuppressive potential, and may therefore increase the risk of cancer, especially skin cancer and lymphomas. In clinical trials and observations after the drug's introduction to the market,

cases of various types of lymphomas were found, and their incidence in clinical trials was higher than would be expected in the general population [45].

The first reports of increased cancer risk came from the FREEDOMS and TRANSFORMS registration trials (Suppl. Tab. 2) [45, 46]. In a long-term (up to 4.5 years) follow-up of patients from the TRANSFORMS trial, an increased risk of non-melanocytic skin cancer was confirmed. No higher risk of melanoma was found [47]. In the INFORMS trial, 25 cases of malignancies (7.4%) were reported in patients with PPMS (n = 336), including particularly skin cancers such as basal cell carcinoma (n = 14), squamous cell carcinoma (n = 6), and melanoma (n = 1), and also breast cancer (n = 1), lymphoma (n = 1), lung cancer (n = 1), ovarian cancer (n = 1) and prostate cancer (n = 1). No correlation was found between the degree of lymphopenia and skin cancer [48]. Cases of basal cell carcinoma (n = 36) were reported in the LONGTERMS trial, which was a long-term (14 years) follow-up of patients treated with FTY (n = 3,480). It was the most common serious adverse event, while eight cases of breast cancer were also reported [49].

There have also been reports of cancer in RWE observations of patients treated with FTY. Cases of melanoma (n = 5) were reported in patients with short-term (12–32 months) therapy with FTY[50]. Additionally, cases of Kaposi's sarcoma were described [45]. In a German study evaluating the efficacy and safety of FTY treatment after five years (n = 4,068), the following cancers were described: basal cell carcinoma (n = 21), melanoma (n = 6) and other skin cancers (n = 4) [51]. In an analysis of a Swedish database of patients with MS, patients treated with FTY (n = 1,620) presented with a 1.5--fold increased risk of malignancy compared to the general population, especially for basal cell carcinoma (n = 15) and cervical intraepithelial neoplasia grade 3 (CIN3) (n = 17). In addition, breast cancer (n = 4), prostate cancer (n = 3), melanoma (n = 4), skin cancers other than melanoma (n = 3), and lymphoma (n = 2) were reported [52].

In 2020, a meta-analysis of 34 studies (n = 64,135) estimated the incidence of cancer in the population of patients treated with FTY at 2% (n = 2,561). A higher incidence of cancer was observed in patients on a higher dose (1.25 mg) (3.0%) compared to 0.5 mg (2.0%) [53]. In connection with reports of an increased incidence of cancer, especially skin cancer, in patients treated with FTY, the European Medicines Agency (EMA) recommended monitoring the patient's skin, which was included in the SmPC in 2015 [44]. Cases of human papillomavirus (HPV) infections, including highly oncogenic variants, were reported in women treated with FTY, which may increase the risk of secondary cervical cancers [54, 55]. In the longitudinal open-label LONGTERMS trial, cases of cervical precancerous stages (n = 7) were found in women on FTY [49].

Ponesimod

In preclinical studies, ponesimod did not show a genotoxic potential *in vitro* or*in vivo*. In the carcinogenicity studies in rats, no cancerous lesions were observed. In mice, however, an association was found with sarcoma and haemangioma at high drug doses (Suppl. Tab. 1) [56].

In the OPTIMUM registration trial, six cases of cancer (1.0%) were reported in the group on ponesimod (n = 567), including five skin cancers, comprising basal cell carcinoma (n = 4) and melanoma (n = 1) (Suppl. Tab. 2) [57].

In a long-term (median 7.9 years) follow-up of patients from the phase II study and extension phases who continued ponesimod therapy (n = 214), eight (1.8%) cases of non-skin cancers were reported: invasive ductal breast cancer (n = 3), breast cancer (n = 2), B-cell lymphoma (n = 1), cervical adenocarcinoma (n = 1) and oesophageal adenocarcinoma (n = 1). Six (1.4%) cases of skin cancer were observed, i.e. basal cell carcinoma (n = 5), squamous cell carcinoma (n = 1) plus anunspecified skin cancer (n = 1) [58]. To estimate the risk of cancer formation in patients treated with ponesimod, long-term observations of large cohorts are warranted.

Ozanimod

In preclinical studies, ozanimod and its major active metabolites were not genotoxic *in vitro* or*in vivo*. No tumours were found in studies evaluating carcinogenicity in animals (Suppl. Tab. 1) [59].

In the SUNBEAM and RADIANCE clinical trials, half of the cancer cases involved malignant skin cancers other than melanoma, the most common being basal cell carcinoma (Suppl. Tab. 2) [60, 61].

An analysis of patient data from phase I, II, and III clinical trials and open-label studies involving 2,787 patients on ozanimod for an average of 32 months showed a total of 25 (1.1%) cases of cancer, including skin cancers (n = 12): basal cell carcinoma (n = 9), squamous cell carcinoma (n = 1), non-melanoma skin cancer (n = 1), and melanoma (n = 1); and 13 cases of other cancers such as ductal breast cancer (n = 1), breast cancer (n = 5), cervical cancer (n = 1), testicular cancer (n = 1), kidney cancer (n = 1), glioma (n = 1), pancreatic cancer (n = 1), thyroid cancer (n = 1) and an unspecified malignant neoplasm (n = 1) [62]. These analyses did not show a higher cancer incidence than in the registration trials. Long-term observations are required.

Siponimod (SIP)

Siponimod is not genotoxic *in vitro* or *in vivo*. In animal studies, it has caused lymphomas, haemangiomas and haemangiosarcomas in mice, and follicular adenomas and thyroid carcinomas in male rats. The occurrence of these tumours was considered species-specific, and the relevance of these studies to humans is unclear (Suppl. Tab. 1) [63]. Basal cell carcinoma and other skin cancers, including squamous cell carcinoma, have been reported in patients on siponimod.

In the EXPAND registration trial in patients with SPMS, cases of skin cancer were observed (Suppl. Tab. 2) [64]. Analysis of patients in the EXPAND trial after five years of

follow-up (n = 1,651) showed an increased risk of skin cancer (n = 78; 5.1%), with an incidence rate of 1.6 per 100 patient-years, mostly basal cell carcinoma, compared to the registration study (n = 21, 1.9%), where the incidence rate was 1.2 per 100 patient-years [65]. These observations are consistent with the data on fingolimod.

Natalizumab (NAT)

Preclinical studies in mice showed no carcinogenic, clastogenic, or mutagenic effects (Suppl. Tab. 1) [66]. The AFFIRM clinical trial did not show a higher incidence of cancer in patients treated with NAT than in a placebo group (Suppl. Tab. 2) [67].

RWE observations indicated cancer cases. In a study of a Swedish population treated with NAT (n = 1,670), 17 (1.01%) cancer cases were described, including basal cell carcinoma (n = 8), breast cancer (n = 2), melanoma (n = 2) and precancerous conditions of the cervix (CIN3) (n = 15). No increased cancer risk was found compared to the general population [52]. In 2017, the World Health Organisation issued a warning regarding NAT therapy, as 16 cases of primary central nervous system lymphoma (PCNSL) had been reported in the VigiBase® database by May 2015, the analysis of which showed that NAT could affect more rapid progression of B-cell lymphoma of the CNS [68]. Case reports of PCNSL in patients treated with NAT are emerging. Acorrelation between PCNSL and NAT is still under discussion [69, 70]. The first suggestions from the analysis of clinical trial data and reported cases after the introduction of the drug to the market highlighted acoincidence between melanoma and NAT therapy. The incidence of melanoma in NAT patients was estimated at 5/100,000 patient-years, which was half that in the general population (10/100,000 patient-years) [71]. Case reports of melanoma still appear in patients on NAT. Additionally, cases of melanoma are reported in adverse event registries [72–74].

Ocrelizumab (OCR)

No preclinical studies of the carcinogenic or mutagenic effects of OCR have been conducted (Suppl. Tab. 1) [75]. In clinical trials, patients with RRMS (OPERA I, OPERA II) showed a higher incidence of cancer, especially breast cancer, in the OCR group (Suppl. Tab. 2) [76]. During the extension phase of the trial (five years in total), further cases of cancer (n = 5) were reported, of which two were associated with breast cancer. An increase in the incidence of breast cancer was observed in the 3rd and 4th years of therapy [77]. The ORATORIO study (PPMS) showed a higher incidence of cancer in the OCR group compared to a placebo group (Suppl. Tab. 2) [78]. During the extension phase of the study, two more cases of skin cancer were reported: basal cell carcinoma (n = 1) and squamous cell carcinoma (n = 1). In a 6.5-year follow-up of patients in the ORATORIO trial, 14 cases of cancer were reported in the group of patients treated with OCR: basal cell carcinoma (n = 4), histiocytoma (n = 1), pancreatic cancer (n = 1), lymphoma (n = 1), endometrial cancer (n = 1), breast cancer (n = 3) and squamous cell carcinoma (n = 2). In the group of patients initially treated with a placebo and then switched to OCR, 10 cases of cancer were reported: bladder cancer (n = 2), lung cancer (n = 1) and basal cell carcinoma (n = 7) [79]. Until January 2020, cancers had been reported with a higher incidence than in the control group in all clinical trials of OCR (11 studies) and their extended phases (n = 5,680) in a 7-year follow-up (0.46/100 patient-years vs. 0.21/100 patient-years in the control group) [80]. Similarly, in a 10-year follow-up (n = 6,155), the incidence of cancer was confirmed (0.49/100 patient-years) [81], although no higher incidence of cancer was found compared to the MS population and the general population [80, 81]. The incidence of breast cancer in women treated with OCR was not higher than in the MS population, but breast cancer was slightly more prevalent compared to the general population, findings which require further follow-up [80]. A higher incidence of cancer was observed in the group of patients with PPMS, which may be associated with the higher age of patients in this study group.

Proper risk assessment will be possible in the long-term follow-up after publishing the results of the VERISMO trial assessing cancer risk in patients treated with OCR in daily clinical practice.

Ofatumumab (OFT)

No *in vitro* or *in vivo* studies have been performed to assess the carcinogenicity and mutagenicity of OFT (Suppl. Tab. 1) [82].

In the ASCLEPIOS I and ASCLEPIOS II registration clinical trials, no higher cancer incidence was shown in the group on OFT compared to the control group treated with teriflunomide (Suppl. Tab. 2) [83]. There have beenno long-term observations to assess the safety of this therapy.

Alemtuzumab (ALZ)

No *in vitro* or *in vivo* studies have been performed to assess the carcinogenic and mutagenic potential of ALZ (Suppl. Tab. 1) [84].

The CARE-MS I and CARE-MS II clinical trials found no higher cancer risk in patients treated with ALZ compared to the control group (Suppl. Tab. 2) [85, 86]. No increased incidence of cancer was observed in the long-term follow-up of patients from the registration studies. Six cases of cancer were reported in a 5-year follow-up of patients with CARE-MS I (n = 376) (0.3/100 patient-years) [87]. After 3–5 years of follow-up of

patients from the CARE-MS II trial (n = 412), two more cases of cancer were found. In total, four cases of cancer were found in the 5-year follow-up (n = 435), which included thyroid cancer (n = 2), melanoma (n = 1) and basal cell carcinoma (n = 1) [88].

In a study evaluating the long-term (8-year follow-up) safety of ALZ, 17 (0.8%) cases of cancer were reported in the ALZ group (n = 811), seven of which occurred in people aged 45 and over. The incidence of cancer increased with age. Cancer was found in 0.9–2.2% of people in younger groups, while malignancies were present in as many as 8.1% of patients aged 45+ [89].

Cancer cases were also described in RWE observations. In a Finnish study, four cases of cancer (3.0%) were reported in a 2-year follow-up (n = 121). They included breast cancer (n = 2), cervical cancer (n = 1) and cervical cancer in situ (n = 1) [90]. Up to 35% of patients treated with ALZ developed secondary autoimmune thyroid diseases, such as Graves-Basedow disease (65%), followed by hypothyroidism (20%) and subacute thyroiditis (12%). They were most often observed in the 3rd and 4th years after the completion of therapy [91]. It is believed that autoimmune thyroid diseases may be a factor increasing the risk of thyroid cancer. Therefore, it is necessary to monitor patients, even after treatment completion [92].

Cladribine

In preclinical studies, no carcinogenicity was found in mice or monkeys (Suppl. Tab. 1) [93]. The carcinogenic potential of cladribine has been demonstrated in indications other than MS. An increased risk of secondary cancers (hairy cell leukaemia) has been reported in patients on cladribine [94].

The CLARITY clinical trial in patients with RRMS showed an increased number of cancers in the group treated with cladribine tablets (0.29/100 patient-years), which resulted in refusal to approve the drug by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2011 (Suppl. Tab. 2) [95, 96]. A higher incidence of a specific cancer type was not demonstrated. However, patients who developed cancer were, on average, seven years older. In the CLARITY extension study, 11 (1.06%) cases of cancer were reported in the next two years of therapy: melanoma (n = 2), basal cell carcinoma (n = 1), breast cancer (n = 1), cervical cancer (n = 1), ovarian cancer (n = 1), kidney cancer (n = 1), colorectal cancer (n = 1), thyroid cancer (n = 1), squamous cell carcinoma (n = 1) and bile duct cancer (n = 1). These findings were not more common than those found in the general population [97]. It was demonstrated that the cancer risk did not increase with the duration of therapy. The above data allowed the drug to be registered.

Analysis of patients from CLARITY, CLARITY EXTENSION, ORACLE-MS and those continuing follow-up in the PREMIERE registry (n = 923) confirmed that the incidence of cancers did not increase with the duration of therapy. From 1–4 years after the first dose, it was 0.29/100 patient-years, and after 5–8 years, it was 0.28/100 patient-years and was not higher compared to other DMTs [98]. A proper risk assessment will be possible in the long-term follow up after publishing the results of the ongoing CLARION trial.

Recommendations

1. Currently, there are no international recommendations regarding how to reduce the risk of cancer formation in patients with MS treated with DMT.
2. Age over 55 and age-related comorbidities, as well as qualitative changes in the immune system (immunosenescence), are risk factors for cancer development.
3. There is insufficient data on the risk of cancer formation from clinical trials in patients over 55 on DMT, which should be reported to patients in this population.
4. Data on the long-term safety of DMT must be collected because the two-year duration of clinical registration trials is insufficient to assess cancer risk.
5. The increasing age of the patient, the duration of therapy, and the number of previously used drugs, especially those with an immunosuppressive mechanism, may lead to an accumulation of the risk of cancer formation.
6. Considering the immunological mechanism of action of individual DMTs, special caution should be exercised in the cases of therapy with alemtuzumab, cladribine, S1P receptor modulators, and natalizumaband anti-CD20 antibodies.
7. If cancer occurs, most DMTs should be discontinued. In a patient with active malignancy, alemtuzumab, cladribine, S1P receptor modulators, natalizumab and anti-CD20 antibodies should not be used in the treatment of MS.

*Beta interferons, glatiramer acetate, dimethyl fumarate and teriflunomide are however not contraindicated.

8. The concomitant use of DMT with anti-cancer drugs has not been studied.
9. Possible DMT continuation/switching in a patient with MS and cancer should lead to consultation with an oncologist to choose the optimal therapy considering the existing cancer disease and the risk of possible rebound effects in the course of MS.
10. The effect of anti-cancer treatment on MS has not been studied.

**Preparations of alemtuzumab, cladribine, ofatumumab and ocrelizumab are used to treat cancers of the bone marrow and the lymphatic system.

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