Targeted biologics for chronic rhinosinusitis with nasal polyps: efficacy and safety comparison of eight monoclonal antibodies via network meta-analysis

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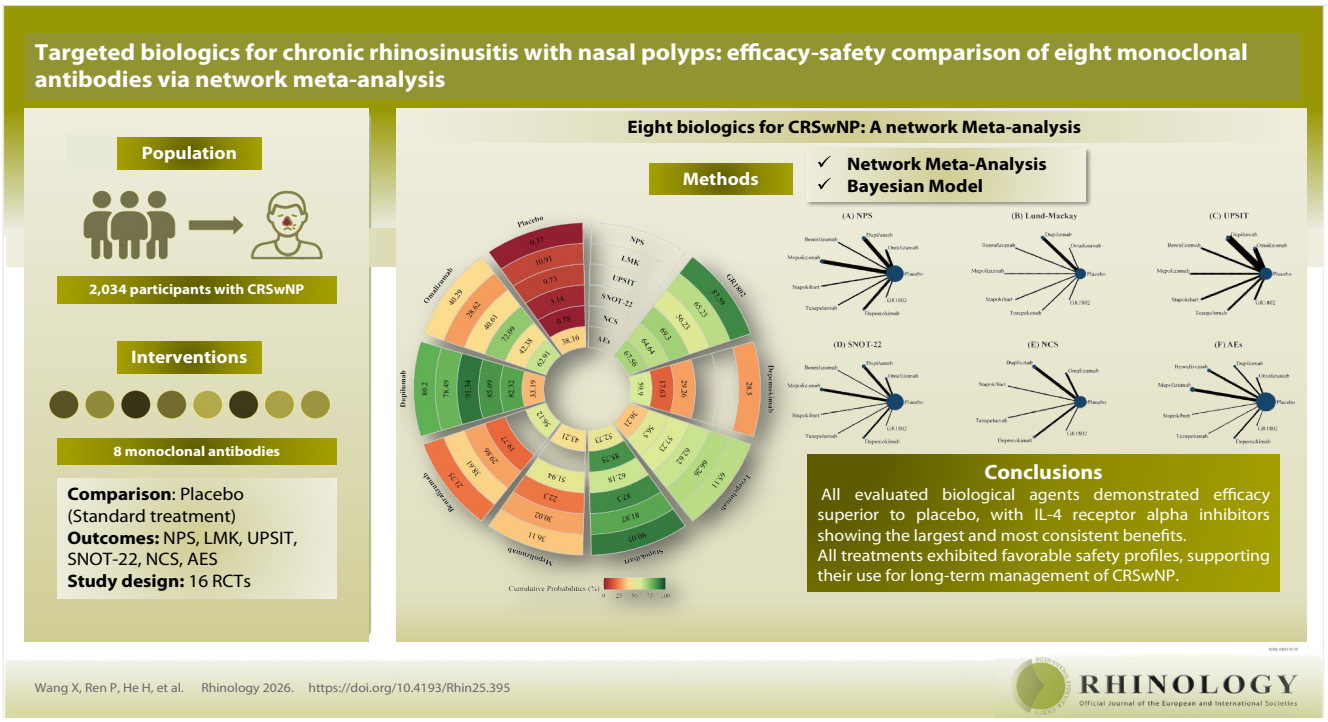

Abstract

Background: Biologics targeting key type 2 inflammatory mediators (e.g., IL-4Rα, IgE, IL-5, TSLP) represent a novel therapeutic approach for chronic rhinosinusitis with nasal polyps (CRSwNP). This network meta-analysis (NMA) aimed to compare the efficacy and safety of eight monoclonal antibodies for CRSwNP.

Methodology: We systematically searched PubMed, Embase, Web of Science, CENTRAL Cochrane, and MEDLINE for randomized controlled trials (RCTs) comparing monoclonal antibodies with placebo CRSwNP. A Bayesian Network meta-analysis (NMA) was performed using the R gemtc package.

Results: Sixteen RCTs (n=2,034) evaluating eight monoclonal antibodies were included. All biologics significantly reduced Nasal Polyp Score (NPS); stapokibart (anti-IL-4Rα) ranked first. Both dupilumab and stapokibart improved the University of Pennsylvania Smell Identification Test (UPSIT) score, indicating a recovery of olfactory function. Dupilumab led in improving Sino-Nasal Outcome Test-22 (SNOT-22) scores, whereas stapokibart was most effective in relieving nasal congestion score (NCS). The risk of adverse events was comparable to placebo across all biologics, with GR1802 exhibiting the most favorable safety.

Conclusions: All evaluated biological agents demonstrated efficacy superior to placebo, with IL-4 receptor alpha inhibitors showing the largest and most consistent benefits. All treatments exhibited favorable safety profiles, supporting their use for long-term management of CRSwNP.

Key words: antibodies, monoclonal, rhinosinusitis, nasal polyps

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a disease characterized by chronic inflammation of the nasal mucosa and sinuses, characterized by the presence of nasal polyps, and symptoms such as nasal obstruction, loss of smell, facial pain or pressure, and rhinorrhea [1]. As a condition primarily driven by type 2 inflammation [2], CRSwNP poses a substantial burden on patients' health and well-being. Persistent nasal congestion, loss of smell, rhinorrhea, headache, sleep disorders and other symptoms seriously affect the quality of life of patients [3]. Comorbidities are common, approximately 65% of CRSwNP patients had asthma and 26% had nonsteroidal anti-inflammatory drug- exacerbated respiratory disease (NSAID-ERD), implying higher severity and recurrence rates [3]. In addition, CRSwNP is frequently accompanied by psychological comorbidities such as depression, anxiety and other psychological disorders [4]. Olfactory dysfunction, one of the most prevalent and persistent symptoms, profoundly affects daily functioning [1] and has been independently linked to poorer quality of life, and higher levels of anxiety, and depression in patients with upper airway disease [5]. Furthermore, the loss of smell may impair the ability to detect environmental hazards, thereby increasing safety risks [6].

Current treatment strategies for CRSwNP include pharmacotherapy, surgery and biological therapy [7]. First-line management typically consists of intranasal corticosteroids (INCS) combined with saline irrigation, which is effective in many patients with mild to moderate symptoms [1]. However, approximately 30% of patients exhibit an inadequate response to corticosteroid-based regimens and require escalation to second-line therapy such as short-term oral corticosteroids (OCS) or functional endoscopic sinus surgery (FESS) to alleviate mechanical obstruction [1]. Although surgery can effectively remove polyps, postoperative recurrence rates remain high, ranging from 20% to 60% [8, 9], and its efficacy is often limited in patients with predominant type 2 inflammation [10]. A key shortcoming of conventional treatments is their incomplete suppression of the type 2 inflammatory pathway, which may manifested as persistent elevations in blood or tissue eosinophils, or total IgE [1]. In this context, monoclonal antibodies that specifically target key cytokines of type 2 inflammation have shown considerable clinical benefit by addressing this underlying pathological mechanism [11].

Several monoclonal antibodies targeting type 2 inflammatory pathways have demonstrated promise in CRSwNP, including dupilumab (anti-IL-4Rα), mepolizumab (anti-IL-5), omalizumab (anti-IgE), among others [12-14]. By inhibiting specific inflammatory mediators, these biologics have been shown to reduce nasal polyp burden, improve nasal congestion and olfactory function, and decrease the risk of asthma exacerbations [14]. Despite these advances, important clinical questions remain unresolved. The comparative efficacy, safety profiles, and optimal patient selection criteria for different monoclonal antibodies are not yet clearly established. Most available evidence focused on comparing single agents to placebo or conventional treatments, and there is a notable lack of high-quality direct comparisons between two or more biologic agents. Network meta-analysis (NMA) offers a robust methodological framework for synthesizing evidence across multiple interventions, enabling indirect comparisons and hierarchical ranking of treatments in the absence of head-to-head trials [15]. The purpose of this study is to construct an NMA model for monoclonal antibodies in CRSwNP, and to systematically evaluate their relative effects on symptom relief, quality of life and risk of adverse reactions, thereby providing evidence to support informed clinical decision-making.

Materials and methods

Materials and methods

We performed a systematic review and network meta-analysis (NMA) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16, 17]. The research protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251013133.

Search strategy and selection process

We conducted comprehensive searches in PubMed, Embase, Web of Science, CENTRAL Cochrane, and MEDLINE from inception to April 3rd, 2025, without language restrictions applied. The search strategy incorporated a combination of relevant keywords and Medical Subject Headings (MeSH) terms. Two authors trained in evidence-based medicine independently screened titles and abstracts to assess eligibility the inclusion criteria for this systematic review. Subsequently, they evaluated the full-text articles against eligibility criteria using the PICOS framework. Any discrepancies were resolved through discussion with a third reviewer.

Inclusion and exclusion criteria

Studies meeting the following criteria were included: a) Population: Patients with CRSwNP; b) Interventions and comparators: studies comparing monoclonal antibody therapy(biologics) with placebo; c) Study design: RCTs; d) Language: Articles written and published in English; and e) Outcomes: Reporting at least one of the following endpoints: nasal polyp score (NPS), Lund-Mackay computed tomography score, University of Pennsylvania Smell Identification Test (UPSIT), Sino-Nasal Outcome Test-22 (SNOT-22), nasal congestion score (NCS), or adverse events (AEs). Studies were excluded for the following reasons: a) Duplicate publications; b) insufficient key data that could not be obtained from the authors; or c) unavailability of the full text.

Data collection

Data were independently extracted by five authors using a

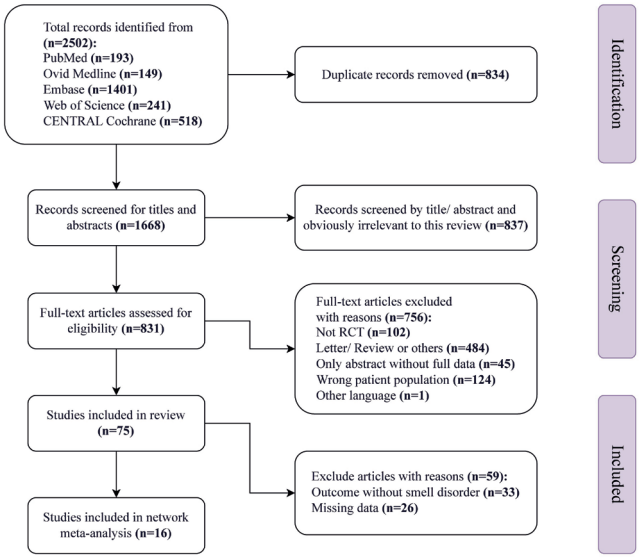

Figure 1. Study Selection Flowchart. This PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram illustrates the process of identifying and selecting randomized controlled trials (RCTs) for inclusion in the network meta-analysis. The diagram details the number of records identified through database searching, screened for eligibility, assessed as full-text, and ultimately included in the quantitative synthesis, along with the reasons for exclusion at each stage.

standardized form. The extracted information included the following fields: a) General information: article title, publication year, journal; b) Study characteristics: sample size, population, intervention details (dose, frequency, duration); c) Participant characteristics: age, sex, history of nasal polyp surgery, prevalence of aspirin-exacerbated respiratory disease (AERD) and asthma, baseline NPS and SNOT-22; d) Outcome data: mean changes from baseline for continuous variables (NPS, LMK, SNOT-22, UPSIT, NCS) and counts of categorical variable (AEs). Data extraction rules: a) Data for primary efficacy endpoints were prioritized for extraction; b) When a study did not clearly define a primary endpoint or reported multiple time points, we prioritized extracting data at the end of treatment or at the longest follow-up time point reported across all assessments. Any disagreements during the data extraction process, a consensus was reached through discussion among the reviewers. Furthermore, corresponding authors were contacted to clarify ambiguities or request missing data as needed.

Risk of bias

Risk of bias assessment was performed independently by two reviewers using the Cochrane risk-of-bias tools [18], including: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias) and other biases. The risk of bias for each study was assessed as "low", "high" or "unclear" for each of 6 domains by two independent reviewers. Any disagreement in the evaluation process is discussed and decided with a third reviewer.

Outcomes and statistical analysis

Our outcomes included continuous variables: the mean change from baseline in NPS (range 0–8), LMK score (range 0–24), SNOT-22 score (range 0–110), UPSIT score (range 0–40), and NCS (range 0–3); categorical variables included the frequency of AEs. The data collection time points across different studies are shown in Table 1. Continuous outcomes were expressed as mean differences (MDs) with 95% credible intervals (CrIs), while dichotomous outcomes were reported as odds ratios (ORs) with 95% CrIs. Network geometry was visualized using Stata 17.0, with node size reflecting sample size and edge thickness indicating direct comparison frequency. Bayesian random-effects NMA was implemented in R 4.3.2 using the gemtc package. Markov chain Monte Carlo (MCMC) simulations employed four chains with 50,000 iterations (20,000 burn-in), with convergence evaluated through potential scale reduction factors (PSRF <1.05), trace plots, density plots, and Gelman-Rubin diagnostics. Treatment rankings were derived from surface under the cumulative ranking curve (SUCRA) values (0% = worst, 100% = best). Heterogeneity was quantified using the I^2 statistic ($I^2 < 50\%$: low; $I^2 \geq 50\%$: high). Publication bias was examined using a funnel plot and Egger's test.

Results

Study characteristics

Our systematic search initially identified 2,502 records. After the removal of duplicates and a two-stage screening process against predefined eligibility criteria, 16 randomized controlled trials were included in the final network meta-analysis. The complete study selection process is detailed in the PRISMA flow diagram (Figure 1). The detailed characteristics of the included studies were shown in Table 1. These studies were published between 2010 and 2025, involving a total of 2,034 subjects. The research covers 8 classes of monoclonal antibodies including omalizumab, dupilumab, benralizumab, mepolizumab, stapokibart, tezepelumab, depemokimab, and GR1802, involving 10 different intervention protocols, primarily including subcutaneous (sc) or intravenous (iv) administration of different drug dosages and frequencies. Baseline characteristics of participants showed a mean age of 37.3–53.45 years, female proportion of 27%–46.4%, history of prior nasal polyp surgery in 27%–100%, and comorbid asthma in 43%–92%. Some studies recorded nasal polyp score and SNOT-22 score, with some data unreported. The study duration ranged from 8 to 56 weeks, with most drug interventions lasting 24–52 weeks.

Table 1. Characteristics of included studies.

Study	Mean age (years) [SD]	% women	% with prior NP surgery	Mean NPS [SD]	Mean SNOT-22 [SD]	% with asthma	Sample size	Intervention	Periods
omalizumab									
Gevaert 2020a (POLYP1)[19]	51.1[13.2]	36.2	57.3	6.3[1.0]	60.1[17.7]	53.6	n=72 vs n=66	75 - 600mg sc 1) q2w 2) q4w	24w
Gevaert 2020b (POLYP2)[19]	50.0[12.0]	34.7	61.7	6.3[0.9]	59.5[19.3]	60.6	n=62 vs n=65	75 - 600mg sc 1) q2w 2) q4w	24w
Pinto 2010[20]	45.9[9.5]	28.6	-	-	-	57.1	n=7 vs n=7	0.016 mg/kg/IgE (IU/mL) sc q4w	52w
Wahba 2019[21]	37.3[10.9]	37.2	-	-	-	-	n=43 vs n=43	0.016 mg/kg/IgE (IU/mL) sc	48w
dupilumab									
Bachert 2019a (SINUS – 24)[10]	NR	43.0	72.0	5.7[1.3]	49.4[20.2]	58.0	n=143 vs n=133	300 mg sc every 2 weeks	24w
Bachert 2019b (SINUS – 52)[10]	-	38.0	58.0	6.1[1.2]	51.9[20.9]	60.0	n=195 vs n=153	300 mg sc 1) q2w 2) q2w ×12 then q4w	52w
Bachert 2016[22]	48.4[9.4]	43.0	58.0	5.8[0.9]	41.0[18.9]	58.0	n=30 vs n=30	600mg loading for 4wk, then 300mg weekly	16w
benralizumab									
Bachert 2022[23]	50.1[13.1]	36.0	73.0	6.1[1.2]	69.2[19.4]	68.0	n=207 vs n=206	30mg sc q4w × 3, then q8w	56w
Tversky 2021[24]	50.3[12.6]	42.0	100.0	6.0[0.9]	61.2[17.6]	92.0	n=12 vs n=12	30mg sc q4w	20w
Takabayashi 2021[25]	53.45[11.7]	46.4	64.3	5.3[1.3]	32.6[18.6]	82.6	n=11 vs n=23	30mg sc on day 1, week4, week8	24w
mepolizumab									
Han 2021 (SYNAPSE)[26]	48.6[12.9]	35.5	100.0	5.5[1.4]	64.1[18.3]	71.0	n=206 vs n=201	100mg sc q4w	52w
Bachert 2017[27]	51.0[10.0]	29.0	100.0	6.3[0.9]	50.5[17.9]	78.0	n=54 vs n=51	750mg iv q4w	25w
Gevaert 2011[28]	50.0[8.0]	27.0	77.0	-	-	43.0	n=20 vs n=10	750mg iv every 28d	8w
Fujieda 2024[29]	52 .0[11.9]	36.0	64.0	6.0[1.3]	56.8[19.3]	79.0	n= 84 vs n=85	loading in for 4 weeks + 100mg sc q4w	52w
stapokibart (CM310)									
Zhang 2023 (CROWNS-1)[30]	47.6[12.3]	43.0	63.0	5.9[0.8]	58.5[25.1]	66.0	n=28 vs n=28	300mg sc q2w	16w
tezepelumab									
Lipworth 2025 (WAYPOINT)[31]	49.7 [13.6]	34.8	71.0	6.1[1.2]	68.7[18.4]	60.8	n=203 vs n=205	210mg sc, q4w	52w
depemokimab									
Gevaert 2025a (ANCHOR-1)[32]	52.5 [13.4]	31.0	63.0	6.0[1.4]	57.4[22.2]	59.0	n=143 vs n=128	100mg sc every 26 weeks	52w
Gevaert 2025b (ANCHOR-2)[32]	50.5 [12.9]	31.0	63.0	5.9[1.3]	60.1[20.0]	51.0	n=129 vs n=128	100mg sc every 26 weeks	52w
GR1802									
Zheng 2025[33]	45.4[12.5]	41.4	61.4	5.9[0.8]	50.4[25.3]	44.3	n=36 vs n=34	300mg sc q2w	16w

SD, standard deviation; sc, subcutaneous; q2w, every 2 weeks

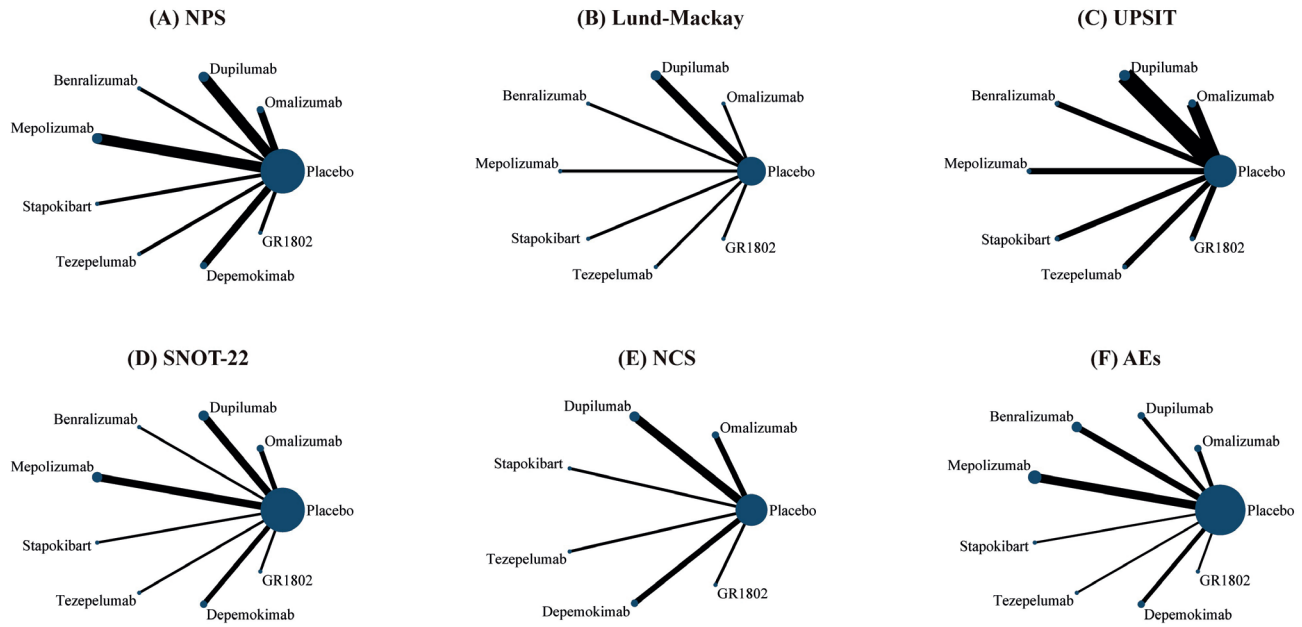

Figure 2. Network of comparisons for monoclonal antibodies in CRSwNP. Each node represents an intervention, and its size is proportional to the number of participants assigned to that treatment. The edges (lines) between nodes represent direct comparisons, and their thickness is proportional to the number of trials comparing the two connected interventions.

Nasal polyp score

The network geometry of all treatment comparisons is presented in Figure 2. The NMA of NPS included 14 studies involving 8 drugs, in which different dosages of the same drug were not considered as separate treatment methods. Omalizumab (MD: -0.87, 95% CrI: -1.33 to -0.41), dupilumab (MD: -1.86, 95% CrI: -2.21 to -1.48), benralizumab (MD: -0.6, 95% CrI: -1.13 to -0.06), mepolizumab (MD: -0.81, 95% CrI: -1.25 to -0.39), stapokibart (MD: -2.19, 95% CrI: -3.14 to -1.26), tezepelumab (MD: -1.5, 95% CrI: -2.07 to -0.93), depemokimab (MD: -0.7, 95% CrI: -1.14 to -0.26), and GR1802 (MD: -2.11, 95% CrI: -2.93 to -1.28) showed superiority to the placebo (Figure 3A). Notably, dupilumab was superior to omalizumab, benralizumab, mepolizumab and depemokimab (MDs ranging between -1.26 and -0.99). Stapokibart demonstrated superiority to omalizumab, benralizumab, mepolizumab and depemokimab (MDs ranging between -1.59 and -1.32). Tezepelumab was superior to benralizumab and depemokimab (MDs ranging between -0.9 and -0.8). GR1802 was superior to omalizumab, benralizumab, mepolizumab and depemokimab (MDs ranging between -1.51 and -1.24). Detailed data are shown in Figure S2. According to the SUCRA values, stapokibart ranked first with a value of 90.07%, followed by GR1802 (87.59%) and dupilumab (80.20%). Benralizumab (21.75%), depemokimab (28.50%), and placebo (0.37%) were the least effective among the treatments (Figure 4, and Figures S1 and S2).

Lund-Mackay score

The NMA of Lund-Mackay score included 9 studies involving 7 drugs, in which different dosages of the same drug were not considered as separate treatment methods. Among omalizumab, dupilumab, benralizumab, mepolizumab, stapokibart, tezepelumab, and GR1802, only dupilumab (MD: -6.63, 95% CrI: -11.25 to -2.6) demonstrated superiority to the placebo (Figure 3B). There were no significant differences in efficacy among these drugs. Stapokibart had the highest SUCRA value (81.87%), followed by dupilumab (78.49%) and tezepelumab (66.26%). Placebo (10.91%) and omalizumab (28.62%) had relatively low SUCRA values (Figure 4 and Figure S2).

UPSIT

The NMA of UPSIT included 10 studies involving 7 drugs, in which different dosages of the same drug were not considered as separate treatment methods. Among omalizumab, dupilumab, benralizumab, mepolizumab, stapokibart, tezepelumab, and GR1802, only dupilumab (MD: 11.43, 95% CrI: 7.99 to 16.18) and stapokibart (MD: 11.1, 95% CrI: 3.75 to 18.4) demonstrated superiority to the placebo (Figure 3C). Notably, dupilumab was superior to omalizumab, benralizumab, and mepolizumab (MDs ranging between 7.61 and 10.19, Figure S1). Dupilumab had the highest SUCRA value (91.34%) for UPSIT, followed by stapokibart (87.30%) and tezepelumab (62.62%). Mepolizumab (22.30%) and placebo (9.73%) had relatively low SUCRA values among these

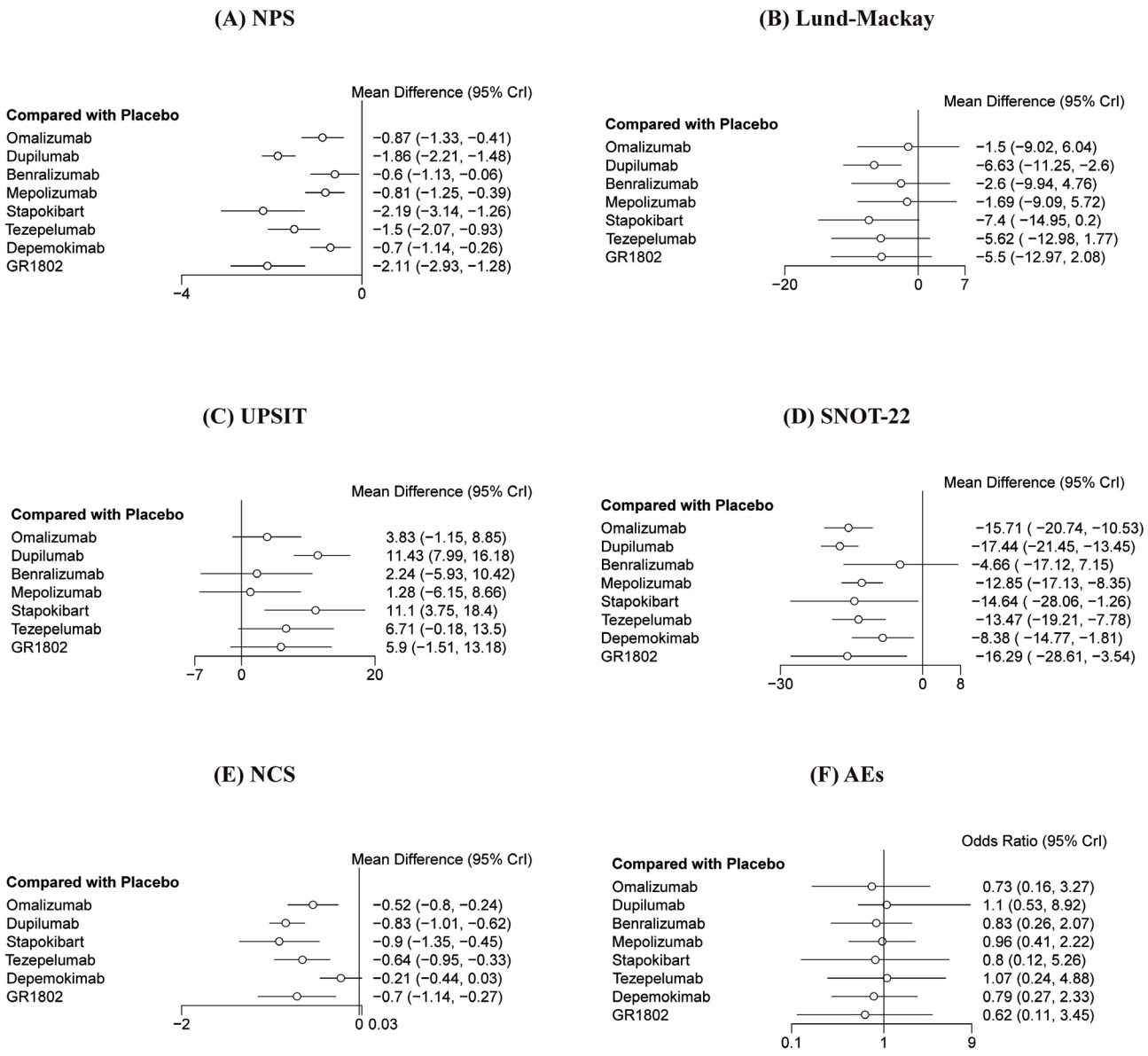

Figure 3. Forest plots of efficacy and safety outcomes compared with placebo. Forest plots display the mean differences (MD) for continuous outcomes and odds ratios (OR) for dichotomous outcomes, with their corresponding 95% credible intervals (CrI), for each biologic treatment versus placebo.

treatments (Figure 4 and Figure S2).

SNOT-22

The NMA of SNOT-22 included 14 studies involving 8 drugs, in which different dosages of the same drug were not considered as separate treatment methods. Omalizumab (MD: -15.71, 95% CrI: -20.74 to -10.53), dupilumab (MD: -17.44, 95% CrI: -21.45 to -13.45), mepolizumab (MD: -12.85, 95% CrI: -17.13 to -8.35), stapokibart (MD: -14.64, 95% CrI: -28.06 to -1.26), tezepelumab (MD: -13.47, 95% CrI: -19.21 to -7.78), depemokimab (MD: -8.38, 95% CrI: -14.77 to -1.81), and GR1802 (MD: -16.29, 95% CrI: -28.61 to -3.54) demonstrated superiority to the placebo (Fig. 3D). Notably, dupilumab was superior depemokimab (MD: -8.99, Figure. S1). According to the SUCRA values for SNOT - 22, dupilumab ranked first with 85.09%, followed by omalizumab (72.09%) and GR1802 (69.30%). Benralizumab (19.77%) and placebo (3.14%) were the least effective among these treatments (Figure 4 and Figure S2).

Nasal congestion score

The NMA of NCS included 10 studies involving 6 drugs, in which different dosages of the same drug were not considered as separate treatment methods. Omalizumab (MD: -0.52, 95% CrI: -0.8 to -0.24), dupilumab (MD: -0.83, 95% CrI: -1.01 to -0.62), stapok-

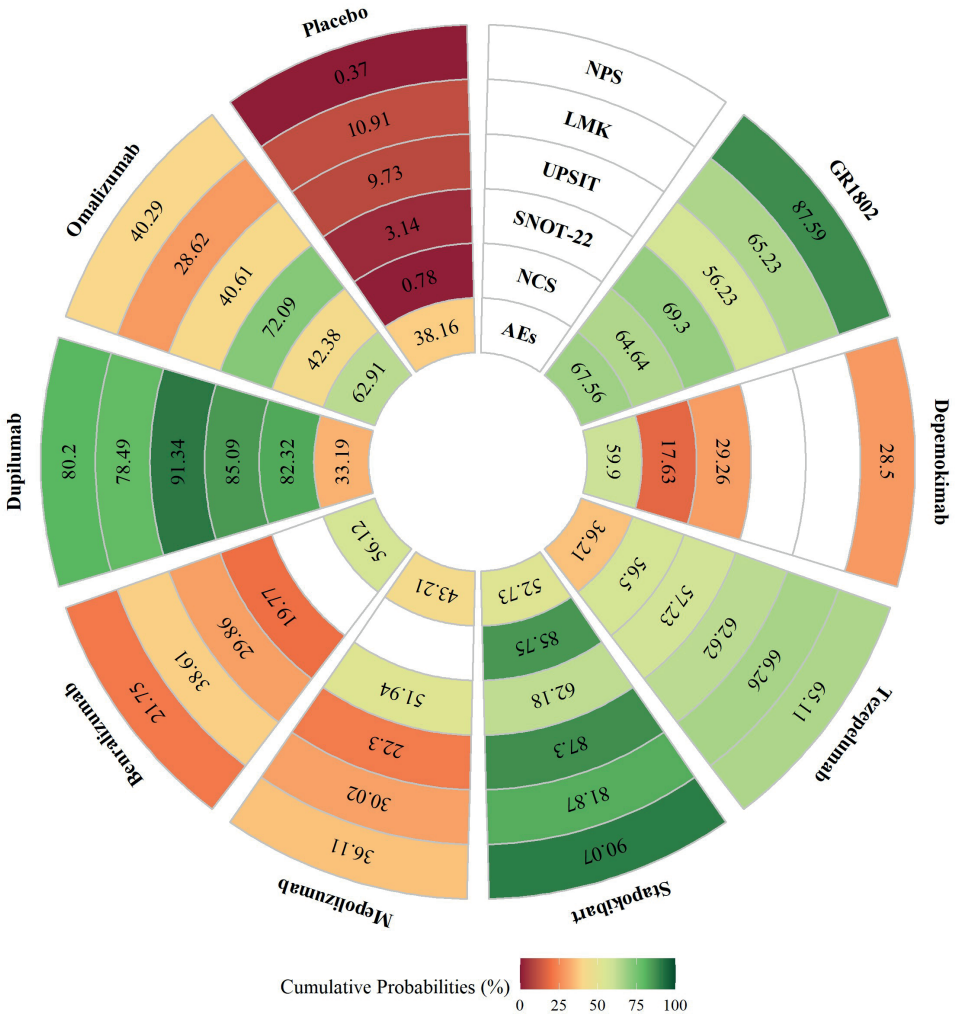

Figure 4. Ranking of treatments by efficacy and safety. The Surface Under the Cumulative Ranking Curve (SUCRA) values for each intervention across all evaluated outcomes. NPS, Nasal Polyp Score; LMK, Lund-Mackay score; UPSIT, University of Pennsylvania Smell Identification Test; SNOT-22, Sino-Nasal Outcome Test-22; NCS, Nasal Congestion Score; AEs, Adverse Events.

ibart (MD: -0.9, 95% CrI: -1.35 to -0.45), tezepelumab (MD: -0.64, 95% CrI: -0.95 to -0.33) and GR1802 (MD: -0.7, 95% CrI: -1.14 to -0.27) showed differences compared to the placebo (Figure S3). Among the six monoclonal antibodies, depemokimab was inferior to dupilumab, stapokibart, tezepelumab and GR1802 (MDs ranging between 0.44 and 0.69). Detailed data are shown in Fig. E1. According to the SUCRA values for NCS, stapokibart had the highest SUCRA value (85.75%), followed by dupilumab (82.32%) and GR1802 (64.64%, Figure 4 and Figure S2).

Adverse events

The NMA of AEs included 16 studies involving 8 drugs, in which different dosages of the same drug were not considered as separate treatment methods. There were no significant differences in the risk of AEs among various interventions (Figure 3F). Detailed data are shown in Figure S1. The results of the ranking according to SUCRA values showed that GR1802 (67.56%) exhibited the highest safety, followed by omalizumab (62.91%), depemokimab (59.90%), benralizumab (56.12%), stapokibart (52.73%), mepolizumab (43.21%), placebo (38.16%), tezepelumab (36.21%), dupilumab (33.19%) (Figure 4 and Figure S2).

Risk of bias and heterogeneity

The risk of bias summary was used to assess the overall quality of the literature (Figure 5), indicating a generally low risk. Except for Takabayashi 2021 et al. [25] with unclear risk, all RCTs adopted adequate random sequence generation methods. All studies provided sufficient data, being considered to have low risk for allocation concealment, and presented clear information on blinding of personnel and outcome assessment. Two studies were evaluated as having high risk of attrition bias due to dropout rates. Moreover, two studies were identified with unclear risk in terms of attrition bias. Concerning other biases, nine studies were classified as having unclear risk, while the rest sho-

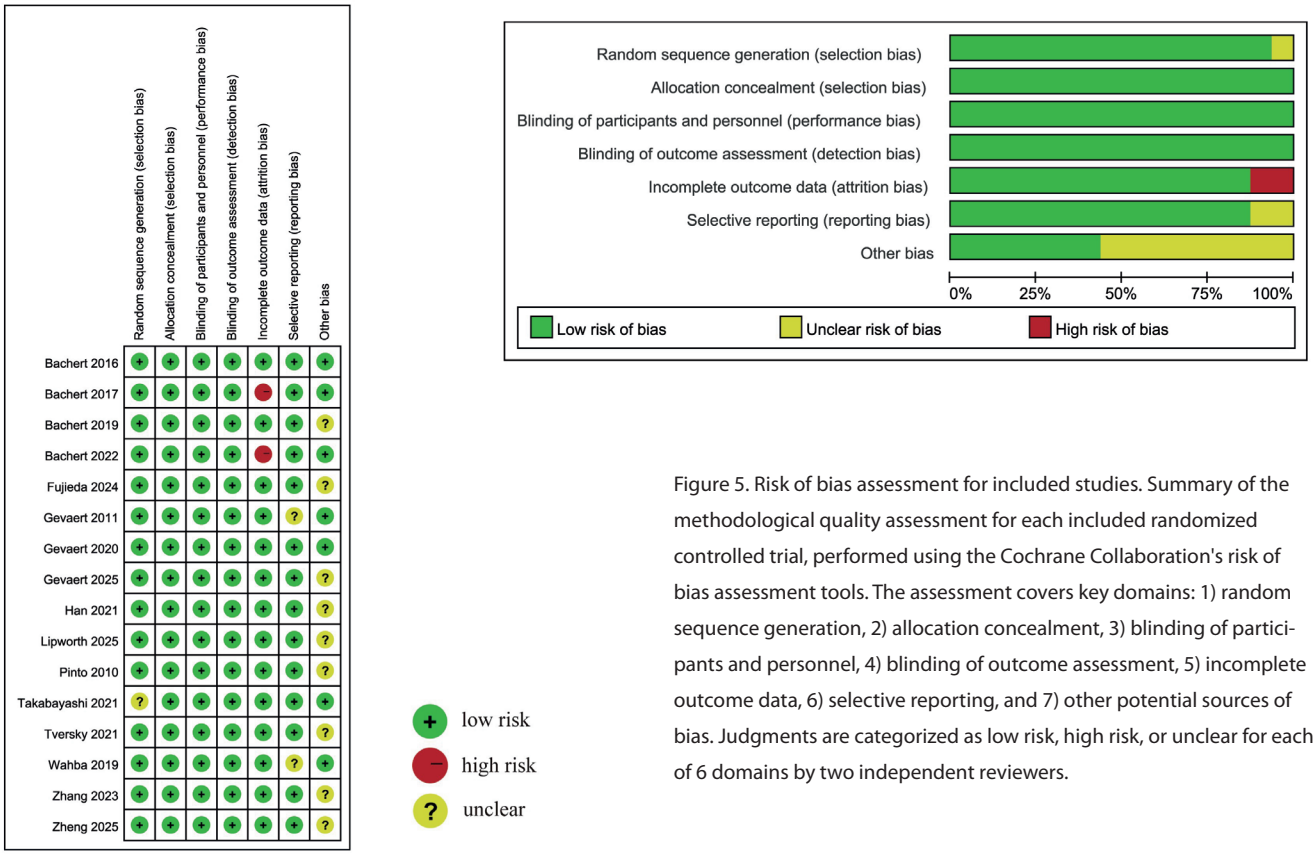

Figure 5. Risk of bias assessment for included studies. Summary of the methodological quality assessment for each included randomized controlled trial, performed using the Cochrane Collaboration's risk of bias assessment tools. The assessment covers key domains: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective reporting, and 7) other potential sources of bias. Judgments are categorized as low risk, high risk, or unclear for each of 6 domains by two independent reviewers.

wed low risk. Funnel plots and egger tests were used to assess publication bias of results, as shown in Figure S3. Funnel plots were symmetrical in appearance and egger tests (all P>0.05) indicated no potential publication bias, which supported the robustness of the study results. In addition, heterogeneity analyses were performed. The results showed that most comparisons showed low heterogeneity (Figure S4), except for the study by Bachert et al. [22].

Discussion

Our network meta-analysis of 16 randomized controlled trials involving 2,034 patients with CRSwNP systematically evaluated eight monoclonal antibodies across six outcomes, revealing distinct efficacy profiles: stapokibart and dupilumab consistently demonstrated superior performance in nasal polyp score (NPS) reduction and smell restoration, respectively, while dupilumab also showed significant improvements in Lund-Mackay score, the only drug surpassing placebo in radiologic severity. For quality of life assessed by SNOT-22, dupilumab and GR1802 outperformed most agents, and stapokibart led in nasal congestion score reduction. omalizumab, mepolizumab, tezepelumab, and depemokimab also showed significant improvements over placebo in various endpoints, though with more modest effects. All biologics exhibited comparable safety to placebo. These findings align with mechanistic differences, as IL-4Rα inhibitors (stapokibart, dupilumab and GR1802), which target both IL-4/ IL-13 signaling, showed broad efficacy across Th2-driven outcomes.

The efficacy hierarchy observed in our NMA is inherently linked to the distinct targets of each biologic and their engagement with Th2 inflammatory pathways: IL-4Rα inhibitors (dupilumab, stapokibart and GR1802), by blocking the shared receptor for IL-4 and IL-13, disrupt dual Th2 signaling axes, comprehensively suppressing eosinophil recruitment, epithelial remodeling, and mucus hypersecretion [34] — mechanisms that underlie their superior performance in polyp reduction (NPS), smell restoration (UPSIT), and radiologic improvement (Lund-Mackay score), as reflected in their top SUCRA rankings for these outcomes. In contrast, IL-5/IL-5Rα-targeted agents (benralizumab, mepolizumab, depemokimab), while effective at depleting eosinophils, fail to address IL-13-driven fibrosis [35], explaining their modest effects on NPS and limited impact on broader Th2-mediated tissue changes. Omalizumab, targeting IgE, demonstrated notable benefits in quality of life (SNOT-22) and nasal congestion (NCS), aligning with its role in dampening allergic sensitization and mast cell activation [36, 37]. Notably, although tezepelumab's upstream blockade of TSLP theoretically offers broad anti-inflammatory potential [38], our NMA revealed its inferiority to IL-4Rα inhibitors across multiple endpoints. This discrepancy may stem from the fact that IL-13 production persists via TSLP-indepen-

dent pathways such as IL-33 or mast cell-derived cytokines [34], diminishing tezepelumab's impact on epithelial remodeling. In addition, TSLP expression dominates in eosinophilic CRSwNP, yet dupilumab's dual IL-4/IL-13 inhibition benefits both eosinophilic and non-eosinophilic subtypes [39].

Our NMA is consistent with the conclusions of previous studies: IL-4Rα inhibitors represented by dpilumab have the best efficacy against CRSwNP and are not significantly different from placebo in safety [40-42]. Surprisingly, in the SYNAPSE trial (NCT03085797), mepolizumab demonstrated significant improvement in olfactory dysfunction [43]. This contrasts with our NMA findings where there was no significant difference in olfactory improvement between mepolizumab and placebo, which may be attributed to differences in the metrics used to evaluate olfaction. In SYNAPSE, olfactory dysfunction recovery was evaluated using the Visual Analogue Scale (VAS), whereas our NMA utilized the University of Pennsylvania Smell Identification Test (UPSIT). As a widely validated objective measure, UPSIT provides a more robust assessment of olfactory impairment, potentially implying a higher level of evidence for its results. Besides, it has been reported that dupilumab therapy may increase the risk of cutaneous T cell lymphoma in patients with atopic dermatitis [44, 45], a potential association hypothesized to be linked to IL-13 receptor blockade [46]. However, this serious complication has not been reported in cases of CRSwNP.

To our knowledge, this represents the first NMA to integrate cutting-edge biologics in CRSwNP (including the recently investigated agents stapokibart, tezepelumab, depemokimab, and GR1802—all currently in phase II/III trials) across five clinically discrete endpoints. Leveraging a Bayesian framework with 50,000 MCMC iterations, we established robust effect hierarchies (SUCRA) for these novel therapies against established biologics [47]. In the absence of direct comparative evidence among various monoclonal antibodies, this study provides indirect comparative data, offering insights for clinical decision [48, 49].

However, there are several limitations in our study. First, based on professional judgment, the efficacy of the biological agents of interest may remain in a relatively stable plateau within a specific time window, the heterogeneity in follow-up duration (ranging from 8 to 56 weeks) may introduce bias into outcome measurement. Additionally, among all 16 studies enrolled, only 6 studies had Asian populations as most of their study participants. In contrast, the remaining 10 studies focused on non-Asian populations, primarily including participants from Europe, North America, and other Western regions. Since the inflammatory phenotypes in Asian populations differ significantly from those in European and American populations among CRSwNP patients [50], the underrepresentation of Asian populations in the dataset is a notable shortfall. Besides, in the SNOT-22 analysis, tezepelumabs' performance differed from that in its original RCTs, possibly due to the placebo-arm combination approach and heterogeneity in patient characteristics across trials. Finally, the limited number of included studies and the absence of direct comparative evidence may have affected the evidence grade of the conclusions. Future research should focus on the efficacy of different administration methods and frequencies, long-term safety, and real-world effectiveness of these monoclonal antibodies or use more refined subgroup analyses or alternative data integration strategies in the meantime.

The validity of our network meta-analysis relies on the transitivity assumption, which requires that the included trials are sufficiently similar in their patient characteristics to allow for meaningful indirect comparisons. We acknowledge the observed variability in baseline features such as the rate of prior nasal surgery and asthma comorbidity across trials. Although we employed a random-effects model to account for between-study heterogeneity, and statistical heterogeneity was generally low, residual clinical heterogeneity may still bias our estimates. Therefore, the treatment rankings and effect sizes reported should be interpreted with caution, considering the differences in the underlying populations.

Conclusion

This comprehensive network meta-analysis demonstrates that all eight evaluated monoclonal antibodies confer significant clinical benefits over placebo in the treatment of CRSwNP. Among them, agents targeting the IL-4 receptor alpha (IL-4Rα)—namely, stapokibart, dupilumab, and GR1802—consistently exhibited the largest and most broad-spectrum efficacy across key endpoints, including nasal polyp reduction, improvement in smell identification, and enhancement of quality of life. The favorable safety profile observed across all biologics supports their potential for long-term management. These findings provide crucial evidence-based hierarchies to guide clinical decision-making in an evolving therapeutic landscape and underscore the central role of dual IL-4/IL-13 pathway inhibition in controlling type 2 inflammation in CRSwNP.

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Author contributions

WXY: study design, search, study selection, data collection, data analysis, drafting the article, revising the article, and final approval. RPH: search, study selection, data collection, data analysis, drafting the article, revising the article, and final approval. HHR: study design, research guidance, study selection, revising the article, and final approval. KZ: Data collection and final approval. ZJY: data collection and final approval. XY: data collection and final approval. WHY: data collection and final approval. RXY: study design, research guidance, and final approval. CJG: study design,

research guidance, revision of the article, supervision.

Conflict of interest

All authors disclosed that there was no potential financial conflict or other conflicts.

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SUPPLEMENTARY MATERIAL

(A) NPS, MD

Placebo	**-0.87 (-1.33, -0.41)**	**-1.86 (-2.21, -1.48)**	**-0.6 (-1.13, -0.06)**	**-0.81 (-1.25, -0.39)**	**-2.19 (-3.14, -1.26)**	**-1.5 (-2.07, -0.93)**	**-0.7 (-1.14, -0.26)**	**-2.11 (-2.93, -1.28)**
0.87 (0.41, 1.33)	Omalizumab	**-0.99 (-1.57, -0.39)**	0.27 (-0.44, 0.97)	0.06 (-0.58, 0.67)	**-1.32 (-2.38, -0.29)**	-0.63 (-1.36, 0.1)	0.17 (-0.47, 0.8)	**-1.24 (-2.18, -0.29)**
1.86 (1.48, 2.21)	**0.99 (0.39, 1.57)**	Dupilumab	**1.26 (0.6, 1.89)**	**1.05 (0.47, 1.59)**	-0.33 (-1.36, 0.65)	0.37 (-0.33, 1.02)	**1.16 (0.58, 1.71)**	-0.25 (-1.16, 0.65)
0.6 (0.06, 1.13)	-0.27 (-0.97, 0.44)	**-1.26 (-1.89, -0.6)**	Benralizumab	-0.21 (-0.9, 0.45)	**-1.59 (-2.67, -0.54)**	**-0.9 (-1.68, -0.12)**	-0.1 (-0.79, 0.59)	**-1.51 (-2.47, -0.53)**
0.81 (0.39, 1.25)	-0.06 (-0.67, 0.58)	**-1.05 (-1.59, -0.47)**	0.21 (-0.45, 0.9)	Mepolizumab	**-1.38 (-2.41, -0.37)**	-0.69 (-1.39, 0.03)	0.11 (-0.5, 0.73)	**-1.3 (-2.21, -0.35)**
2.19 (1.26, 3.14)	**1.32 (0.29, 2.38)**	0.33 (-0.65, 1.36)	**1.59 (0.54, 2.67)**	**1.38 (0.37, 2.41)**	Stapokibart	0.7 (-0.39, 1.8)	**1.49 (0.46, 2.53)**	0.08 (-1.16, 1.35)
1.5 (0.93, 2.07)	0.63 (-0.1, 1.36)	-0.37 (-1.02, 0.33)	**0.9 (0.12, 1.68)**	0.69 (-0.03, 1.39)	-0.7 (-1.8, 0.39)	Tezepelumab	**0.8 (0.07, 1.52)**	-0.61 (-1.6, 0.4)
0.7 (0.26, 1.14)	-0.17 (-0.8, 0.47)	**-1.16 (-1.71, -0.58)**	0.1 (-0.59, 0.79)	-0.11 (-0.73, 0.5)	**-1.49 (-2.53, -0.46)**	**-0.8 (-1.52, -0.07)**	Depemokimab	**-1.41 (-2.33, -0.47)**
2.11 (1.28, 2.93)	**1.24 (0.29, 2.18)**	0.25 (-0.65, 1.16)	**1.51 (0.53, 2.47)**	**1.3 (0.35, 2.21)**	-0.08 (-1.35, 1.16)	0.61 (-0.4, 1.6)	**1.41 (0.47, 2.33)**	GR1802

(B) Lund-Mackay, MD

Placebo	-1.5 (-9.02, 6.04)	**-6.63 (-11.25, -2.6)**	-2.6 (-9.94, 4.76)	-1.69 (-9.09, 5.72)	-7.4 (-14.95, 0.2)	-5.62 (-12.98, 1.77)	-5.5 (-12.97, 2.08)
1.5 (-6.04, 9.02)	Omalizumab	-5.14 (-14.11, 3.29)	-1.1 (-11.61, 9.38)	-0.18 (-10.69, 10.39)	-5.89 (-16.58, 4.85)	-4.11 (-14.67, 6.43)	-4.01 (-14.56, 6.66)
6.63 (2.6, 11.25)	5.14 (-3.29, 14.11)	Dupilumab	4.01 (-4.2, 12.81)	4.94 (-3.34, 13.81)	-0.75 (-9.19, 8.28)	0.99 (-7.25, 9.88)	1.15 (-7.19, 10.11)
2.6 (-4.76, 9.94)	1.1 (-9.38, 11.61)	-4.01 (-12.81, 4.2)	Benralizumab	0.92 (-9.45, 11.33)	-4.8 (-15.22, 5.78)	-3.02 (-13.4, 7.49)	-2.91 (-13.38, 7.79)
1.69 (-5.72, 9.09)	0.18 (-10.39, 10.69)	-4.94 (-13.81, 3.34)	-0.92 (-11.33, 9.45)	Mepolizumab	-5.74 (-16.22, 4.84)	-3.94 (-14.41, 6.53)	-3.82 (-14.35, 6.79)
7.4 (-0.2, 14.95)	5.89 (-4.85, 16.58)	0.75 (-8.28, 9.19)	4.8 (-5.78, 15.22)	5.74 (-4.84, 16.22)	Stapokibart	1.78 (-8.81, 12.33)	1.9 (-8.75, 12.59)
5.62 (-1.77, 12.98)	4.11 (-6.43, 14.67)	-0.99 (-9.88, 7.25)	3.02 (-7.49, 13.4)	3.94 (-6.53, 14.41)	-1.78 (-12.33, 8.81)	Tezepelumab	0.12 (-10.42, 10.68)
5.5 (-2.08, 12.97)	4.01 (-6.66, 14.56)	-1.15 (-10.11, 7.19)	2.91 (-7.79, 13.38)	3.82 (-6.79, 14.35)	-1.9 (-12.59, 8.75)	-0.12 (-10.68, 10.42)	GR1802

(C) UPSIT, MD

Placebo	3.83 (-1.15, 8.85)	**11.43 (7.99, 16.18)**	2.24 (-5.93, 10.42)	1.28 (-6.15, 8.66)	**11.1 (3.75, 18.4)**	6.71 (-0.18, 13.5)	5.9 (-1.51, 13.18)
-3.83 (-8.85, 1.15)	Omalizumab	**7.61 (1.76, 14.65)**	-1.57 (-11, 7.91)	-2.54 (-11.45, 6.3)	7.27 (-1.53, 16.11)	2.86 (-5.6, 11.33)	2.04 (-6.84, 10.84)
-11.43 (-16.18, -7.99)	**-7.61 (-14.65, -1.76)**	Dupilumab	**-9.27 (-18.79, -0.67)**	**-10.19 (-19.27, -2.32)**	-0.36 (-9.33, 7.5)	-4.7 (-13.42, 2.61)	-5.57 (-14.54, 2.21)
-2.24 (-10.42, 5.93)	1.57 (-7.91, 11)	**9.27 (0.67, 18.79)**	Benralizumab	-1 (-11.97, 9.98)	8.83 (-2.08, 19.64)	4.45 (-6.2, 14.98)	3.63 (-7.4, 14.56)
-1.28 (-8.66, 6.15)	2.54 (-6.3, 11.45)	**10.19 (2.32, 19.27)**	1 (-9.98, 11.97)	Mepolizumab	9.82 (-0.51, 20.22)	5.42 (-4.68, 15.5)	4.61 (-5.82, 15.05)
-11.1 (-18.4, -3.75)	-7.27 (-16.11, 1.53)	0.36 (-7.5, 9.33)	-8.83 (-19.64, 2.08)	-9.82 (-20.22, 0.51)	Stapokibart	-4.4 (-14.44, 5.66)	-5.18 (-15.58, 5.12)
-6.71 (-13.5, 0.18)	-2.86 (-11.33, 5.6)	4.7 (-2.61, 13.42)	-4.45 (-14.98, 6.2)	-5.42 (-15.5, 4.68)	4.4 (-5.66, 14.44)	Tezepelumab	-0.82 (-10.85, 9.17)
-5.9 (-13.18, 1.51)	-2.04 (-10.84, 6.84)	5.57 (-2.21, 14.54)	-3.63 (-14.56, 7.4)	-4.61 (-15.05, 5.82)	5.18 (-5.12, 15.58)	0.82 (-9.17, 10.85)	GR1802

(D) SNOT-22, MD

Placebo	**-15.71 (-20.74, -10.53)**	**-17.44 (-21.45, -13.45)**	-4.66 (-17.12, 7.15)	**-12.85 (-17.13, -8.35)**	**-14.64 (-28.06, -1.26)**	**-13.47 (-19.21, -7.78)**	**-8.38 (-14.77, -1.81)**	**-16.29 (-28.61, -3.54)**
15.71 (10.53, 20.74)	Omalizumab	-1.72 (-8.38, 4.69)	10.97 (-2.38, 23.9)	2.83 (-3.85, 9.64)	1.07 (-13.4, 15.29)	2.22 (-5.48, 9.81)	7.31 (-0.94, 15.66)	-0.66 (-14.02, 13.11)
17.44 (13.45, 21.45)	1.72 (-4.69, 8.38)	Dupilumab	12.73 (-0.21, 25.23)	4.6 (-1.15, 10.59)	2.8 (-11.34, 16.83)	3.93 (-2.97, 10.95)	**8.99 (1.55, 16.77)**	1.1 (-11.75, 14.7)
4.66 (-7.15, 17.12)	-10.97 (-23.9, 2.38)	-12.73 (-25.23, 0.21)	Benralizumab	-8.13 (-20.68, 5.07)	-9.79 (-28.58, 7.97)	-8.76 (-22.05, 4.8)	-3.68 (-17.37, 10.12)	-11.46 (-28.89, 6.01)
12.85 (8.35, 17.13)	-2.83 (-9.64, 3.85)	-4.6 (-10.59, 1.15)	8.13 (-5.07, 20.68)	Mepolizumab	-1.81 (-16.02, 12.21)	-0.63 (-7.96, 6.4)	4.42 (-3.36, 12.12)	-3.44 (-16.56, 9.98)
14.64 (1.26, 28.06)	-1.07 (-15.29, 13.4)	-2.8 (-16.83, 11.34)	9.79 (-7.97, 28.58)	1.81 (-12.21, 16.02)	Stapokibart	1.2 (-13.47, 15.84)	6.28 (-8.78, 21.15)	-1.56 (-19.57, 16.59)
13.47 (7.78, 19.21)	-2.22 (-9.81, 5.48)	-3.93 (-10.95, 2.97)	8.76 (-4.8, 22.05)	0.63 (-6.4, 7.96)	-1.2 (-15.84, 13.47)	Tezepelumab	5.1 (-3.49, 13.7)	-2.78 (-16.38, 11.15)
8.38 (1.81, 14.77)	-7.31 (-15.66, 0.94)	**-8.99 (-16.77, -1.55)**	3.68 (-10.12, 17.37)	-4.42 (-12.12, 3.36)	-6.28 (-21.15, 8.78)	-5.1 (-13.7, 3.49)	Depemokimab	-7.9 (-21.76, 6.39)
16.29 (3.54, 28.61)	0.66 (-13.11, 14.02)	-1.1 (-14.7, 11.75)	11.46 (-6.01, 28.89)	3.44 (-9.98, 16.56)	1.56 (-16.59, 19.57)	2.78 (-11.15, 16.38)	7.9 (-6.39, 21.76)	GR1802

(E) NCS, MD

Placebo	**-0.52 (-0.8, -0.24)**	**-0.83 (-1.01, -0.62)**	**-0.9 (-1.35, -0.45)**	**-0.64 (-0.95, -0.33)**	-0.21 (-0.44, 0.03)	**-0.7 (-1.14, -0.27)**
0.52 (0.24, 0.8)	Omalizumab	-0.31 (-0.63, 0.05)	-0.38 (-0.91, 0.15)	-0.12 (-0.54, 0.29)	0.31 (-0.04, 0.68)	-0.18 (-0.7, 0.34)
0.83 (0.62, 1.01)	0.31 (-0.05, 0.63)	Dupilumab	-0.07 (-0.57, 0.41)	0.19 (-0.2, 0.53)	**0.62 (0.3, 0.91)**	0.13 (-0.36, 0.59)
0.9 (0.45, 1.35)	0.38 (-0.15, 0.91)	0.07 (-0.41, 0.57)	Stapokibart	0.26 (-0.28, 0.81)	**0.69 (0.19, 1.21)**	0.2 (-0.42, 0.83)
0.64 (0.33, 0.95)	0.12 (-0.29, 0.54)	-0.19 (-0.53, 0.2)	-0.26 (-0.81, 0.28)	Tezepelumab	**0.44 (0.05, 0.83)**	-0.06 (-0.59, 0.47)
0.21 (-0.03, 0.44)	-0.31 (-0.68, 0.04)	**-0.62 (-0.91, -0.3)**	**-0.69 (-1.21, -0.19)**	**-0.44 (-0.83, -0.05)**	Depemokimab	-0.49 (-0.99, -0.01)
0.7 (0.27, 1.14)	0.18 (-0.34, 0.7)	-0.13 (-0.59, 0.36)	-0.2 (-0.83, 0.42)	0.06 (-0.47, 0.59)	0.49 (0.01, 0.99)	GR1802

(F) AEs, OR

Placebo	0.73 (0.16, 3.27)	1.1 (0.53, 8.92)	0.83 (0.26, 2.07)	0.96 (0.41, 2.22)	0.8 (0.12, 5.26)	1.07 (0.24, 4.88)	0.79 (0.27, 2.33)	0.62 (0.11, 3.45)
1.36 (0.31, 6.15)	Omalizumab	1.51 (0.39, 24.53)	1.13 (0.16, 6.1)	1.31 (0.23, 7.37)	1.08 (0.1, 11.98)	1.46 (0.18, 12.47)	1.07 (0.17, 6.87)	0.85 (0.09, 8.24)
0.91 (0.11, 1.9)	0.66 (0.04, 2.59)	Dupilumab	0.74 (0.06, 2.12)	0.86 (0.08, 2.33)	0.68 (0.04, 4.37)	0.97 (0.06, 3.79)	0.71 (0.06, 2.12)	0.54 (0.03, 2.83)
1.21 (0.48, 3.85)	0.88 (0.16, 6.19)	1.35 (0.47, 17.74)	Benralizumab	1.16 (0.34, 4.97)	0.97 (0.13, 9.22)	1.29 (0.24, 9.15)	0.95 (0.24, 4.78)	0.75 (0.11, 6.21)
1.04 (0.45, 2.44)	0.76 (0.14, 4.29)	1.16 (0.43, 11.82)	0.86 (0.2, 2.93)	Mepolizumab	0.83 (0.11, 6.59)	1.11 (0.2, 6.43)	0.82 (0.21, 3.27)	0.65 (0.1, 4.37)
1.26 (0.19, 8.09)	0.92 (0.08, 9.53)	1.48 (0.23, 25.77)	1.03 (0.11, 7.9)	1.21 (0.15, 9.25)	Stapokibart	1.35 (0.12, 14.35)	0.99 (0.11, 8.27)	0.78 (0.06, 9.47)
0.93 (0.2, 4.23)	0.69 (0.08, 5.69)	1.03 (0.26, 16.47)	0.78 (0.11, 4.19)	0.9 (0.16, 5.01)	0.74 (0.07, 8.24)	Tezepelumab	0.74 (0.11, 4.77)	0.58 (0.06, 5.65)
1.27 (0.43, 3.77)	0.93 (0.15, 5.94)	1.41 (0.47, 16.86)	1.05 (0.21, 4.17)	1.22 (0.31, 4.82)	1.01 (0.12, 8.85)	1.36 (0.21, 8.88)	Depemokimab	0.79 (0.11, 6)
1.6 (0.29, 9.08)	1.18 (0.12, 11.37)	1.86 (0.35, 32.19)	1.33 (0.16, 8.87)	1.54 (0.23, 10.42)	1.28 (0.11, 16.33)	1.72 (0.18, 16.85)	1.26 (0.17, 9.5)	GR1802

Figure S1. League table of network of comparisons for monoclonal antibodies in CRSwNP.

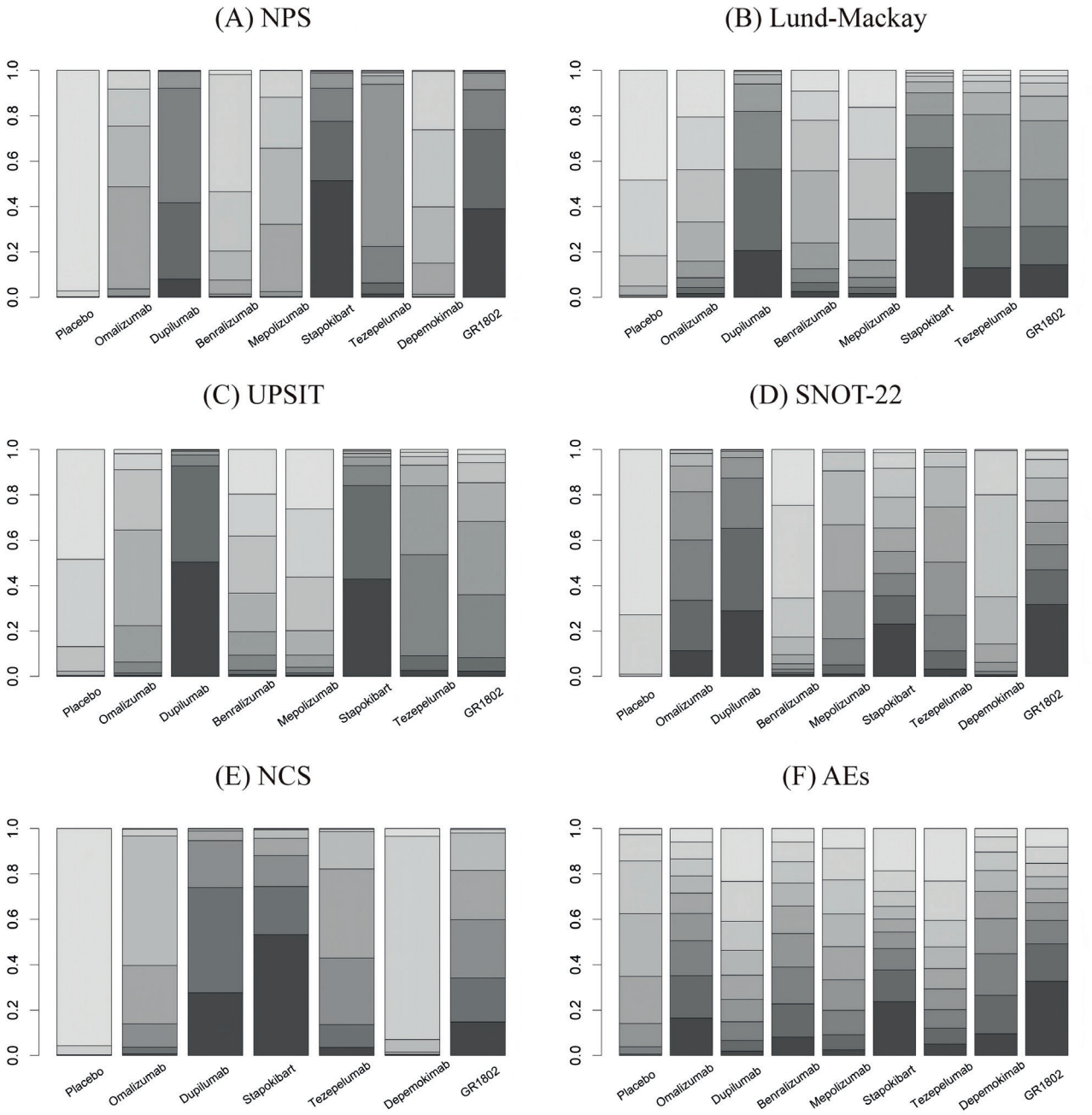


Figure S2. Cumulative ranking probability plots of network of comparisons for monoclonal antibodies in CRSwNP.

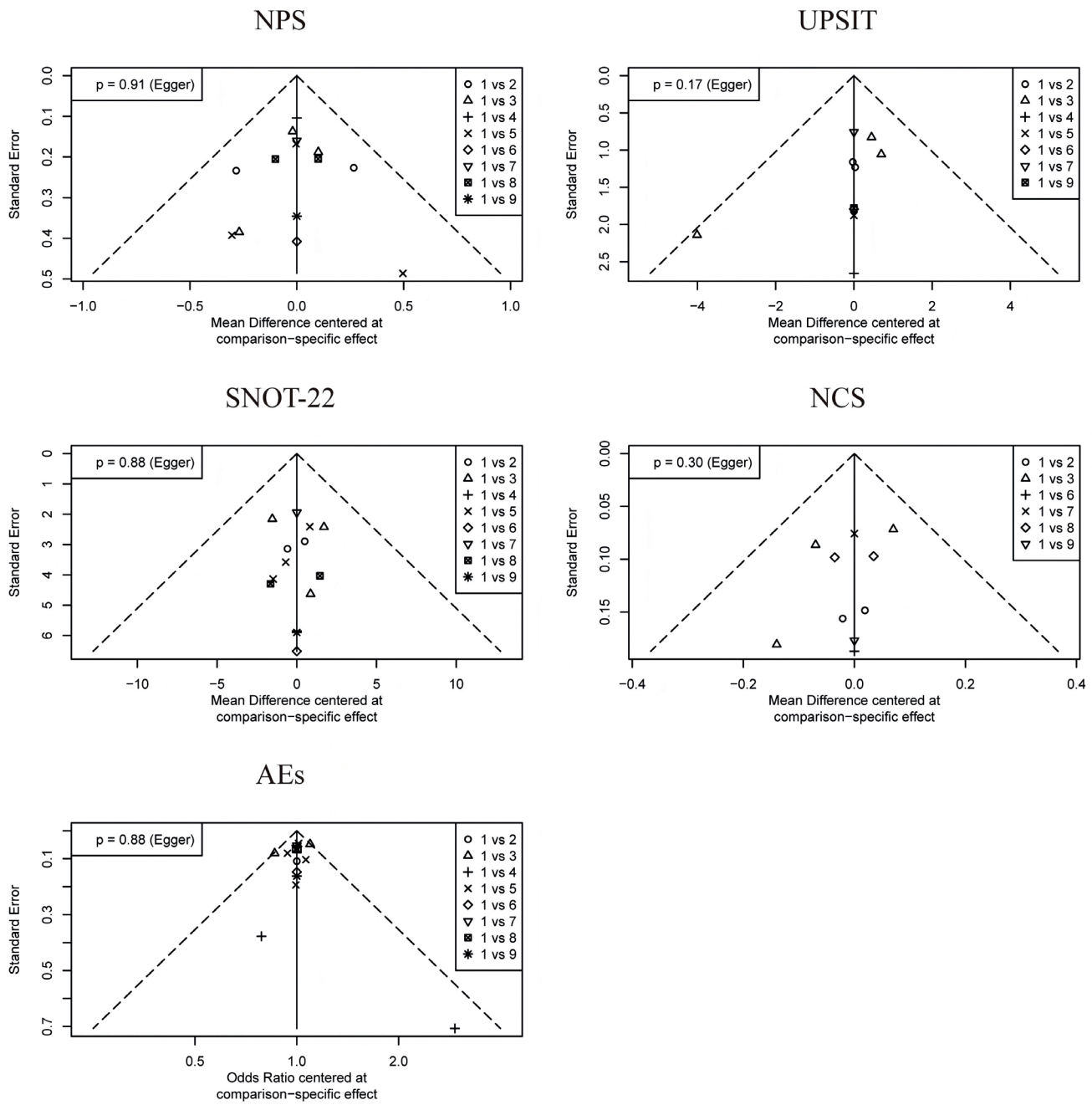
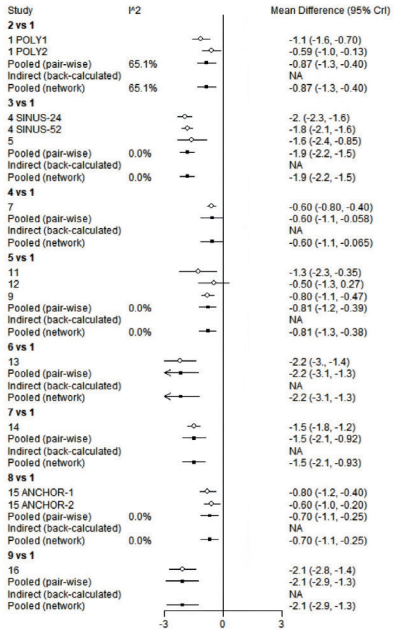
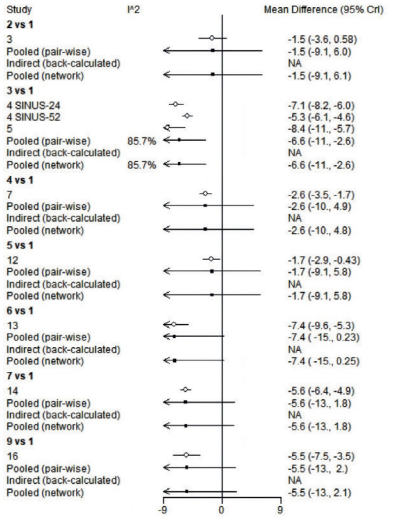


Figure S3. Funnel plot of network of comparisons for monoclonal antibodies in CRSwNP.

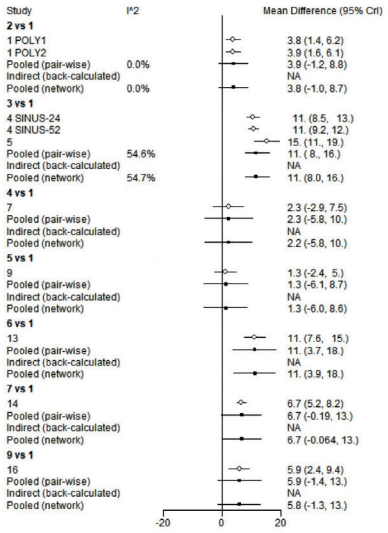
NPS



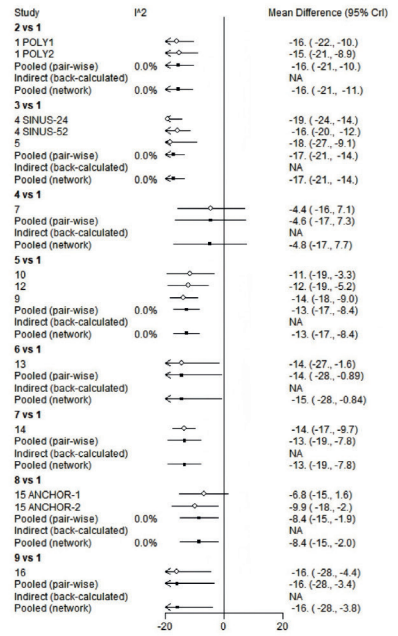
Lund-Mackay



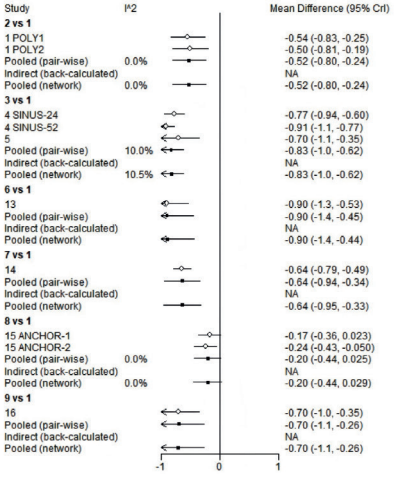
UPSIT



SNOT-22



NCS



AEs

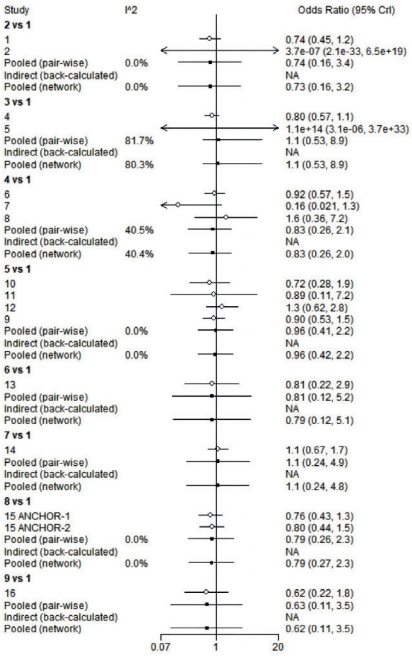


Figure S4. Risk of heterogeneity of network of comparisons for monoclonal antibodies in CRSwNP.