

Supplementary Materials

Systematic review and network meta-analysis (NMA) for cladribine tablets in achieving sustained disability improvement (SDI) in multiple sclerosis

Table S.1. Description of systematic review method.

| Item | Description |
|--|--|
| Last search date | 6 July 2021 yr |
| Information sources | Medline/Pubmed-not-MEDLINE and EMBASE (via Elsevier) and CENTRAL (Cochrane Central Register of Controlled Trials), references of identified publications |
| Keywords | <p>Interventions: ocrelizumab, alemtuzumab, cladribine, natalizumab, fingolimod</p> <p>Disease: multiple sclerosis</p> <p>Outcome: 'disability improvement' OR 'improvement of disability'; 'disability improved' OR 'improved disability'; 'edss improvement' OR 'improvement of edss'; 'expanded disability status scale improvement' OR 'improvement of expanded disability status scale'; 'expanded disability status scale improvement' OR 'improvement of expanded disability status scale'; 'improved edss' OR 'edss improved'; 'improved expanded disability status scale' OR 'expanded disability status scale improved'; 'edss regression' OR 'regression of edss'; 'expanded disability status scale regression' OR 'regression of expanded disability status scale'; 'accumulation of disability' OR 'disability accumulation'; 'disability regression' OR 'regression of disability'</p> |
| Date Restrictions | none |
| Languages | English or Polish |
| Population | relapsing multiple sclerosis |
| Intervention | cladribine in tablets* [CT] |
| Comparators | fingolimod* [FTY] natalizumab* [NAT] alemtuzumab* [ALE] ocrelizumab* [OKR] |
| Outcome | sustained disability improvement (SDI) in EDSS confirmed after 6 months – SDI6 |
| Study design | randomized controlled clinical trials, non-RCTs with the control group |
| Method of heterogeneity testing for samples used in an indirect comparison | DIC (Deviance Information Criterion) |
| Number of persons involved in data search and extraction | 2 analysts; uncertainties resolved with the help of the third analyst |

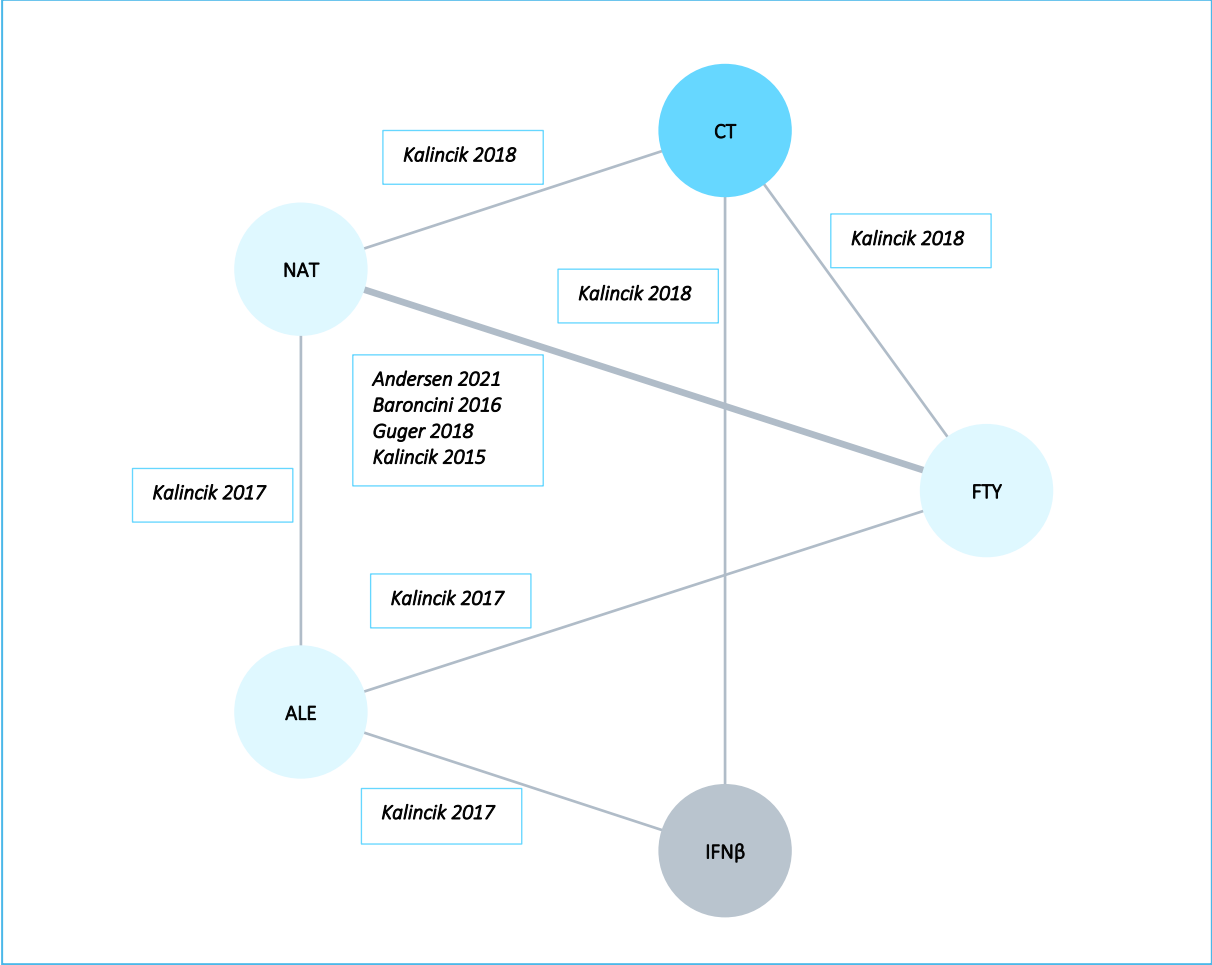
* dosed according to the actual version of the Summary of Product Characteristics (SmPC)

Table S.2. Definitions of sustained disability improvement (SDI) in included studies.

| Study | Definition |
|------------------------------------|---|
| Kalincik et al. (2018) | a decrease in EDSS by 1 step (1.5 step if baseline EDSS was 1.5 and 0.5 step if baseline EDSS was >6; decrease from EDSS step 1 to step 0 was not to be evaluated as confirmed disability improvement) confirmed by subsequent EDSS scores over ≥ 6 months |
| Guger et al. (2018) | a decrease from baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score >5.5) confirmed after 6 months |
| Kalincik et al. (2015) | decrease of ≥ 1 EDSS step (1.5 EDSS step if baseline EDSS was 1.5) sustained for ≥ 6 months |
| Kalincik et al. (2017) | a decrease in EDSS by 1 step (1.5 step if baseline EDSS was 1.5 and 0.5 step if baseline EDSS was >6; decrease from EDSS step 1 to step 0 was not to be evaluated as confirmed disability improvement) confirmed by subsequent EDSS scores over ≥ 6 months |
| Baroncini et al. (2016) | an EDSS score decrease of ≥ 1 point in patients with baseline EDSS ≥ 1.5 , confirmed after 6 months |
| Andersen et al. (2021) | a decrease by ≥ 1 EDSS step if EDSS at baseline was ≤ 6 and ≥ 1.5 ; ≥ 0.5 step if EDSS at baseline was > 6 ; and 1.5 step if EDSS at baseline was 1.5, of which all should be confirmed by EDSS scores recorded over ≥ 6 months |
| CARE-MS II (Coles et al., 2012) | a decrease from baseline by at least one EDSS point confirmed over 6 months for patients with baseline EDSS scores of at least 2.0 |
| CAMMS223 (Coles et al., 2011) | ≥ 1 point decrease on the EDSS sustained for 6 consecutive months for patients with a baseline EDSS ≥ 2 (patients with a baseline EDSS score of 0 are not assessable) |

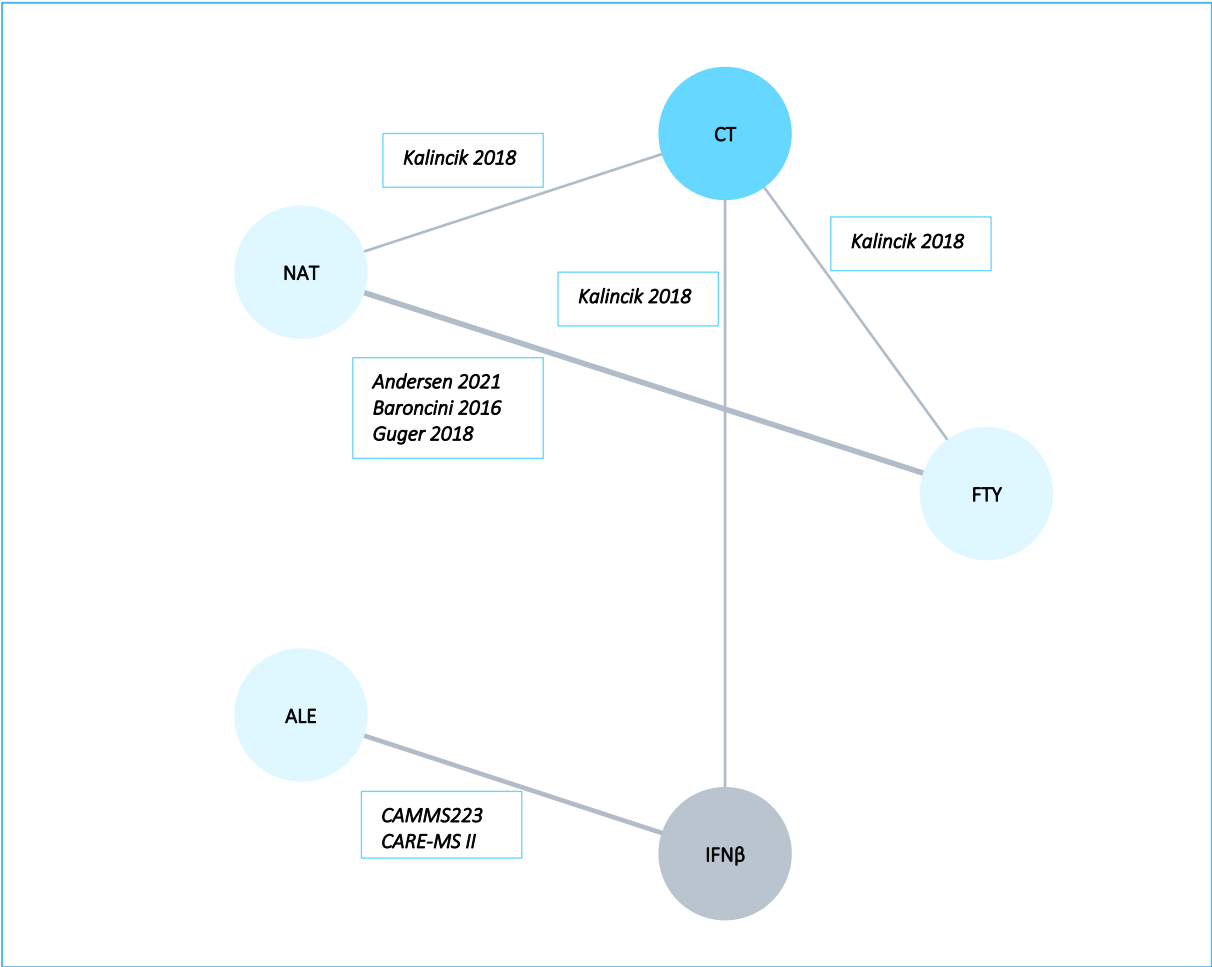
EDSS – Expanded Disability Status Scale

Figure. S.1. Evidence network for the network meta-analysis (NMA) of achieving sustained disability improvement (SDI) – sensitivity analysis 1.



CT – cladribine tablets; FTY – fingolimod; NAT – natalizumab; ALE – alemtuzumab; IFNβ – interferon β.

Figure. S.2. Evidence network for the network meta-analysis (NMA) of achieving sustained disability improvement (SDI) – the sensitivity analysis 2.



CT – cladribine tablets; FTY – fingolimod; NAT – natalizumab; ALE – alemtuzumab; IFNβ – interferon β.

Table S.3. Characteristics of studies included in the indirect comparison.

| Study | Study type | AOTMiT classification; Jadad score/NOS | Follow-up period | Cohorts | Site number | Main inclusion criteria |
|---|---|---|------------------|----------------------------|---------------------|---|
| Andersen et al. (2021) (pooled cohort) | Cohort study weighted by stabilized inverse probability of treatment from longitudinal registries of clinical outcomes data | IVC <u>NOS:</u> S: **** C: ** O: ** | NA | FTY vs NAT: 1479 vs 968 | 129 in 34 countries | RRMS patients (three MS registries: OFSEP, DMSR and MSBase), commenced treatment with either natalizumab or fingolimod for the first time on or after 1st of January 2011; continuous treatment with either natalizumab or fingolimod for 3 months; no prior exposure to immunotherapies with extended effect (mitoxantrone, alemtuzumab, ocrelizumab, daclizumab, rituximab, cyclophosphamide, or cladribine); no prior participation in any interventional randomized controlled trials; exposure to DMD treatment for more than 90 consecutive days within the 12 months immediately prior to commencing natalizumab or fingolimod; sufficient EDSS follow-up (consisting of EDSS recorded 6 months to +1 months of baseline; more than one EDSS assessment recorded on study therapy and more than one EDSS assessment recorded 6 months later (irrespective of the treatment status at that time)). EDSS scores recorded <= 30 days after a prior relapse were ignored. |
| Baroncini et al. (2016) | Cohort study weighted by stabilized inverse probability of treatment calculated from | IIID <u>NOS:</u> | 24 msc | FTY vs NAT: 102 vs 102 | 2 (Italy) | all consecutive patients who started FTY or NAT from June 2011 to February 2014 due to failure of first-line injectable agents (IFNs or glatiramer acetate (GA)) were enrolled in two Italian MS centers |

| Study | Study type | AOTMiT classification; Jadad score/NOS | Follow-up period | Cohorts | Site number | Main inclusion criteria |
|------------------------------------|--|---|--|---|---|---|
| | propensity scores based on longitudinal registries of clinical outcomes data | S: **** C: ** O: ** | | | | (S. Antonio Abate Hospital of Gallarate and S. Raffaele Hospital of Milan) according to European Medicines Agency (EMA) criteria, age ≥ 18 years |
| CAMMS223 (Coles et al., 2011) | RCT | IIA Jadad score: 4 (R2, B1, W1) | 36 msc | ALE 12 mg** vs INF β : 107 vs 107 | multicenter (including Poland) | untreated RRMS (fulfilling the 2001 McDonald diagnostic criteria), disease duration of less than or equal to 3 years, at least two relapses in the previous 2 years, and evidence of at least one gadolinium-enhancing lesion EDSS ≤ 3.0 |
| CARE-MS II (Coles et al., 2012) | RCT | IIA Jadad score: 4 (R2, B1, W1) | 24 msc | INF β vs ALE 12 mg**: 202 vs 426 | 194 in 23 countries (including Poland) | RRMS (fulfilling the 2005 McDonald diagnostic criteria), disease duration of 10 years or less, ≥ 2 attacks in the previous 2 years with at least one in the previous year, at least one relapse while on interferon beta or glatiramer after at least 6 months of treatment, cranial and spinal MRI lesions fulfilling protocol-defined criteria, age 18–55 years, EDSS ≤ 5.0 |
| Guger et al. (2018) | Cohort study with propensity score matching based on longitudinal registries of clinical outcomes data | IIID <u>NOS</u> : S: *** C: ** O: *** | mean \pm SD: FTY: 23.4 \pm 1.1 msc NAT: 23.5 \pm 1.1 msc | FTY vs NAT: 332 vs 246 | multicenter (Austria) | all RRMS patients, who started treatment with natalizumab or fingolimod in the AMSTR from 2011 and stayed on therapy for at least 24 months |
| Kalincik et al. (2015) | Cohort study with propensity score matching based on longitudinal | IIID/ <u>NOS</u> : | median: FTY: 14 msc NAT: 21 msc | FTY vs NAT: 171 vs 407 | 45* (international) | RRMS patients (MSBase register) who had switched therapy from interferon β or glatiramer acetate to either natalizumab or fingolimod (treatment gap < 3 |

| Study | Study type | AOTMiT classification; Jadad score/NOS | Follow-up period | Cohorts | Site number | Main inclusion criteria |
|------------------------|--|---|--|--|---------------------|---|
| | registries of clinical outcomes data | S: **** C: ** O: *** | | | | months; no unified escalation protocol was used) after on-treatment relapse and/or progression of disability documented within the preceding 6 months ^^, Minimum 3-month persistence on natalizumab or fingolimod was required, The minimal required dataset# |
| Kalincik et al. (2017) | Cohort study with propensity score matching based on longitudinal registries of clinical outcomes data | IIID <u>NOS:</u> S: **** C: ** O: *** | median: ALE vs FTY: 1.7 yrs ALE vs INFβ: 2.1 yrs ALE vs NAT: 2.1 yrs | ALE vs FTY: 114 vs 195 ALE vs INFβ: 156 vs 282 ALE vs NAT: 138 vs 223 | 77* (international) | RRMS patients (MSBase register): ≥ relapse in the year before treatment, time from first symptom up to 10 years, age ≤ 65 yrs, exposure to one of the study therapies (alemtuzumab, interferon beta, fingolimod, natalizumab), no previous haemopoietic stem cell transplantation, no participation in randomized clinical trials, minimum required recorded follow-up (12 months before the start of treatment and two on treatment disability scores ≥6 months apart), EDSS ≤ 6.5, the minimal required dataset#, 6 months or longer of continuous study therapy |
| Kalincik et al. (2018) | Cohort study with propensity score matching from longitudinal registries of clinical outcomes data | IIID <u>NOS:</u> S: *** C: ** O: *** | 1 yr | CT vs FTY: 32 vs 258 CT vs INFβ: 22 vs 167 CT vs NAT: 26 vs 174 | 57* (international) | Relapsing MS patients (MSBase register): exposure to one of the study therapies (cladribine, interferon β, fingolimod, natalizumab), ≥1 year of continuous study monotherapy (in the cladribine group, patients were considered to be treated for 1 year after their exposure to oral cladribine), |

| Study | Study type | AOTMiT classification; Jadad score/NOS | Follow-up period | Cohorts | Site number | Main inclusion criteria |
|-------|------------|--|------------------|---------|-------------|--|
| | | | | | | no prior exposure to alemtuzumab, mitoxantrone, rituximab or haematopoietic stem cell transplantation, minimum required recorded follow-up (3 months prior to starting treatment and two disability scores ≥ 6 months apart with at least one score recorded while on the study therapy), the minimal required dataset# |

* calculated from the available data;

** cohort administered ALE at dose 12 mg, according to the actual version of the Summary of Product Characteristics (SmPC);

^^ The pre-switch disability progression was defined as an increase in the Expanded Disability Status Scale (EDSS) by at least 1 step over the year immediately preceding the baseline (no EDSS scores recorded within 30 days of a clinical relapse were included);

The minimal required dataset consisted of sex, age, time of first symptoms, dates of clinical relapses, clinical MS course, disability quantified with EDSS

NOS - Newcastle-Ottawa quality assessment scale cohort studies: S – selection (max.: ****), C – comparability (max.: **), O – outcome (max.: ***); Jadad score: R – randomization, B – blinding, W – withdrawals;

AOTMiT - The Agency for Health Technology Assessment and Tariff System; CT – cladribine tablets; FTY – fingolimod; NAT – natalizumab; ALE – alemtuzumab; INF β – interferon β ; RRMS – relapsing-remitting multiple sclerosis; EDSS – Expanded Disability Status Scale; NA – not available

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Table S.4. Baseline characteristics of subjects in trials included in the indirect comparison.

| Study | Intervention, N | Age (years), mean (SD) | Disease duration (years) | Disease course, n (%) | Female, n (%) | Disability, EDSS | Previous therapies, no. |
|---------------------------------------|---------------------|------------------------|-----------------------------------|-----------------------|---------------|--|---|
| Andersen et al. (2021) [^] | NAT (N = 968) | 38.8 (10.5) | mean: 9.0 (SD: 7.8) | RRMS: 968 (100%) | 681* (70.3%) | mean: 2.71 (SD: 1.50) | mean: 1.61 (SD: 0.84) |
| | FTY (N = 1479) | 38.6 (9.5) | mean: 8.9 (SD: 6.8) | RRMS: 1479 (100%) | 1050* (71.0%) | mean: 2.65 (SD: 1.57) | mean: 1.62 (SD: 0.84) |
| Baroncini et al. (2016) ^{^^} | FTY (N = 102) | 38.1 (9.3) | mean: 11.2 (SD: 7.8; range: 1-33) | RRMS: 102 (100%) | 77 (75.5%*) | median: 2.0 (IQR: 1.5 - 3.0) | NA |
| | NAT (N = 102) | 37.7 (9.3) | mean: 10.3 (SD: 6.2; range: 2-28) | RRMS: 102 (100%) | 73 (71.6%*) | median: 2.0 (IQR: 1.5 - 2.5) | NA |
| CAMMS22 3 (Coles et al., 2011) | ALE 12 mg (N = 107) | 32.2 (8.01) | NA | RRMS: 107 (100%) | 69 (64%) | mean: 1.9 (SD: 0.75) median: 2.0 (range: 0.0-3.0) | 0 |
| | INFβ (N = 107) | 32.9 (8.94) | NA | RRMS: 107 (100%) | 70 (65%) | mean: 1.9 (SD: 0.84) median: 2.0 (range: 0.0-3.5) | 0 |
| CARE-MS II (Coles et al., 2012) | INFβ (N = 202) | 35.8 (8.77) | mean: 4.7 (SD: 2.86) | RRMS: 107 (100%) | 131 (65%) | mean: 2.7 (SD: 1.21) | mean: 1 (SD: 0.6) median: 1 (range: 1-4) |
| | ALE 12 mg (N = 426) | 34.8 (8.36) | mean: 4.5 (SD: 2.68) | RRMS: 107 (100%) | 281 (66%) | mean: 2.7 (SD: 1.26) | mean: 1 (SD: 0.7) median: 1 (range: 1-4) |
| Guger et al. (2018) ^{^^} | FTY (N = 332) | 39.3 (9.8) | mean: 9.9 (SD: 7.2) | RRMS: 332 (100%) | 226 (68.1%) | mean: 2.7 (SD: 1.5) | NA |
| | NAT (N = 246) | 34.1 (10.3) | mean: 6.6 (SD: 5.7) | RRMS: 246 (100%) | 174 (70.7%) | mean: 2.5 (SD: 1.6) | NA |
| Kalincik et al. (2015) ^{^^} | NAT (N = 407) | 37 (9) | mean: 9.4 (SD: 6.2) | RRMS: 407 (100%) | 301* (74%) | mean: 3.4 (SD: 1.5) median: 3.5 (IQR: 2.0 - 4.0) | NA |
| | FTY (N = 171) | 38 (10) | mean: 9.5 (SD: 8.0) | RRMS: 171 (100%) | 127* (74%) | mean: 3.1 (SD: 1.7) median: 3.0 (IQR: 2.0 - 4.0) | NA |
| | ALE (N = 156) | 33 (8) | median: 3.1 (IQR: 1.9; 6) | RRMS: 156 (100%) | 110 (71%) | median: 3.0 (IQR: 2 - 4) | median: 0 (IQR: 0 - 1) |

| Study | Intervention, N | Age (years), mean (SD) | Disease duration (years) | Disease course, n (%) | Female, n (%) | Disability, EDSS | Previous therapies, no. |
|--------------------------------------|-----------------|------------------------|-------------------------------|-----------------------------------|---------------|--------------------------------|-------------------------|
| Kalincik et al. (2017) ^{^^} | INFβ (N = 282) | 33 (9) | median: 2.8 (IQR: 1.3; 6.5) | RRMS: 282 (100%) | 209 (74%) | median: 3.0 (IQR: 2 - 4) | median: 0 (IQR: 0 - 1) |
| | ALE (N = 114) | 33 (8) | median: 3.9 (IQR: 2.4; 6.6) | RRMS: 114 (100%) | 82 (72%) | median: 3.0 (IQR: 1.6 - 4.0) | median: 1 (IQR: 0 - 1) |
| | FTY (N = 195) | 34 (10) | median: 4.2 (IQR: 1.6; 8.1) | RRMS: 195 (100%) | 142 (73%) | median: 3.0 (IQR: 1.5 - 4.5) | median: 1 (IQR: 0 - 2) |
| | ALE (N = 138) | 33 (9) | median: 3.3 (IQR: 2.1; 6.3) | RRMS: 138 (100%) | 97 (70%) | median: 3.0 (IQR: 2.0 - 4.5) | median: 0 (IQR: 0 - 1) |
| | NAT (N = 223) | 33 (10) | median: 2.7 (IQR: 1.0; 7.6) | RRMS: 223 (100%) | 147 (66%) | median: 3.0 (IQR: 2.0 - 4.5) | median: 0 (IQR: 0 - 1) |
| Kalincik et al. (2018) ^{^^} | CT (N = 32) | 50 (SD: 10) | median: 14.1 (IQR: 7.6; 23.8) | RRMS: 24 (75%) SPMS: 8 (25%) | 26 (81%) | median: 4.5 (IQR: 3 - 6) | median: 2 (IQR: 1 - 3) |
| | FTY (N = 258) | 48 (SD: 8) | median: 13.8 (IQR: 8; 19.5) | RRMS: 216 (84%) SPMS: 42 (16%) | 201 (78%) | median: 3.5 (IQR: 2 - 5.5) | median: 2 (IQR: 1 - 3) |
| | CT (N = 26) | 50 (SD: 9) | median: 14 (IQR: 6.2; 17.9) | RRMS: 22 (85%) SPMS: 4 (15%) | 20 (77%) | median: 4 (IQR: 2 - 6) | median: 1 (IQR: 1 - 3) |
| | NAT (N = 174) | 44 (SD: 10) | median: 10 (IQR: 4.5; 17.2) | RRMS: 154 (89%) SPMS: 20 (11%) | 125 (72%) | median: 3.5 (IQR: 2 - 5.5) | median: 1 (IQR: 1 - 2) |
| | CT (N = 22) | 49 (10) | median: 13.5 (IQR: 5.6; 18.3) | RRMS: 19 (86%) SPMS: 3 (14%) | 17 (77%) | median: 3.75 (IQR: 2.25 - 5.9) | median: 1 (IQR: 1 - 2) |
| | INFβ (N = 167) | 45 (8) | median: 11.2 (IQR: 6.5; 17.1) | RRMS: 151 (90%) SPMS: 16 (10%) | 125 (75%) | median: 3.5 (IQR: 2 - 4.5) | median: 1 (IQR: 1 - 2) |

* calculated from the available data;

[^] weighted by sIPTW (stabilized inverse probability of treatment weighting) calculated from propensity scores;

^{^^} matched by propensity score;

CT – cladribine tablets; FTY – fingolimod; NAT – natalizumab; ALE – alemtuzumab; INFβ – interferon β; RRMS – relapsing-remitting multiple sclerosis; SPMS – secondary-progressive multiple sclerosis; IQR – interquartile range; SD – standard deviation; EDSS – Expanded Disability Status Scale; NA – not available

Table S.5. Indirect comparison results of achieving sustained disability improvement (SDI); main and sensitivity analyses (model with lower DIC value is preferred - underlined).

| Comparison/analysis | HR (95% CrI) | |
|------------------------|------------------------------------|-------------------------------------|
| | <u>Model fixed</u> DIC = 29,594 | <u>Model random</u> DIC = 21,038 |
| Main analysis | | |
| CT vs FTY | 4,85 (2,75; 8,58) | 4,98 (2,11; 11,79) |
| CT vs NAT | 3,33 (1,89; 5,86) | 3,12 (1,31; 7,27) |
| CT vs ALE | 9,57 (4,97; 18,51) | 9,29 (3,40; 25,21) |
| CT vs INF β | 15,22 (7,64; 30,38) | 15,74 (5,52; 45,12) |
| Sensitivity analysis 1 | <u>Model fixed</u> DIC = 20,046 | <u>Model random</u> DIC = 17,758 |
| CT vs FTY | 5,17 (2,93; 9,14) | 5,38 (2,29; 12,87) |
| CT vs NAT | 3,55 (2,01; 6,25) | 3,42 (1,44; 7,97) |
| CT vs ALE | 10,54 (5,45; 20,39) | 10,73 (3,91; 30,13) |
| CT vs INF β | 10,64 (5,16; 21,94) | 11,34 (3,75; 36,19) |
| Sensitivity analysis 2 | <u>Model fixed</u> DIC = 11,966 | <u>Model random</u> DIC = 13,720 |
| CT vs FTY | 4,28 (2,31; 7,94) | 4,37 (2,03; 9,85) |
| CT vs NAT | 3,70 (2,01; 6,83) | 3,58 (1,62; 7,72) |
| CT vs ALE | 6,28 (1,48; 26,82) | 6,29 (1,21; 32,63) |
| CT vs INF β | 15,00 (3,71; 60,81) | 14,93 (3,21; 69,14) |

HR – hazard ratio; CrI – credible interval; DIC – deviance information criterion; CT – cladribine tablets; FTY – fingolimod; NAT – natalizumab; ALE – alemtuzumab; INF β – interferon β ; Sensitivity analysis 1: excluded randomized trials CARE-MS II (Coles et al., 2012) and CAMMS223 (Coles et al., 2011) trials, which differed in methodology from the others; Sensitivity analysis 2: excluded trials other than Kalincik et al. (2018), which assessed subjects data from MSBase registry to avoid multiple subjects participation (in the case of the Andersen et al. (2021) study, instead of presenting total results, which also included the MSBase registry, only results from the other two registries were used - DMSTR and OFSEP)

Table S.6. Input data for the NMA.

| Study | Comparison | HR (95% CI) | lnHR* | se lnHR* |
|---|--------------------|--------------------|-------------|-------------|
| Kalincik et al. (2018) | CT vs INF β | 15 (3.6 - 59) | 2.7080502 | 0.713432 |
| | CT vs FTY | 3.9 (1.6 - 9.6) | 1.3609766 | 0.45709 |
| | CT vs NAT | 4 (1.8 - 9.2) | 1.3862944 | 0.416185 |
| Baroncini et al. (2016) | | 2.82 (1.01 - 7.86) | 1.0367369 | 0.523437 |
| Guger et al. (2018) | | 1.04 (0.71 - 1.52) | 0.0392207 | 0.194187 |
| Kalincik et al. (2015) | | 2.8 (1.7 - 4.6) | 1.0296194 | 0.25394 |
| Andersen et al. (2021) (MSBase, OFSEP, DMSTR) | NAT vs FTY | 1.4 (1.08 - 1.8) | 0.3364722 | 0.130315 |
| Andersen et al. (2021) (DMSTR cohort) | | 1.11 (0.79 - 1.57) | 0.104360015 | 0.175206779 |
| Andersen et al. (2021) (OFSEP cohort) | | 1.57 (0.62 - 3.96) | 0.451075619 | 0.47303926 |
| Kalincik et al. (2017) | ALE vs NAT | 0.35 (0.2 - 0.59) | -1.049822 | 0.275976 |
| | ALE vs FTY | 0.5 (0.25 - 1.01) | -0.693147 | 0.356191 |
| | | 0.98 (0.65 - 1.49) | -0.020203 | 0.211626 |
| CARE-MS II (Coles et al., 2012) | ALE vs INF β | 2.57 (1.57 - 4.2) | 0.943905899 | 0.251027293 |
| CAMMS223 (Coles et al., 2011) | | 2.14 (1.18 - 3.9) | 0.7608058 | 0.30497 |

* calculated from the available data; HR – hazard ratio; CI – confidence interval; CT – cladribine tablets; FTY – fingolimod; NAT – natalizumab; ALE – alemtuzumab; INF β – interferon β

Figure. S.3. League tables showing the results of the NMA comparing the effects of all drugs including hazard ratios (HR) and 95% credible intervals (95% CrI); sensitivity analysis 1 (random model). Statistically significant results are bolded.

| | | | | |
|---------------------------------------|--------------------------------------|-----------------------|-----------------------|-------------|
| CT | | | | |
| 3.42 (1.44 - 7.97) | NAT | | | |
| 5.38 (2.29 - 12.87) | 1.57 (0.99 - 2.66) | FTY | | |
| 10.73 (3.91 - 30.13) | 3.14 (1.48 - 7.03) | 1.99 (0.90 - 4.38) | ALE | |
| 11.34 (3.75 - 36.19) | 3.32 (1.18 - 10.36) | 2.11 (0.72 - 6.42) | 1.06 (0.43 - 2.73) | INFβ |

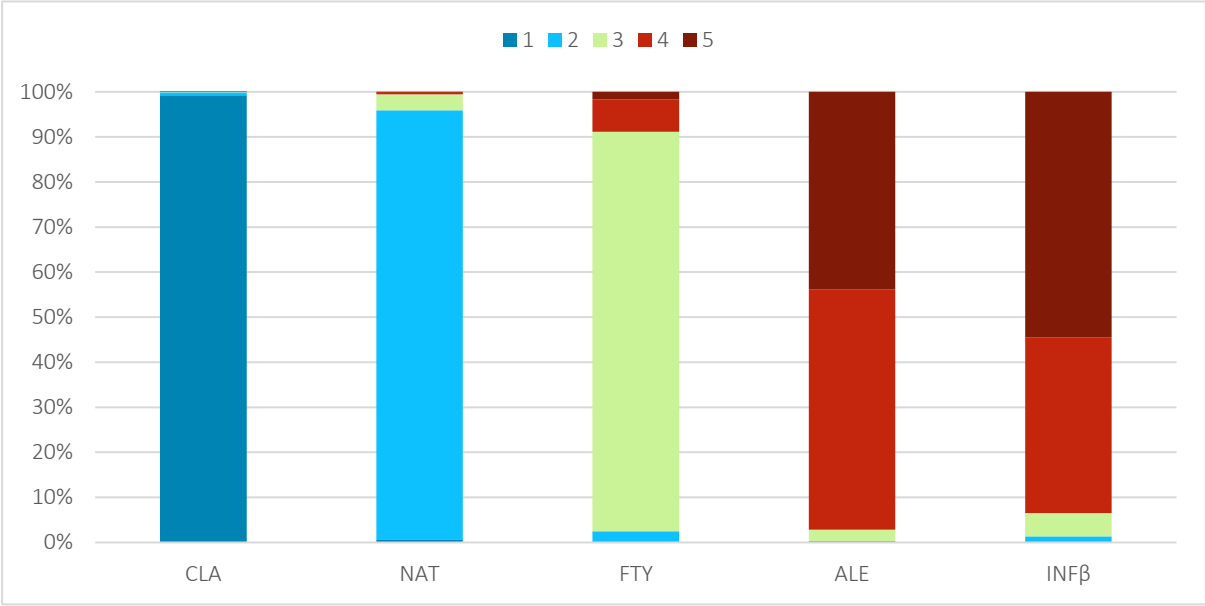
CT – cladribine tablets; FTY – fingolimod; NAT – natalizumab; ALE – alemtuzumab; INFβ – interferon β.

Figure. S.4. League tables showing the results of the NMA comparing the effects of all drugs including hazard ratios (HR) and 95% credible intervals (95% CrI); sensitivity analyses 2 (fixed model). Statistically significant results are bolded.

| | | | | |
|--------------------------------|------------------------|------------------------|------------------------------|-------------|
| CT | | | | |
| 3.70 (2.01 - 6.83) | NAT | | | |
| 4.28 (2.31 - 7.94) | 1.16 (0.91 - 1.46) | FTY | | |
| 6.28 (1.48 - 26.82) | 1.70 (0.35 - 8.20) | 1.47 (0.30 - 7.09) | ALE | |
| 15.00 (3.71 - 60.81) | 4.05 (0.88 - 18.63) | 3.50 (0.76 - 16.12) | 2.39 (1.63 - 3.49) | INFβ |

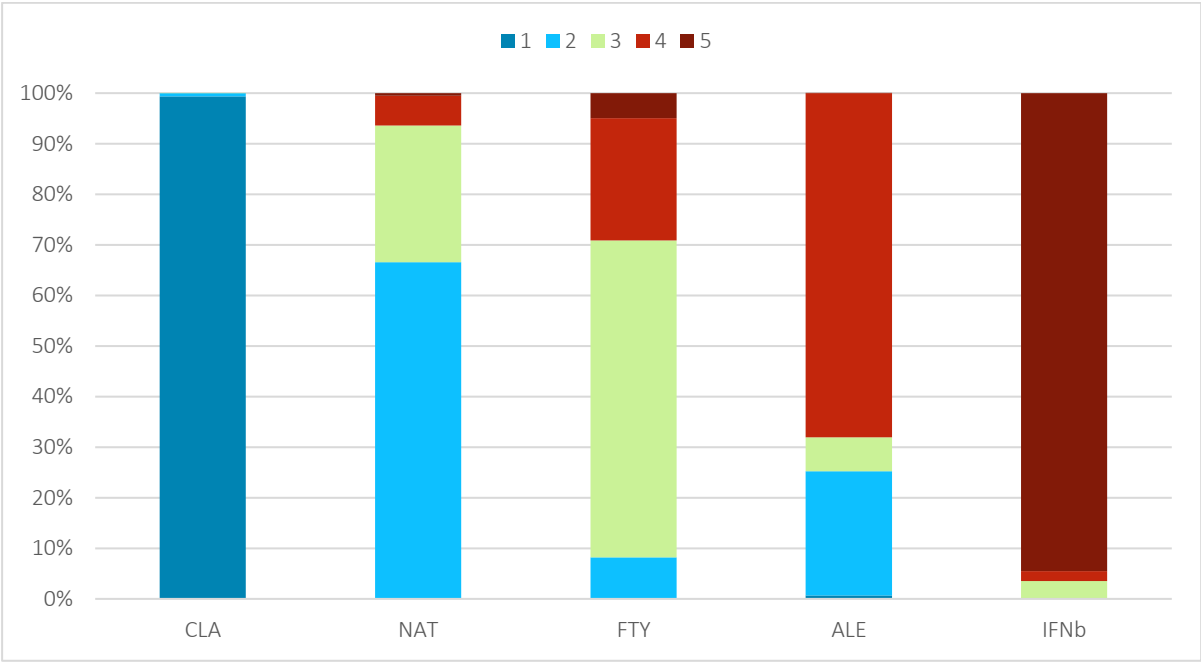
CT – cladribine tablets; FTY – fingolimod; NAT – natalizumab; ALE – alemtuzumab; INFβ – interferon β.

Figure. S.5. Rankogram for the treatment efficacy of achieving sustained disability improvement (SDI) in the NMA, sensitivity analysis 1 (random model).



CT – cladribine tablets; FTY – fingolimod; NAT – natalizumab; ALE – alemtuzumab; INFβ – interferon β.

Figure. S.6. Rankogram for the treatment efficacy of achieving sustained disability improvement (SDI) in the NMA, sensitivity analysis 2 (fixed model).



CT – cladribine tablets; FTY – fingolimod; NAT – natalizumab; ALE – alemtuzumab; IFNβ – interferon β.

Table S.7. Ranking probability of each treatment effect, with rank 1 being the best and rank 5 being the worst, and the surface under the cumulative ranking (SUCRA) curve (preferred model with lower DIC value is presented).

| Intervention | 1 | 2 | 3 | 4 | 5 | SUCRA |
|--|-------|-------|-------|-------|-------|-------|
| Main analysis (random model) | | | | | | |
| CT | 99.2% | 0.7% | 0.1% | 0.0% | 0.0% | 99.8% |
| NAT | 0.7% | 96.0% | 3.1% | 0.2% | 0.0% | 74.3% |
| FTY | 0.0% | 2.8% | 91.5% | 4.9% | 0.8% | 49.1% |
| ALE | 0.0% | 0.5% | 4.9% | 91.2% | 3.4% | 25.6% |
| INF β | 0.0% | 0.1% | 0.5% | 3.7% | 95.7% | 1.2% |
| Sensitivity analysis 1 (random model) | | | | | | |
| CT | 99.3% | 0.6% | 0.1% | 0.0% | 0.0% | 99.8% |
| NAT | 0.6% | 95.3% | 3.6% | 0.4% | 0.1% | 74.0% |
| FTY | 0.1% | 2.4% | 88.7% | 7.2% | 1.7% | 48.0% |
| ALE | 0.0% | 0.3% | 2.5% | 53.4% | 43.8% | 14.9% |
| INF β | 0.0% | 1.3% | 5.2% | 39.0% | 54.4% | 13.4% |
| Sensitivity analysis 2 (fixed model) | | | | | | |
| CT | 99.3% | 0.6% | 0.0% | 0.0% | 0.0% | 99.8% |
| NAT | 0.0% | 66.6% | 27.0% | 5.9% | 0.5% | 64.9% |
| FTY | 0.0% | 8.2% | 62.7% | 24.2% | 4.9% | 43.5% |
| ALE | 0.7% | 24.6% | 6.7% | 68.0% | 0.0% | 39.5% |
| INF β | 0.0% | 0.0% | 3.5% | 1.9% | 94.5% | 2.3% |

CT – cladribine tablets; FTY – fingolimod; NAT – natalizumab; ALE – alemtuzumab; INF β – interferon β

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