Orofacial Treatment Emergent Adverse Events of Antibody Drug Conjugates (ADCs) Targeting Human Epidermal Growth Factor Receptor 2 (HER2): A Systematic Review and Meta-Analyses

A thesis

Presented to the Faculty of Tufts University School of Dental Medicine

In Partial Fulfillment of the Requirements for the Degree of

Master of Science in Dental Research

By

Abdullatif Burahmah, DDS

April 2025

Tufts University School of Dental Medicine
Department of Diagnostic Sciences
Division of Oral Medicine
Boston, MA

THESIS COMMITTEE MEMBERS

Principal Investigator

Yuanming Xu, DDS, MMSc
Assistant Professor
Department of Diagnostic Sciences, Oral Medicine Division
Tufts University School of Dental Medicine

Co-Investigators

Vidya Sankar, DMD, MHS
Associate Professor and Division Director for Oral Medicine
Department of Diagnostic Sciences, Postgraduate Program Director Oral Medicine Division
Tufts University School of Dental Medicine, Florida International University

Reshma S. Menon, BDS, DMSc
Assistant Professor
Department of Diagnostic Sciences, Oral and Maxillofacial Pathology Division
Tufts University School of Dental Medicine

Alessandro Villa, DDS, PhD, MPH
Professor
Chief of Oral Medicine, Oral Oncology and Dentistry at Miami Cancer Institute
Herbert Wertheim College of Medicine, Florida International University

Sarah Pagni, MPH, PhD
Assistant Professor
Public Health and Community Service
Tufts University School of Dental Medicine

ABSTRACT

Aim: This systematic review and meta-analyses aimed to evaluate and compare the prevalence and severity of orofacial adverse events (AEs) associated with FDA-approved HER2-targeted antibody-drug conjugates (ADCs), trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), utilizing data from peer-reviewed published literature and clinical trials from ClinicalTrials.gov.

Methods: Comprehensive systematic searches were conducted across multiple databases (PubMed, Embase, Cochrane Library) and ClinicalTrials.gov to identify relevant clinical trials evaluating orofacial AEs for T-DM1 and T-DXd. The data extraction and meta-analyses focused on orofacial events reported in three or more studies. Meta-analyses were conducted using random-effects models to assess overall prevalence, severity of all grades, and severe (grade ≥3), and to compare HER2-targeted ADCs. Risk of bias assessments were performed using the revised Cochrane Risk of Bias (RoB 2) tool for randomized studies, Methodological Index for Non-Randomized Studies (MINORS), Eager's test to asses study effect size and funnel plot for assessment of publication bias.

Results: The pooled prevalence of orofacial adverse events from published literature among patients treated with HER2-targeted ADCs was as follows: oral mucositis (14%), dry mouth (19%), dysgeusia (9%), thrush (6%), and dysphagia (2%). Oral mucositis and dysgeusia prevalence were significantly higher with T-DXd compared to T-DM1. ClinicalTrials.gov analyses confirmed higher oral mucositis prevalence with T-DXd (16%) compared to T-DM1 (4%). Dysgeusia, dysphagia, and dry mouth prevalences ranged from 2% to 13%. Severe adverse events (grade ≥3) were negligible in both sources. Funnel plots and Egger's tests suggested significant publication bias for multiple adverse events, requiring cautious interpretation.

Conclusions: This review identified significant differences in the prevalence and severity of orofacial adverse events between T-DM1 and T-DXd, particularly for oral mucositis and dysgeusia. There was also notable variability between published literature and ClinicalTrials.gov methodologies, highlighting the need for standardized reporting thresholds to improve consistency and comparability across clinical studies.

DEDICATION

To the memory of my beloved mother, whose love, strength, and prayers continue to guide me every day, and whose devotion to dentistry and compassion for others sparked my passion for healthcare and shaped the path I walk today.

To my sisters, Esraa and Anfal, for their unwavering support, endless patience, and the light they bring into my life.

To my family, for their constant encouragement and belief in me.

To Hussain and my closest friends, for standing by me through every challenge and celebration.

And to my oral medicine mentors, for inspiring my passion and guiding my professional journey with wisdom and care.

With heartfelt gratitude, I dedicate this thesis to all of you.

ACKNOWLEDGMENTS

I would like to extend my sincere gratitude to Hannah Ellingson from Tufts Hirsh Library and Grace Hwang, a senior dental student, for their invaluable assistance and dedication throughout this research. Hannah's kindness, expertise, and outstanding support in navigating library resources were instrumental to the completion of this work. Grace's insights, unwavering commitment, and valuable contributions significantly enriched the study. I am genuinely grateful for their remarkable support and collaboration.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

HER2: Human Epidermal Growth Factor Receptor 2

FDA: Food and Drug Administration

ADC: Antibody Drug Conjugate

mAbs: Monoclonal antibodies

IgG: Immunoglobulin G

ADCC: Antibody-dependent cell-mediated cytotoxicity

CDC: Complement-dependent cytotoxicity

ADCP: Antibody-dependent cell-mediated phagocytosis

DAR: Drug–antibody ratio

EMA: European Medicines Agency

NSCLC: Non-small cell lung cancer

AEs: Adverse events

CTCAE: Common Terminology Criteria for Adverse Events

T-DM1: Trastuzumab emtansine

T-DXd: Trastuzumab deruxtecan

Orofacial Treatment Emergent Adverse Events of Antibody Drug Conjugates (ADCs) Targeting Human Epidermal Growth Factor Receptor 2 (HER2): A Systematic Review and Meta-Analyses

Cancer prevalence and targeted therapy

Solid organ cancers remain the most prevalent cancer type globally and in the United States, with an estimated two million new cancer diagnoses expected in the U.S. in 2025, approximately half of which will involve solid organ cancers.[1] Molecular studies have identified subsets of solid organ cancers linked to overexpression or amplification of Human Epidermal Growth Factor Receptor 2 (HER2).[2] In a study examining the prevalence of HER2 mutations in solid organ cancers, Pahuja et al. analyzed 111,176 tumors and identified HER2 mutations in 3,851 cases, representing 3.5% of all analyzed tumors.[3] The most common HER2-mutated solid organ cancers are bladder cancers (9-18%), uterine cervical (6%), colorectal (5.8%), lung (4%), and breast (4%).[2] Conventionally, radiotherapy, surgery, and cytotoxic chemotherapy have been linked to many drawbacks. [4-6]

Over 100 years ago, Paul Ehrlich, an American physician, developed the "magic bullet" concept, which conceptualizes the creation of a drug targeting the intended cell structure directly and remains inoffensive to other tissues.[7, 8] A general paradigm shift occurred with further identification of cancer subsets based on molecular makeup, allowing chemotherapy agents to be more targeted towards cancer cells.[8] A novel concept developed in 1976, known as antibody drug conjugate (ADC), allowed for more precise targeting of cancer cells with robust effectiveness, leading to enhanced therapeutic effect.[6]

Key components of ADC, conjugation methods, mechanism of action

General ADC structures consist of three main components, including an antibody, a chemical linker, and a cytotoxic payload. Ideally, an ADC should remain stable during administration and circulation in the body until it accurately reaches the targeted cancer cells and releases

the cytotoxic payload.[6] Each component of the ADC structure, including the conjugation method, can significantly affect the safety and efficacy of the ADC.[6]

Prior to selecting the structure and components of an ADC, the appropriate selection of the target antigen is essential. The chosen antigen will guide the mechanism by which the ADC delivers its cytotoxic payload into cancer cells, such as via endocytosis.[6] It is also important that the target antigen is expressed predominantly or exclusively on cancer cells, with minimal or no expression in normal tissues, to minimize off-target toxicity.[6] Optimally, the target antigen should be present on the cell surface and not be secreted to aid ADC recognition of the targeted cells and prevent off-site toxicity.[6] Additionally, the antigen should be efficiently internalized upon antibody binding to enable intracellular delivery and release of the cytotoxic payload.[5, 6]

Monoclonal antibodies (mAbs) are essential for directing ADCs toward their specific target antigens. These antibodies are large molecules and account for more than 90% of an ADC's total mass. This large size is advantageous, as it limits their distribution into healthy tissues, including vital organs involved in drug metabolism and elimination.[5] Several important factors should be taken into consideration, including binding affinity, effective internalization, low immunogenicity, and a prolonged half-life. In the early development of ADCs, murine antibodies were commonly used; however, their high immunogenicity often led to severe side effects.[9] Today, chimeric, humanized, and fully human antibodies with reduced immunogenicity are more widely employed.[9]Among the five immunoglobulin classes, immunoglobulin G (IgG) is the most frequently used in ADCs.[6] Although IgGs are divided into subclasses IgG1 to IgG4, IgG3 is generally avoided due to its short half-life.[6] Most therapeutic anti-tumor mAbs used in ADCs are based on the IgG1 subclass due to its

ability to engage Fc-dependent immune mechanisms such as antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cell-mediated phagocytosis (ADCP).[6] These additional immune-mediated actions can further enhance the therapeutic efficacy of ADCs. Consequently, the IgG1 subclass is commonly selected in ADC design to leverage both targeted delivery and immune effector functions.[6, 9, 10] Additionally, antibody affinity influences the extent to which the ADC is internalized into the target cell, as well as how effectively it binds to available surface antigens. Once internalized, the ADC is trafficked to the lysosomal compartment, where it is degraded, leading to the intracellular release of its cytotoxic payload.[10]

Linkers serve as a bridge between the antibody and the cytotoxic drug, playing a critical role in both the stability of the ADC and the controlled release of the payload. As such, they are essential to maintaining the therapeutic index and overall efficacy of ADCs.[6] Optimally, linkers should minimize premature release of the payload in the plasma, prevent aggregation of the ADC, and promote efficient release of the drug at the target site.[6] Linkers can generally be classified based on how they release the payload within cells into two main types: cleavable linkers, such as those containing disulfide bonds, and non-cleavable linkers, such as those based on thioether or maleimidocaproyl groups.[6, 9, 10] Cleavable linkers release their payload in response to specific conditions within the target or cancer cells, such as acidic pH, lysosomal proteases, reduction, or hydrolysis. These linkers also offer the advantage of enabling a bystander effect, allowing the payload to affect neighboring tumor cells.[10] However, non-cleavable linkers are more resistant to chemical or enzymatic digestion and more stable in plasma than cleavable ones, as the payload is only released following complete lysosomal degradation of the antibody.[5, 9] This controlled release mechanism can

help reduce off-target toxicity associated with ADCs, making non-cleavable linkers particularly suitable for targeting cells with homogeneous antigen expression.[5, 9] Among all FDA-approved ADCs, the payload is conjugated using cleavable linkers except for trastuzumab emtansine and belantamab mafodotin, which utilize non-cleavable linkers.[9, 11]

The payload is the potent cytotoxic agent conjugated to the antibody, designed to exert the cytotoxic effect after the ADC is internalized into cancer cells.[6, 10] Ideal properties of an ADC payload include high potency, strong stability in circulation, favorable biochemical characteristics for conjugation, and good solubility in aqueous environments.[5] Many ADC payloads exhibit very low half maximal inhibitory concentration (IC_{50}) values, reflecting their extreme potency; thus, they cannot be used as standalone drugs due to their significant toxicity.[9] Payloads can be classified into three main categories: topoisomerase I inhibitors, such as deruxtecan and SN-38; tubulin-binding agents, such as auristatins and maytansinoids; and DNA-targeting agents, such as calicheamicins and duocarmycins.[9] Another important concept related to the payload is the drug-antibody ratio (DAR), which is reflective of the amount of payload loaded onto the antibody and plays an important role in determining ADCs' efficacy and toxicity.[9, 10]

Another conjugation method utilizes lysine and cystine sites or amide coupling. Lysine and cysteine residues present on antibodies provide accessible reaction sites for conjugation, and early ADCs commonly employed stochastic conjugation methods targeting these pre-existing residues via appropriate coupling reactions.[5] Amide coupling, which utilizes an active carboxylic acid ester, is one of the most employed methods for conjugating payloads to antibodies.[6] This technique is exemplified by clinically approved ADCs such as gemtuzumab ozogamicin, T-DM1, and inotuzumab ozogamicin.[6] Antibodies typically

contain around 80–90 lysine residues, approximately 40 of which are accessible for modification.[6] These lysine residues are widely distributed across both heavy and light chains of the antibody.[6] Random conjugation at lysine residues may therefore inadvertently occur near antigen recognition sites, potentially decreasing the ADC's binding affinity to its intended target.[6] Additionally, this random attachment at accessible lysine sites can lead to variability in the number of payload molecules per antibody, resulting in a heterogeneous DAR.[6]

ADCs exert their therapeutic effect through a targeted mechanism. As ADCs reach their target cells, the monoclonal antibody component recognizes and binds to specific cell-surface antigens, forming an ADC-antigen complex.[9] This complex is subsequently internalized into the target cell via endocytosis, leading to the formation of an endosome, which matures into late endosomes and subsequently fuses with lysosomes.[9] If the ADC contains a cleavable linker, the payload is released within the lysosomal compartment in response to specific enzymes, localized conditions, and other factors.[9] In contrast, ADCs with non-cleavable linkers release their payload only after the antibody component undergoes complete lysosomal degradation.[9] The released cytotoxic payload molecules from degraded lysosomes enter the cell cytosol, causing cell death primarily through DNA damage or disruption of microtubule dynamics.[9] Additionally, some payload molecules can diffuse across the cell membrane, affecting neighboring cancer cells that may lack antigen expression—a phenomenon known as the bystander effect.[9] This bystander effect is particularly important for treating cancers with heterogeneous antigen expression.[9]

FDA approved HER2-targeted ADCs

In 2000, the Food and Drug Administration (FDA) approved the first ADC, gemtuzumab ozogamicin, which is comprised of a humanized monoclonal IgG4 conjugated with cytotoxic Nacetyl-γ-calicheamicin via a cleavable hydrazone linker that targets CD33 for acute myeloid leukemia (AML) treatment.[6]

As of 2025, thirteen ADCs have been approved by the FDA and one breakthrough therapy designation (BTD) with over 100 others in various stages of clinical trials that designed to target cancer cell surface antigens including CD30, CD22, CD79b, CD19, Trophoblast Cell Surface Antigen 2 (TROP2), Nectin Cell Adhesion Molecule 4 (Nectin-4), Folate Receptor Alpha (FRα), and Tissue Factor (TF). There are two ADCs, trastuzumab Emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), which target HER2 in solid tumors.[4, 11]

HER2-targeted ADCs are among the most prevalent therapeutic modalities in clinical development, with twenty-eight HER2-targeted ADCs under investigation.[12] These agents leverage established cytotoxic mechanisms, such as anti-mitotic, DNA alkylation, and topoisomerase 1 inhibition, and typically require high tumor-specific HER2 expression to effectively and safely deliver the payload.[12] Next-generation carriers, innovative conjugation strategies, and advanced payload linkers are being developed to enhance both the therapeutic effectiveness and safety profiles of HER2-targeted ADC therapies.[12]

Trastuzumab Emtansine (T-DM1)

Trastuzumab Emtansine, also known as ado-trastuzumab emtansine, T-DM1, or Kadcyla®, is a second-generation ADC and the first to be approved for solid organ cancer.[6] T-DM1 consists of humanized anti-HER2 IgG1 and emtansine that function as inhibitors of microtubule polarization and is connected via a non-cleavable thioether-based linker with an average DAR of 3.5, making it stable in the circulation and tumor microenvironment.[5, 6, 13] Upon binding of T-DM1 to the HER2 receptor subdomain IV, the complex undergoes internalization followed by lysosomal proteolytic degradation, resulting in the intracellular release of the cytotoxic payload DM1.[9] Subsequently, DM1 binds to tubulin, disrupting the microtubule network and causing cell-cycle arrest, ultimately leading to cell apoptosis.[9] Notably, DM1 is charged under physiological pH and thus unable to mediate the bystander effect.[6]

Consequently, its action is limited specifically to HER2-positive cancer cells, where it also retains trastuzumab-like signaling mechanisms, including ADCC and CDC.[6] Approval from FDA and European Medicines Agency (EMA) was obtained in 2013 for adult patients with HER2-positive unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, either combined or separately.[14] Later in 2019, the FDA extended the approval of T-DM1 to be used as an adjuvant treatment for patients with early HER2-positive breast cancer with residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.[6]

Trastuzumab deruxtecan (T-DXd)

Trastuzumab deruxtecan, also known as fam-trastuzumab deruxtecan, DS-8201, T-DXd, or Enhertu®, is a third-generation ADC that was approved by the FDA and EMA in December 2019 and January 2021, respectively.[6, 15] T-DXd consists of a humanized IgG1 antibody targeting HER2 and an exatecan derivative as a topoisomerase I inhibitor linked via a protease-cleavable tetrapeptide linker with an average DAR of 7-8.[4, 6, 15] In addition, this ADC exhibits several novel improvements over its predecessors, including a high DAR enabling delivery of a highly potent payload, enhanced membrane permeability that enhances the bystander effect, and increased plasma stability due to the use of a novel tetrapeptide-based linker technology.[5] Thus, preclinical studies have predicted T-DXd to be effective against cancers with mutated, low, or high HER2 expression.[5] T-DXd has been approved for unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens in the setting of metastasis.[15] Subsequent FDA approvals for additional indications include the treatment of locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma, HER2-mutated non-small cell lung cancer (NSCLC), adults with unresectable or metastatic HER2-low breast cancer, adult patients with unresectable or metastatic HER2-positive solid tumors, and unresectable or metastatic NSCLC with activating HER2 mutations.[16]

Treatment Emergent Adverse Events of ADCs

Despite significant advances in the field of pharmacology aimed at reducing off-site toxicity, it remains an unavoidable side effect of cytotoxic medications, including ADCs. The severity and incidence of toxicity associated with ADCs are consistent with those of their payloads, as evidenced by the fact that different ADCs with similar payloads exhibit comparable levels of toxicity, despite targeting different antigens.[17] Thus, ADC toxicities can be classified as

either “off-target, off-tumor” effects or “on-target, off-tumor” effects. While the former is the most common type of ADC toxicity and is unrelated to the targeted antigen by the ADC, the latter results from the engagement of the monoclonal antibody with targets in non-malignant tissue locations.[17] Other factors likely play a crucial role in toxicity, including linker stability, which would cause unintentional toxicities if unstable.[17] The general incidence of all grade ADC-related adverse events (AEs) reported is 91.2%; the incidence of grade ≥3 AEs is 46.1%.[18] Some of the most common all-grade AEs related to ADCs are nausea, neutropenia, blurred vision, and peripheral neuropathy. Some of the most common grade ≥3 AEs are neutropenia, hypoesthesia, thrombocytopenia, febrile neutropenia, and lymphopenia.[16, 18]

Furthermore, AEs related to HER2-targeted ADCs have been estimated to be around 98.29% overall mean incidence of all-grade AEs and 47.88% for ≥3 high-grade AEs.[19] The most common all-grade AEs were nausea (41.57%), fatigue (35.86%), and decreased appetite (28.84%).[19] Also, the most common high-grade AEs were thrombocytopenia (8.37%), anemia (6.49%), and neutropenia (6.42%).[19] In the phase 3 EMILIA trial (ClinicalTrials.gov identifier NCT00829166), T-DM1 was associated with fewer AEs compared to T-DXd. Specifically, grade ≥3 AEs were observed in 41% of patients treated with T-DM1, versus 57% of those treated with T-DXd.[8]

ADC-related Orofacial AEs

Based on the Common Terminology Criteria for Adverse Events (CTCAE), AEs affecting the orofacial area fall into various categories, such as gastrointestinal disorders (e.g., cheilitis, dry mouth, oral mucositis, oral dysesthesia, etc.); infections and infestations (e.g., gingival infection, lip infection, oral candidiasis, etc.); musculoskeletal and connective

tissue disorders (e.g., osteonecrosis of the jaw, trismus, etc.); and nervous system disorders (e.g., dysgeusia). [20]

Some orofacial AEs related to ADC have been reported, including oral mucositis with a frequency of 10-20%, which encompasses almost grade 1 or 2 AEs and <1% reported with T-DXd, T-DM1, and sacituzumab govitecan.[21] However, the overall prevalence of HER2-targeted ADC-related oral mucositis and other orofacial AEs has not been systematically investigated.

Accurately determining the prevalence rate of orofacial AEs can significantly assist healthcare providers by assessing their potential impact on the quality of life for oncological patients. This understanding can also help minimize the risk of deviations from the cancer therapy protocol, prevent discontinuation of treatment, and reduce the need for additional supportive care. Hagiwara et al. observed a statistically significant decline in quality of life and health utility among patients undergoing first-line chemotherapy for metastatic breast cancer who developed grade 1 or 2 oral mucositis.[22] Alsheyyab et al. found that in patients with severe oral mucositis, modifications to chemotherapy treatment led to dose changes in 60% of cases, treatment delays in 38%, and discontinuations in 2%.[23] Additionally, median health costs increased, ranging from $ 2,100 to $18,515, depending on the necessity for clinic visits and hospitalization to manage oral mucositis secondary to cancer therapy.[23]

Methodological Approaches

Utilizing a single methodological approach to study adverse events in clinical trials can be challenging, especially when aiming for comprehensiveness and addressing inherent limitations. Thus, systematically identifying, critically appraising, and statistically pooling existing data, systematic reviews minimize bias and enhance transparency and

reproducibility of findings.[24] As such, this approach is particularly valuable in studying AEs from clinical trials, as it enables the detection and quantification of rare and infrequent events that individual trials may not adequately capture.[25] However, a general discrepancy has been observed between registered clinical trial outcomes and their corresponding published results across various domains, including the statistical methods employed and the reporting of AEs, consequently significantly undermining the transparency of clinical trials.[26] In a study conducted by Pranić and Marušić examining 81 randomized controlled trials (RCTs), issues with AE reporting were identified. They found that serious adverse events (SAEs) and other AEs were absent in publications for 23.8% and 4.8% of RCTs, respectively, despite being registered. Furthermore, under-reporting of AEs in publications compared to clinical trial registries was noted among 43 trials (53.1%) explicitly stating no occurrence of SAEs in the registry; only five trials (23.8%) accurately reported this non-occurrence in the published articles.[26] Additionally, a study by Hartung et al. involving 110 clinical trials revealed that 38 trials inconsistently reported the number of individuals with SAEs; notably, 33 of these trials (87%) reported a higher number of SAEs in ClinicalTrials.gov compared to their published reports.[27]

Given the notable underreporting of orofacial AEs in the current literature on ADCs and the lack of systematic reports specifically addressing HER2-targeted ADCs, there is a clear gap in documented evidence regarding these toxicities. This is particularly concerning as HER2-targeted ADCs represent the largest category in ongoing clinical development, encompassing 28 agents (15 in phase I, 8 in phase II, 2 in phase III, and 3 either launched or under regulatory review).[12, 26, 27] Furthermore, as previously mentioned, discrepancies have been noted between outcomes reported in clinical trial registries and those published in peer-

reviewed literature, especially in terms of the frequency and severity of the AEs.[26] These inconsistencies underscore the rationale for a comparative assessment of both reporting methodologies. Clinical trial registries often provide standardized and more comprehensive data on adverse events (AEs), while published articles may offer additional clinical context, including significance and correlations that are not captured in registry reports. This underscores the complementary value of analyzing both sources.

Aims of the Study

1. Explore the prevalence of oral mucosal adverse events, salivary glands adverse events and other orofacial AEs including cheilitis, dental caries, dry mouth, dysphagia, gingival pain, lip pain, mucositis oral, oral cavity fistula, oral dysesthesia, oral hemorrhage, oral pain, periodontal disease, salivary duct inflammation, salivary gland fistula, tooth development disorder, tooth discoloration, toothache, gum infection, herpes simplex reactivation, lip infection, edema face, facial pain, lymph gland infection, mucosal infection, salivary gland infection, thrush, tooth infection, osteonecrosis of jaw, dysesthesia, dysgeusia, glossopharyngeal nerve disorder, trigeminal nerve disorder, oropharyngeal pain, erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis in patient who had treatment with HER2-targeted ADCs (T-DM1, T-DXd).
2. Assess the severity of orofacial AEs reported with HER2-targeted ADCs.
3. Investigate and compare orofacial AEs identified across different databases.

Significance

By identifying the prevalence, severity, and specific types of orofacial AEs associated with HER2-targeted ADCs through a comparative evaluation of two distinct methodologies, a systematic literature review, and analysis of clinical trial registries (clinicaltrials.gov), this study provides critical insights for clinical practice. Utilizing both approaches allows healthcare providers to obtain a comprehensive and balanced understanding of orofacial AEs. Clinical trial registries offer structured, consistent, and extensive AE reporting, effectively reducing the risk of underreporting often encountered in published literature. In contrast, systematic reviews of published studies contribute additional context, nuanced details, and

clinical insights not systematically captured by registries. Consequently, this combined approach facilitates enhanced accuracy in estimating the likelihood of patients developing orofacial AEs, improves risk-benefit analyses when considering HER2-targeted ADC treatments, and optimizes the management and care strategies for affected patients. Additionally, this comprehensive approach enriches healthcare practitioners' awareness and familiarity with the spectrum and prevalence of orofacial adverse events associated with HER2-targeted ADC therapy.

Methodology

Study Registration

- Approval was obtained from the Dental Research Administration, and an exemption was granted by the Institutional Review Board committee at Tufts University School of Dental Medicine. The study protocol was registered with the National Institute for Health and Care Research via the PROSPERO International Prospective Register of Systematic Reviews under the registration number CRD420250645169.
- This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Study Design

This study employs a systematic review and meta-analyses approach to evaluate orofacial adverse events associated with T-DXd and T-DM1, from both published clinical trials in the literature and the database on ClinicalTrials.gov.

Research Question

- **P (Population):** Patients with solid HER2 organ cancer who are receiving at least a single dose of HER2-targeted ADCs
- **I (Intervention):** Treatment with HER2-targeted ADCs
- **C (control):** None
- **O (Outcome):** Rate, severity, and types of orofacial adverse events observed in the population receiving HER2-targeted ADCs

Inclusion Criteria

1. Human subjects
2. Clinical trials involving human subjects that received at least a single dose of HER2-targeted ADCs (trastuzumab Emtansine (T-DM1) or trastuzumab deruxtecan (T-DXd))
3. Available count data regarding treatment-related adverse events in search engines or clinical trials listed in the National Clinical Trial database (ClinicalTrials.gov), including phase 0, I, II, III, and IV trials, regardless of randomization or the presence of a control group
4. English language
5. No location requirement for included papers
6. No restriction on the publication date; all time frames will be considered

Exclusion Criteria

Studies conducted in vitro, case reports, observational studies, conference abstracts, letters to the editors, correspondence, systematic reviews, and trials that do not involve T-DXd or T-DM1 as an intervention.

Databases

Databases included were PubMed, Embase, Cochrane Library, and the National Clinical Trials Database from ClinicalTrials.gov.

Keywords

Systematic Review Keywords

- ("Ado-Trastuzumab Emtansine"[Mesh] OR "Kadcyla" [tiab] OR "T-DM1" OR "Trastuzumab-DM1" OR "Trastuzumab Emtansine" OR "Trastuzumab-MCC-DM1" OR "huN901-DM1" OR "huN901DM1" OR "huN901 DM1" OR "trastuzumab deruxtecan" [Supplementary Concept] OR "trastuzumab deruxtecan" OR "DS-8201a" OR "DS-8201" OR " Enhertu"[tiab] OR "T-DXd" OR "Trastuzumab-DXd" OR "Fam-trastuzumab deruxtecan-nxki") AND (Safety OR "treatment emergent adverse event" OR "treatment associated adverse event" OR "treatment related adverse events" OR "Drug-Related Side Effects and Adverse Reactions"[Mesh]) NOT ("animals"[mesh] NOT "humans"[mesh]) NOT "review" [pt] NOT "systematic review" [pt] NOT "case reports" [pt] NOT "editorial" [pt] NOT "comment" [pt] NOT "in vitro" [ti] NOT "case series" [ti]

ClinicalTrials.gov search

- T-DM1, T-DXd, DS-8201a

Data Extraction and Management

- The following data collected for each included article/trial: (1) NCT identifier, (2) study title and study acronym, (3) database collected from, (4) condition treated (type of cancer), (5) interventions, (6) outcome measures, (7) sample size, (8) sex, (9) age, (10) study phase, (11) study design, (12) funding type, (13) sponsors and collaborators, (14) study location, (15) relevant study dates, including start date, primary completion date, completion date,

first posted, results first posted, and last update posted, (16) type of orofacial adverse events, and (17) severity of orofacial adverse events.

- All search results from databases were initially imported into EndNote version 20 for deduplication.
- After removing duplicates, the cleaned references were imported into Covidence, a systematic review management tool, to streamline and facilitate the processes of screening, selection, and data extraction.

Data Screening

- A pilot screening was conducted on 5% of the total deduplicated papers by two independent, blinded reviewers before the title and abstract screening stage. The rationale behind screening decisions was documented, and interrater reliability was assessed using the kappa statistic.
- The initial screening of titles and abstracts, followed by the full-text review, was conducted by two independent, blinded reviewers for all papers. Any disagreements during these phases were resolved through consensus or by consultation with a third reviewer.
- Data collection was performed independently and manually by two blinded reviewers, and the collected data were organized using a spreadsheet to ensure accuracy and facilitate analysis. Any discrepancies identified during data collection were resolved through revision and consensus.
- Additional relevant trials were identified through the manual screening of reference lists from review articles, enhancing the comprehensiveness of the data.

Risk of Bias Assessment

- Two reviewers independently evaluated the methodological quality and risk of bias of RCTs using the Cochrane Risk of Bias 2 (RoB 2) tool.[28]
- RoB 2 tool assesses five key domains: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selective reporting of results. Each domain was classified as low, unclear, or high risk of bias.
- For non-randomized studies, methodological quality and risk of bias were assessed using the Methodological Index for Non-Randomized Studies (MINORS) criteria.[29]
- MINORS evaluates non-randomized studies based on clearly stated aims, prospective collection of data, appropriate endpoint selection, unbiased endpoint assessment, follow-up duration, and loss to follow-up, among other criteria.
- Any discrepancies during assessments were resolved through discussion and consensus or, when necessary, consultation with a third reviewer. The results of these assessments were summarized in tabular form and visualized in risk-of-bias summary plots.

Data Analysis

All AEs were graded according to a standardized severity scale, such as the CTCAE. The severity of AEs is classified into five distinct grades: Grade 1 represents mild adverse events characterized by asymptomatic conditions or mild symptoms, typically requiring only clinical or diagnostic observation without intervention. Grade 2 denotes moderate events that may necessitate minimal, local, or noninvasive interventions. Grade 3 includes severe or medically significant events that, while not immediately life-threatening, often require

hospitalization or extend existing hospitalization due to their disabling nature. Grade 4 comprises life-threatening events that demand urgent medical intervention. Grade 5 represents fatalities directly attributed to the adverse event.

The prevalence of adverse events was calculated, and random-effects models were applied in the meta-analysis, with results illustrated using forest plots. Statistical heterogeneity among the studies was assessed through Cochran's Q test, tau^2 statistic, and the I^2 statistic. The potential for publication bias was evaluated using Egger's test and visual inspection of funnel plots. Ninety-five percent confidence intervals were calculated for all estimates, and the significance threshold was set at $\alpha = 0.05$. All statistical analyses were performed using Stata version 18 (StataCorp LLC, College Station, TX).

Results

Published literature study selection and PRISMA flowchart

A total of 1431 papers were initially collected from multiple databases (PubMed: 312, Embase: 701, Cochrane Library: 421) as shown in Figure 1. One paper was flagged for a retraction alert by EndNote (version 20.6). 353 papers were removed due to duplication (324 duplicates were removed by EndNote, 25 additional duplicates were identified and removed through Covidence, and 4 duplicates were identified manually), leaving 1077 papers for title and abstract screening. A pilot screening on around 5% (n=56) of randomly selected de-duplicated records showed a moderate level of agreement for inter-rater reliability (IRR) between two reviewers, with Cohen's Kappa of 0.68. Following discussions to refine inclusion criteria, specifically limiting the selection to include clinical trials evaluating HER2-targeted ADC monotherapy and ADC-targeted HER2 combined with a placebo compared to ADC-targeted HER2 combined with a cytotoxic medication and explicitly excluding retrospective studies. Thus, full title and abstract screening achieved a substantial Cohen's kappa of 0.801 for IRR. After reviewing the title and abstract, 639 papers were excluded as they were considered irrelevant and inconsistent with the inclusion criteria, which resulted in 439 papers selected for full-text screening. A total of 409 studies were excluded during the full-text evaluation stage. The primary reasons for exclusion were abstracts (n=117), registered protocols without results (n=82), absence of reported orofacial AEs (n=51), news articles (n=26), letters to the editor (n=18), NCT protocol registration (n=16), non-clinical trials (n=12), reviews (n=11), commentaries (n=21), reports (n=6), conference abstracts (n=5), retrospective studies (n=4), duplicate NCT entries (n=4), T-DM1 not used as monotherapy (n=4), articles not in English

(n=4), multiple trials (n=4), cohort studies (n=3), expert opinions (n=3), conference symposiums (n=3), clinical trial protocols (n=3), T-DXd not used as monotherapy (n=3), absence of adverse event information (n=3), in vitro studies (n=2), publisher corrections (n=1), not a final analysis (n=1), no full text available (n=1), and in vivo studies (n=1) as shown in Figure 1. Ultimately, 30 papers met the eligibility criteria and were included for detailed data collection and bias assessment of randomized and non-randomized studies.

Clinicaltrials.gov Trials Selection

A total of 347 clinical trials were initially identified from ClinicalTrials.gov, including 172 for T-DM1 and 175 for T-DXd. Trials were included regardless of their result status (e.g., terminated, completed, withdrawn). Of these, 269 trials were excluded due to no reports of results (T-DM1: 121, T-DXd: 148), leaving 78 trials for further screening. After detailed assessment, an additional 39 trials were excluded for reasons including the absence of relevant orofacial adverse events, non-monotherapy T-DM1 trials (n=28), and irrelevant or duplicate T-DXd trials (n=11). Thirty-nine clinical trials (T-DM1: 23 trials, T-DXd: 16 trials) met the eligibility criteria and were included in this analysis, as illustrated in Figure 2.

Characteristics of the included clinical trials from the published literature

The 30 included studies comprised predominantly breast cancer studies (n=17), followed by gastric or gastroesophageal cancers (n=6), and other cancers (colorectal, biliary tract, non-small cell lung cancer, uterine carcinosarcoma, and other HER2-positive solid tumors; n=7).

The phases of the studies include phases 1 (n=8), phase 2 (n=15), phase 3 (n=5), combined phases 2/3 (n=1), and phase 3b (n=1).

Twenty-two studies reported ClinicalTrials.gov registration numbers, whereas eight studies did not. Of these eight, four provided alternative registration identifications (JAPIC, CTRI, UMIN, jRCT), while the remaining four were not registered in any clinical trial registry. Study designs were primarily single-arm (T-DM1: 10 studies; T-DXd: 13 studies), with fewer randomized controlled trials (T-DM1: 4 studies; T-DXd: 3 studies). ADC dosage ranged from 0.3-4.8 mg/kg for T-DM1 and 0.8-8 mg/kg for T-DXd. The thresholds for reporting adverse events in the included published literature varied considerably. Of the 30 studies reviewed, half (n = 15) reported AEs using a threshold of ≥10% for all grades. Some studies applied more specific thresholds based on AE severity: for example, six studies reported only grade 1–2 AEs with a prevalence ≥10%, while reporting grade ≥3 AEs with a lower prevalence range of 1–2%. A few studies used different thresholds, including ≥5% for all grades (n = 1), ≥15% for all grades (n = 1), and ≥20% for all grades (n = 2). One study applied a threshold of >10% for all grades, while another study differentiated thresholds by severity, reporting grade 1–3 AEs at ≥10% and grade ≥4 AEs at ≥2%. In six studies, the reporting threshold was either not available or not clearly stated. Full details are provided in Table 1.

Characteristics of the included studies from ClinicalTrials.gov

The 39 studies included from ClinicalTrials.gov comprised 23 trials involving T-DM1 and 16 involving T-DXd. These studies included various cancers: breast cancer (n=19), gastric or gastroesophageal cancers (n=5), colorectal cancers (n=3), non-small cell lung cancer (NSCLC, n=3), and advanced HER2-positive solid tumors (n=9). Trial phases included phase 1 (n=3), phase 2 (n=24), phase 3 (n=11), and combined phases 2 and 3 (n=1). Studies were either

completed (C: 26 studies), active not recruiting (ANR: 10 studies), or terminated (T: 3 studies). Study included 21 randomized controlled trials and 18 single-arm studies. Dosage ranges for ADCs were 0.3-7.4 mg/kg for T-DM1 and 0.8-8 mg/kg for T-DXd, administered most every three weeks. Enrollment sizes ranged from small-scale trials (3 subjects) to larger trials (2185 subjects). All the included clinical trials (n=39) applied uniform reporting thresholds for adverse events, typically reporting non-serious adverse events occurring at a frequency of ≥5%, and serious adverse events reported at >1%. Detailed characteristics are presented in Table 2.

Risk of Bias Assessment Results

Risk of bias for randomized controlled trials (RCTs) was assessed using the revised Cochrane Risk of Bias tool (RoB 2).[28] For non-randomized studies, the Methodological Index for Non-Randomized Studies (MINORS) tool was applied.[29]

Cochrane Risk of Bias tool (RoB 2) result

Risk of bias for RCTs assessed using the Cochrane RoB 2 tool indicated predominantly low risk across most studies. All trials demonstrated low risk in domains of randomization process, deviations from intended interventions, missing outcome data, and outcome measurement. However, some concerns were noted in the domain of selective reporting of results in one trial by Véronique Diéras et al., which led to an overall rating of "some concerns" for this specific study. All other trials maintained an overall low risk of bias. Domain-level details are summarized visually in Figure 3 and Figure 4.

MINORS risk of bias assessment results

The methodological quality of 23 non-randomized studies was evaluated using the MINORS. The total scores ranged from 8 to 15 points out of a possible 16, reflecting variable methodological quality. Specifically, two studies were classified as good quality (15 points), 19 studies as moderate quality (scores ranging from 9–14 points), and two studies as poor quality (≤8 points). Frequently encountered limitations included inadequate reporting of unbiased endpoint assessments, unclear inclusion of consecutive patients, and inadequate reporting of prospective calculation of sample sizes. Comprehensive details of MINORS scores by individual study are provided in Figure 5.

Meta-analysis results

A meta-analysis was conducted only for adverse events reported in three or more studies or clinical trials, ensuring sufficient data for reliable statistical pooling. Adverse events reported in fewer than three studies were qualitatively summarized within the systematic review. Additionally, due to time constraints, data from ClinicalTrials.gov were analyzed separately for T-DM1 and T-DXd, and a combined meta-analysis for both medications was not conducted.

Meta-analysis based on clinical trials from the published literature

Out of the 40 predefined orofacial AEs identified from the published literature, meta-analyses were conducted specifically for the reported adverse events: oral mucositis, dysgeusia, dry mouth, thrush, and dysphagia, for both T-DM1 and T-DXd individually, as well as combined (overall).

Oral Mucositis prevalence based on the published literature

The pooled prevalence of oral mucositis among patients treated with HER2-targeted ADCs across all included studies was 14% (95% CI: 10–18%), with substantial heterogeneity noted ($I^2 = 91.12\%$, $p < 0.01$). When analyzed by ADC medication type, the pooled prevalence was 9% (95% CI: 4–16%) for T-DM1 studies, with notably high heterogeneity ($I^2 = 96.02\%$, $p < 0.01$), and higher at 17% (95% CI: 13–22%) for T-DXd studies, demonstrating moderate heterogeneity ($I^2 = 68.15\%$, $p < 0.01$). This difference between medication groups was statistically significant ($p = 0.04$), suggesting a higher prevalence of oral mucositis in patients receiving T-DXd compared to T-DM1 (Figure 6). The overall pooled prevalence for Grade 3 or higher oral mucositis was extremely low, at 0% (95% CI: 0-0%). Separate analysis by medication type showed similarly negligible prevalence: 0% for T-DM1 (95% CI: 0-0%; $I^2 = 31.30\%$, $p = 0.28$) and 0% for T-DXd (95% CI: 0–1%; $I^2 = 0.00\%$, $p = 0.95$). Although a statistically significant difference between medication groups was detected ($p < 0.01$), its clinical relevance is minimal given the overall negligible event rate (Figure 7).

Assessment of publication bias revealed noticeable asymmetry upon visual inspection of the funnel plot (Figure 8), suggesting potential bias. This was further supported by Egger's test, confirming statistically significant evidence of small-study effects ($p = 0.0006$).

Thrush prevalence based on the published literature

The overall pooled prevalence of thrush among patients treated with HER2-targeted ADCs was 6% (95% CI: 0–25%), with substantial heterogeneity ($I^2 = 84.31\%$, $p < 0.01$). In subgroup analyses by medication type, the prevalence was 4% (95% CI: 0–17%) based on a single T-DM1 study and slightly higher at 8% (95% CI: 0–47%) for T-DXd, also exhibiting

considerable heterogeneity ($I^2 = 91.00\%$, $p < 0.01$). However, the difference between these subgroups was not statistically significant ($p = 0.76$), suggesting a similar prevalence of thrush across both medications (Figure 9). The pooled prevalence of Grade 3 or higher thrush was negligible at 0% (95% CI: 0–2%), with no observed heterogeneity ($I^2 = 0.00\%$, $p = 0.99$). Medication subgroup analysis similarly showed very low prevalences: 0% (95% CI: 0–7%) for T-DM1 and 0% (95% CI: 0–2%) for T-DXd, both with no heterogeneity. No statistically significant difference between medications was detected ($p = 0.92$), indicating consistently minimal risk for severe thrush across both ADCs (Figure 10).

Assessment of publication bias revealed asymmetry in the funnel plot (Figure 11), suggesting potential bias, further supported statistically by Egger's test ($p = 0.02$). These results indicate the possible presence of publication or selective reporting bias affecting the pooled estimates for thrush.

Dysphagia prevalence based on the published literature

The overall pooled prevalence of dysphagia among patients treated with HER2-targeted ADCs was 2% (95% CI: 0–6%), with substantial heterogeneity noted ($I^2 = 79.39\%$, $p < 0.01$).

In subgroup analysis, the pooled prevalence was similar between medications: T-DM1 at 2% (95% CI: 0–7%) exhibiting high heterogeneity ($I^2 = 84.68\%$, $p < 0.01$), and T-DXd slightly higher at 4% (95% CI: 0–13%), also demonstrating significant heterogeneity ($I^2 = 80.59\%$, $p = 0.02$). No statistically significant difference was found between these subgroups ($p = 0.83$), indicating a comparable likelihood of dysphagia across both medications (Figure 12).

The pooled prevalence of Grade 3 or higher dysphagia was very low at 0% (95% CI: 0–3%). Medication-specific subgroup analyses showed negligible prevalences, with T-DM1 at 0% (95% CI: 0–4%) and significant heterogeneity (I^2 = 86.14%, p = 0.01), and T-DXd similarly low at 1% (95% CI: 0–7%), also displaying notable heterogeneity (I^2 = 78.42%, p = 0.03). The difference between medication subgroups was not statistically significant (p = 0.80), suggesting consistently minimal risk for severe dysphagia across both ADCs (Figure 13).

Assessment of publication bias through funnel plot inspection (Figure 14) showed mild asymmetry. However, Egger's test did not indicate statistically significant evidence of small-study effects (Egger's test, p = 0.10), suggesting limited risk of publication or reporting bias influencing these pooled prevalence estimates.

Dysgeusia prevalence based on the published literature

The overall pooled prevalence of dysgeusia among patients treated with HER2-targeted ADCs was 9% (95% CI: 6–13%), with considerable heterogeneity observed (I^2 = 76.88%, p < 0.01). When analyzed by medication type, the prevalence in patients treated with T-DM1 was 5% (95% CI: 4–6%) with moderate heterogeneity (I^2 = 28.11%, p = 0.32). In contrast, T-DXd showed a higher prevalence of 14% (95% CI: 10–19%) with no observed heterogeneity (I^2 = 0.00%, p = 0.99). The difference between the two medications was statistically significant (p < 0.01), suggesting a greater likelihood of dysgeusia with T-DXd compared to T-DM1 (Figure 15). The overall pooled prevalence of Grade 3 or higher dysgeusia among patients treated with HER2-targeted ADCs was negligible at 0% (95% CI: 0-0%), without observed heterogeneity (I^2 = 0.01%, p = 0.81). Similarly, subgroup analyses revealed

minimal prevalence in both medication groups: T-DM1 at 0% (95% CI: 0-0%; $I^2 = 0.02\%$, $p = 0.66$) and T-DXd at 0% (95% CI: 0-0%; $I^2 = 0.00\%$, $p = 0.98$). The comparison between these medication groups was not statistically significant ($p = 0.12$), reflecting uniformly low rates of severe dysgeusia across both ADCs (Figure 15).

Visual assessment of the funnel plot (Figure 16) demonstrated notable asymmetry, suggesting potential publication bias. Egger's test further supported this, showing statistically significant evidence of small-study effects (Egger's test, $p = 0.0004$). Thus, the possibility of publication or selective reporting bias affecting the pooled prevalence estimates for dysgeusia should be considered.

Dry mouth prevalence based on the published literature

Dry mouth in clinical trials from the published results reported only in T-DM1, yielding the pooled prevalence of 19% (95% CI: 11–28%) with significant heterogeneity ($I^2 = 96.03\%$, $p < 0.01$) (Figure 18). For Grade 3 or higher dry mouth, the pooled prevalence was negligible at 0% (95% CI: 0-0%), with minimal heterogeneity ($I^2 = 11.61\%$, $p = 0.73$), indicating a very low likelihood of severe dry mouth events with T-DM1 treatment (Figure 19). Assessment of publication bias via funnel plot showed mild asymmetry; however, Egger’s test did not provide statistically significant evidence of small-study effects (Egger’s test, $p = 0.05$), suggesting limited evidence of publication bias for this outcome (Figure 20).

ClinicalTrials.gov Meta-analysis Results

The second methodological approach is the analysis of clinical trials registered on ClinicalTrials.gov. This section provides an independent assessment of the prevalence and severity of orofacial adverse events associated with HER2-targeted ADCs, specifically evaluating data from T-DM1 and T-DXd trials separately. The subsequent subsections detail the meta-analysis results for each adverse event reported in these clinical trials.

Oral Mucositis prevalence of T-DM1 based on ClinicalTrials.gov search

The pooled prevalence of oral mucositis in patients treated with T-DM1 across clinical trials was 4% (95% CI: 2–6%). Significant heterogeneity was noted among the included studies (I^2 = 80.40%, $p < 0.001$), indicating variability in reported rates (Figure 21).

The funnel plot suggested asymmetry, raising concerns about potential publication bias. Egger's test confirmed statistically significant evidence of small-study effects (Egger's test, $p = 0.0184$), highlighting possible publication or reporting bias affecting the prevalence estimates (Figure 22).

Dysphagia prevalence of T-DM1 based on ClinicalTrials.gov search

The overall pooled prevalence of dysphagia among patients receiving T-DM1 across clinical trials was 2% (95% CI: 0–6%), with moderate heterogeneity (I^2 = 71.88%, $p = 0.02$) (Figure 23). The pooled prevalence of serious dysphagia among patients treated with T-DM1 in clinical trials was negligible at 0% (95% CI: 0-2%). Moderate heterogeneity was observed (I^2 = 62.01%, $p = 0.03$), indicating some variability across trials (Figure 24). Despite low

prevalence, these findings underscore the overall minimal risk of severe dysphagia associated with T-DM1.

Visual inspection of the funnel plot (Figure 25) showed potential asymmetry, and Egger's test supported this observation, confirming statistically significant small-study effects indicative of publication bias ($p = 0.0035$).

Dysgeusia prevalence of T-DM1 based on ClinicalTrials.gov search

The pooled prevalence of dysgeusia among patients receiving T-DM1 across clinical trials was 6% (95% CI: 4–9%), with significant heterogeneity observed ($I^2 = 78.95\%$, $p < 0.001$) (Figure 26).

Funnel plot inspection suggested asymmetry indicative of publication bias, and Egger's test statistically confirmed the presence of significant small-study effects (Egger's test, $p = 0.0087$) (Figure 27).

Dry mouth prevalence of T-DM1 based on ClinicalTrials.gov search

The overall pooled prevalence of dry mouth among patients treated with T-DM1 was 13% (95% CI: 8–18%) with a high degree of heterogeneity observed among trials ($I^2 = 93.09\%$, $p < 0.01$), reflecting considerable variability in reported rates of dry mouth (Figure 28).

Visual assessment of the funnel plot (Figure 29) revealed notable asymmetry, indicative of possible publication bias or small-study effects. Egger's test statistically

supported these observations, confirming significant evidence of small-study effects (Egger's test, $p = 0.0016$).

Oral Mucositis prevalence of T-DXd based on ClinicalTrials.gov search

The overall pooled prevalence of oral mucositis in patients treated with T-DXd across clinical trials was 16% (95% CI: 12–20%), demonstrating high heterogeneity ($I^2 = 82.68\%$, $p < 0.01$) (Figure 30). Pooled prevalence of serious oral mucositis (Grade ≥3) among patients receiving T-DXd across clinical trials was 6% (95% CI: 3–9%), with no heterogeneity observed among studies ($I^2 = 0.00\%$, $p = 0.34$), indicating consistent results across trials. This prevalence was statistically significant ($p < 0.01$), suggesting a relevant risk of serious oral mucositis with T-DXd (Figure 31).

Visual inspection of the funnel plot (Figure 32) indicated noticeable asymmetry, suggesting potential publication bias. This asymmetry was statistically confirmed by Egger's test, indicating significant small-study effects or publication bias (Egger's test, $p = 0.0347$).

Thrush prevalence of T-DXd based on ClinicalTrials.gov search

The overall pooled prevalence of thrush among patients receiving T-DXd in clinical trials was low at 1% (95% CI: 0–4%), with no observed heterogeneity ($I^2 = 0.00\%$, $p = 0.47$) (Figure 33).

The funnel plot (Figure 34) visually suggested asymmetry, indicating potential small-study effects or publication bias, and Egger's test confirmed this statistically (Egger's test, p =

0.0103). This suggests possible reporting or publication bias influencing the observed prevalence estimates for thrush.

Dysphagia prevalence of T-DXd based on ClinicalTrials.gov search

The pooled prevalence of dysphagia among patients treated with T-DXd across clinical trials was 5% (95% CI: 3–7%), with no observed heterogeneity ($I^2 = 0.00\%$, $p = 0.60$) (Figure 35). The prevalence of serious dysphagia was negligible at 0% (95% CI: 0–1%), though moderate heterogeneity was observed ($I^2 = 56.48\%$, $p = 0.03$) (Figure 36).

Visual inspection of the funnel plot indicated notable asymmetry, suggesting potential publication bias (Figure 37). This asymmetry was statistically confirmed by Egger's test ($p = 0.0015$), indicating significant evidence of small-study effects or reporting bias in the trials assessing dysphagia related to T-DXd.

Dysgeusia prevalence of T-DXd based on ClinicalTrials.gov search

The overall pooled prevalence of dysgeusia in patients treated with T-DXd across clinical trials was 6% (95% CI: 4–8%), exhibiting substantial heterogeneity ($I^2 = 72.07\%$, $p < 0.01$) (Figure 37). For serious dysgeusia (Grade ≥3), the prevalence was considerably lower at 1% (95% CI: 0–3%), with no observed heterogeneity ($I^2 = 0.00\%$, $p = 0.91$) (Figure 38).

Examination of the funnel plot revealed notable asymmetry, indicative of potential publication bias or small-study effects (Figure 39). This visual observation was statistically supported by Egger's test, which confirmed significant small-study effects (Egger's test, $p = 0.0046$) (Figure 40).

Dry mouth prevalence of T-DXd based on ClinicalTrials.gov search

The overall pooled prevalence of dry mouth among patients treated with T-DXd across clinical trials was 13% (95% CI: 8–18%), with substantial heterogeneity observed (I^2 = 93.09%, $p < 0.01$) (Figure 41).

Examination of the funnel plot (Figure 42) suggested asymmetry, confirmed statistically by Egger's test, which indicated significant small-study effects, suggestive of potential publication bias (Egger's test, $p = 0.0016$).

Comparison of AEs across Methodologies

By comparing the types of orofacial AEs reported across clinical trials from published literature with those listed in the clinical trials database (ClinicalTrials.gov), we identified several unique AEs reported only in clinical trials database (ClinicalTrials.gov). Specifically, oropharyngeal pain, toothache, and gingival bleeding were reported individually for both T-DM1 and T-DXd clinical trials but were not reported in the published literature. Additionally, mouth ulceration, oral herpes, dental caries, and periodontal disease were exclusively reported in T-DXd trials, while serious osteonecrosis of the jaw AE, was uniquely reported in T-DM1 trials.

The prevalence of these uniquely identified AEs, based on the clinical trials database, differed by agent. In T-DM1 clinical trials, the prevalence was 6% (95% CI: 4–8%) for oropharyngeal pain, 2% (95% CI: 0–5%) for toothache, 6% (95% CI: 4–7%) for gingival bleeding, and a negligible 0% (95% CI: 0–0%) for serious osteonecrosis of the jaw. In T-DXd trials, the prevalence was 4% (95% CI: 2–7%) for oropharyngeal pain, 4% (95% CI: 1–

8%) for toothache, 5% (95% CI: 1–11%) for gingival bleeding, 6% (95% CI: 3–9%) for mouth ulceration, 4% (95% CI: 0–12%) for oral herpes, 1% (95% CI: 0–5%) for dental caries, and 5% (95% CI: 0–16%) for periodontal disease.

Further differences were noted in the prevalence of the same orofacial adverse events of oral mucositis, thrush, dysphagia, dysgeusia, and dry mouth for both T-DM1 and T-DXd when comparing the two methodologies as shown in detailed in Table 3.

Oral mucositis prevalence for T-DM1 was higher in published literature (9%, 95% CI: 4–16%) compared to ClinicalTrials.gov (4%, 95% CI: 4–9%). For T-DXd, prevalence was similar between published literature (17%, 95% CI: 13–22%) and ClinicalTrials.gov data (16%, 95% CI: 12–20%).

Thrush prevalence for T-DM1 was reported in published literature (4%, 95% CI: 0–17%), with no cases identified in ClinicalTrials.gov. T-DXd had a higher thrush prevalence in published literature (8%, 95% CI: 0–47%) compared to ClinicalTrials.gov (1%, 95% CI: 0–4%).

Dysphagia prevalence for T-DM1 was similar between methodologies, with published literature reporting (2%, 95% CI: 0–7%) and ClinicalTrials.gov reporting (2%, 95% CI: 0–6%). For T-DXd, dysphagia prevalence was slightly lower in published literature (4%, 95% CI: 0–13%) compared to ClinicalTrials.gov (5%, 95% CI: 3–7%). Severe (Grade ≥3) dysphagia was negligible in both sources.

Dysgeusia prevalence for T-DM1 was slightly lower in published literature (5%, 95% CI: 4–6%; $p < 0.01$) compared to ClinicalTrials.gov (6%, 95% CI: 4–9%). For T-DXd, dysgeusia

prevalence was notably higher in published literature (14%, 95% CI: 10–19%) compared to ClinicalTrials.gov (6%, 95% CI: 4–8%). Severe (Grade ≥3) dysgeusia remained negligible across both medications and methodologies.

Dry mouth prevalence for T-DM1 was higher in published literature (19%, 95% CI: 11–28%) compared to ClinicalTrials.gov (13%, 95% CI: 8–18%). For T-DXd, no eligible studies from published literature reported dry mouth, whereas ClinicalTrials.gov indicated a prevalence (13%, 95% CI: 8–18%).

Discussion

This study aimed to comprehensively explore the prevalence and characteristics of oral mucosal, salivary gland, and various other orofacial AEs associated with HER2-targeted ADCs, specifically T-DM1 and T-DXd. Additionally, this investigation assessed the severity of these orofacial AEs, highlighting clinical implications for patient management and supportive care. Furthermore, we examined variations in reporting across multiple databases, aiming to clarify the consistency and comprehensiveness of orofacial AEs documentation and to identify potential gaps or discrepancies in pharmacovigilance practices.

Based on the overall prevalence reported in the published literature, oral mucositis was the most commonly identified orofacial AE associated with T-DM1 and T-DXd, followed by dysgeusia and dry mouth. Thrush and dysphagia were among the least frequently reported AEs. However, meta-analysis of the published literature for T-DM1 specifically indicated that dry mouth was the most prevalent AE (19%, 95% CI: 11–28%), followed by oral mucositis (9%, 95% CI: 5–15%), dysgeusia (5%, 95% CI: 4–6%), thrush (4%, 95% CI: 0–17%), and dysphagia (2%, 95% CI: 0–7%). For T-DXd, oral mucositis remained the most common (17%, 95% CI: 13–22%), followed by dysgeusia (14%, 95% CI: 10–19%), thrush (8%, 95% CI: 0–47%), and dysphagia (4%, 95% CI: 0–13%), with dry mouth not reported in any of the studies reviewed. These findings align closely with those reported by Mercadante et al. (2015) in a study of 669 advanced cancer patients, where dry mouth was the most frequent oral AE (40.4%), followed by oral mucositis (22.3%) and dysphagia (15.4%). [30]

Our result highlighted that the overall pooled prevalence of oral mucositis among patients treated with HER2-targeted ADCs across published literature was 14% (95% CI: 10–18%),

indicating a notable frequency of this adverse event. Thus, this prevalence aligns closely with the narrative review by D'Arienzo et al. (2023), which also documented a comparable frequency range of 10–20% for oral mucositis in the context of ADC treatments generally. Furthermore, Suzuki et al. (2023) conducted a meta-analysis assessing ADC-related toxicities across 17 clinical trials reporting oral mucositis, finding an increased odds ratio (OR = 0.69; 95% CI: 0.43–1.09); however, the observed association did not reach statistical significance ($p = 0.11$).

Thrush was an infrequently reported AE among patients who received HER2-targeted ADCs. Pooled prevalence across published literature was 6% (95% CI: 0–25%). Our findings closely match the 5% frequency of oral candidiasis reported in early-phase trials of the anti-EGFR ADC serclutamab talirine (ABBV-321) used in patients with solid tumors.[31] In contrast, other ADCs, such as PF-06647263, an anti-EFNA4 calicheamicin compound, demonstrated a notably higher oral candidiasis incidence of 16% in phase I clinical trials.[32]

Dysphagia was consistently reported with a relatively low prevalence among patients receiving HER2-targeted ADCs. The pooled prevalence from published literature was 2% (95% CI: 0–6%). Comparatively, the meta-analysis by Suzuki et al. (2023) reported odds ratios for dysphagia of all grades and severe dysphagia as 0.48 (95% CI: 0.18–1.25; p=0.13) and 1.04 (95% CI: 0.19–5.78; p=0.97), respectively, neither of which reached statistical significance.

Dysgeusia was a relatively common orofacial adverse event associated with HER2-targeted ADCs. Overall pooled prevalence from published literature was 9% (95% CI: 6–13%), with significant heterogeneity ($I^2 = 76.88\%$, $p < 0.01$). In comparison, the meta-

analysis by Suzuki et al. (2023) on general ADC treatments reported a non-significant odds ratio of 1.17 (95% CI: 0.75–1.81; p = 0.49) for dysgeusia of all grades, without reporting any severe dysgeusia events.[33] On the other hand, a Japanese cohort study by Imai et al. (2013) observed a substantially higher prevalence of dysgeusia reported as 38.8% among chemotherapy patients, particularly those receiving 5-fluorouracil and its analogs, who showed prevalence rates as high as 48.1%.[34]

Dry mouth was frequently reported among patients treated with HER2-targated ADCs. In published literature, all studies reporting this adverse event involved T-DM1, yielding a pooled prevalence of 19% (95% CI: 11–28%). There were no eligible published studies reporting dry mouth specifically for T-DXd, precluding direct statistical comparison between the two ADCs based on published data. In comparison, the meta-analysis conducted by Suzuki et al. (2023) on general ADC therapies reported a statistically significant odds ratio of 4.46 (95% CI: 2.56–7.75; p < 0.00001) for dry mouth across all severity grades, but a non-significant odds ratio of 1.04 (95% CI: 0.19–5.77; p = 0.97) for severe (Grade ≥3) dry mouth events.[33] On the other hand, although the prevalence of chemotherapy-induced dry mouth is not well-established, reported prevalence rates range from 32% to 92% , whereas for immune checkpoint inhibitors, the prevalence ranges from 53% to 58%.[35] Thus, they are both higher in prevalence range compared to our study.

Regarding the methodological consideration Our screening process showed robust reliability, with moderate-to-substantial agreement between reviewers as shown in Cohen's Kappa statistics with 0.68 initially and improved to 0.801 following clarification of inclusion

criteria. This high IRR strengthens confidence in the systematic and unbiased nature of our study selection and inclusion processes.

Additionally, the risk of bias assessments indicated predominantly low risk across randomized controlled trials evaluated by the Cochrane RoB 2 tool, except for minor concerns regarding selective reporting in Véronique Diéras et al. Non-randomized studies assessed via MINORS demonstrated moderate methodological quality overall, highlighting common limitations such as inadequate reporting of unbiased endpoint assessments and prospective sample-size calculations. Thus, these assessments suggest that the included evidence is reliable to for meta-analyses. A notable methodological difference between published literature and ClinicalTrials.gov data was observed in AE) reporting thresholds. ClinicalTrials.gov trials consistently used standardized reporting criteria of reporting threshold of non-serious AEs ≥5%, serious AEs <1%, facilitating uniform data collection and comparability. In contrast, thresholds in published literature varied widely ranging from ≥5% to ≥20% and often differed by severity grades. Such inconsistency could significantly affect the real prevalence estimates of AEs and would explain the differences in prevalence differences between two methodologies.

To the best of our knowledge, this is the first study to systematically evaluate the prevalence and severity of orofacial adverse events associated with HER2-targeted ADCs and to compare findings derived from two distinct methodologies of systematic review with meta-analysis of published literature and analysis of clinical trial data from ClinicalTrials.gov. Despite the comprehensive approach and novel findings presented in this study, several limitations should be acknowledged when interpreting our results. Firstly, the

general high heterogeneity observed across the meta-analyses could be attributed to multiple factors, including variations in cancer types, study phases, medication doses, and administration frequencies. These differences could potentially be explored and addressed through additional grouping and subgroup analyses. Secondly, there was frequent evidence of small-study effects, highlighting the need for further sensitivity analyses, such as meta-regression or trim-and-fill methods, to better assess and potentially mitigate the impact of smaller studies on the pooled prevalence estimates. Thirdly, the absence of combined pooled analyses and subgroup comparisons between T-DM1 and T-DXd for adverse events identified from the ClinicalTrials.gov data may limit the comprehensiveness of our findings derived from this methodology. Consequently, potential differences or similarities in adverse event profiles between these two ADCs within the clinical trials data may not have been fully captured, suggesting the need for future studies to perform such comparative analyses explicitly. Fourthly, data extraction and analysis from the ClinicalTrials.gov database were conducted by a single reviewer, potentially introducing data collection bias or oversight. Furthermore, the absence of a qualitative risk of bias assessment for studies from ClinicalTrials.gov could affect the robustness and interpretation of findings. Future research should incorporate multiple reviewers and comprehensive qualitative bias assessments to strengthen the validity and reliability of results obtained from this methodology. Lastly, a potential limitation of this study was the decision to perform meta-analyses exclusively on adverse events reported in three or more studies or clinical trials. Adverse events identified in fewer than three sources were qualitatively summarized, possibly limiting the quantitative evaluation of less frequently reported or rare adverse events. Consequently, important but infrequently observed adverse effects might have been overlooked or insufficiently

characterized. Future research with larger-scale or more comprehensive data collection is needed to address this limitation adequately.

Future research should prioritize comprehensive, combined meta-analyses that integrate data from both published literature and clinical trial databases, thereby enhancing the robustness and accuracy of findings related to orofacial AEs associated with HER2-targated ADCs. Given the high heterogeneity observed in this review, further subgroup and meta-regression analyses are needed to investigate the impact of factors such as cancer type, treatment phase, medication dosing frequency, and patient population characteristics. Additionally, it is recommended to either unify or dedicate specific categories within standardized assessment tools, such as the CTCAE, explicitly addressing orofacial AEs. This standardization would facilitate monitoring, reporting consistency, and future research in this area. Lastly, establishing uniform thresholds for adverse event reporting and severity criteria across clinical trials would significantly enhance comparability and the precision of pooled analyses.

Conclusion

This systematic review and meta-analysis evaluated the prevalence and severity of orofacial AEs associated with FDA-approved HER2-targeted ADCs, T-DM1 and T-DXd. Oral mucositis and dry mouth were among the most observed AEs, with oral mucositis notably more prevalent with T-DXd compared to T-DM1. Dysgeusia was also more frequently reported with T-DXd. However, dysphagia and thrush were relatively uncommon and showed no significant differences between the ADCs. Variability in prevalence and severity between literature-based reviews and clinical trial registry data highlights the need for standardized reporting and tailored monitoring approaches to enhance patient safety and clinical care.

APPENDIX A

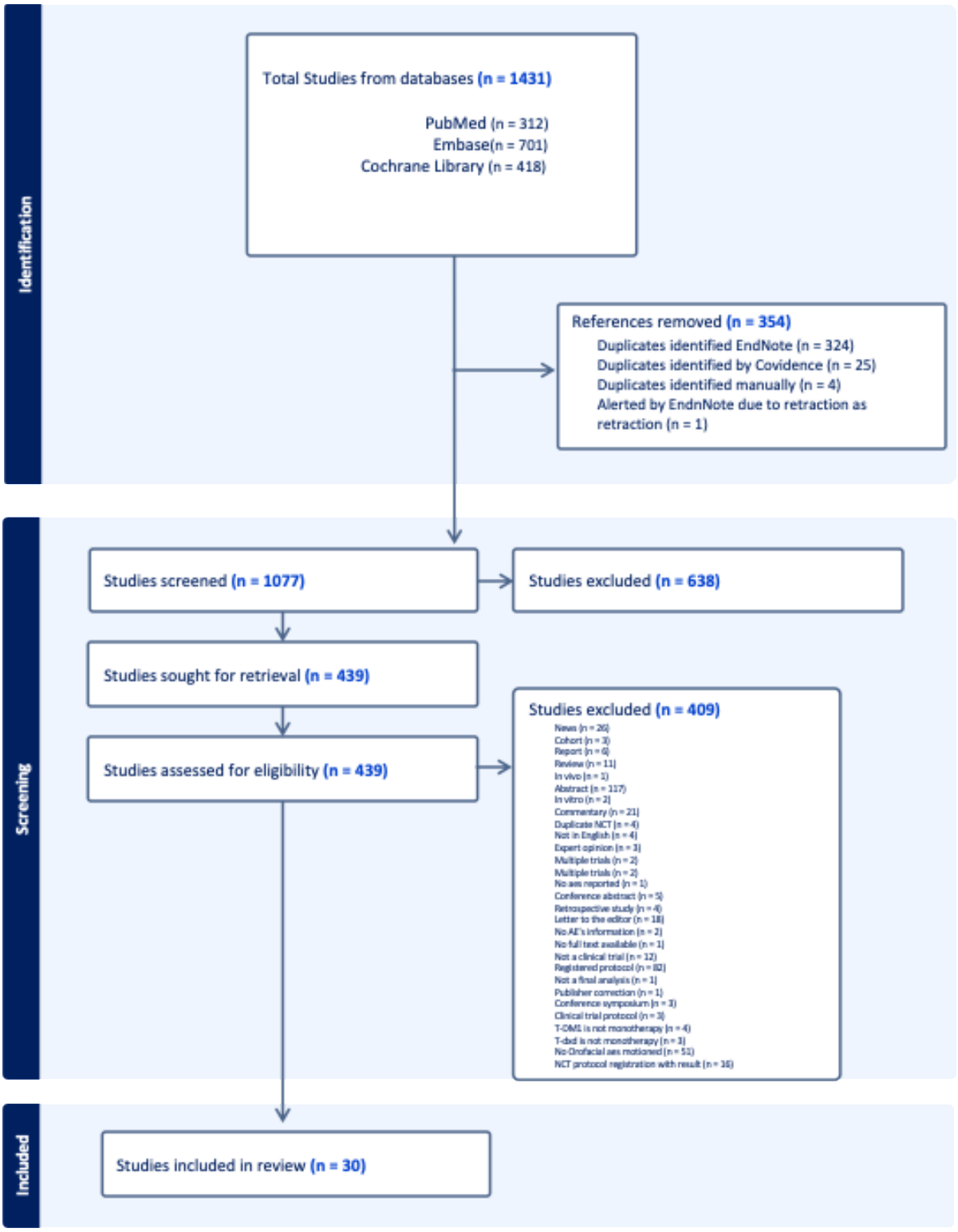


Figure 1 PRISMA 2020 checklist illustrating the systematic review and study selection process followed in this study generated by Coivdence.

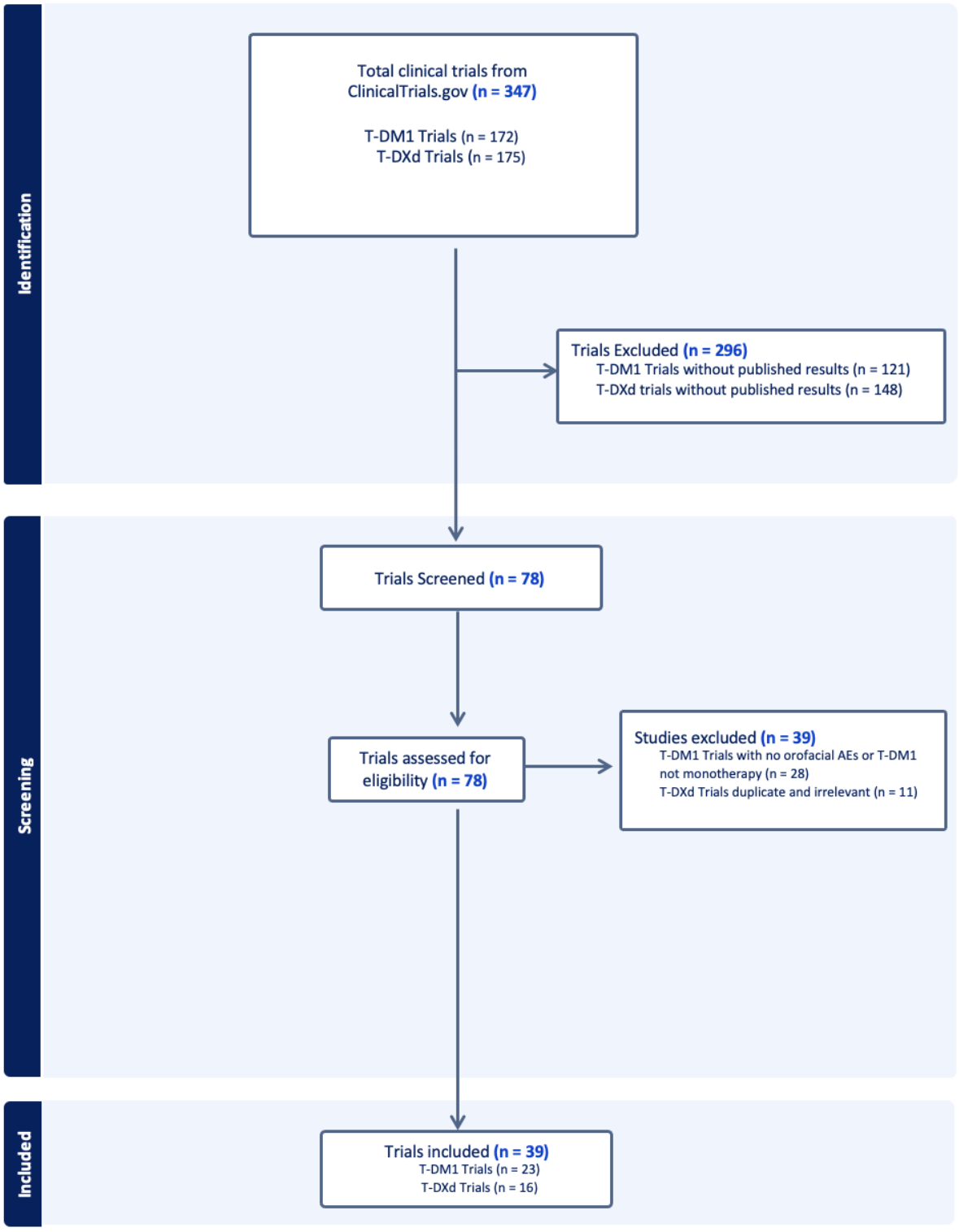


Figure 2 Flow diagram summarizing the selection of clinical trials from ClinicalTrials.gov

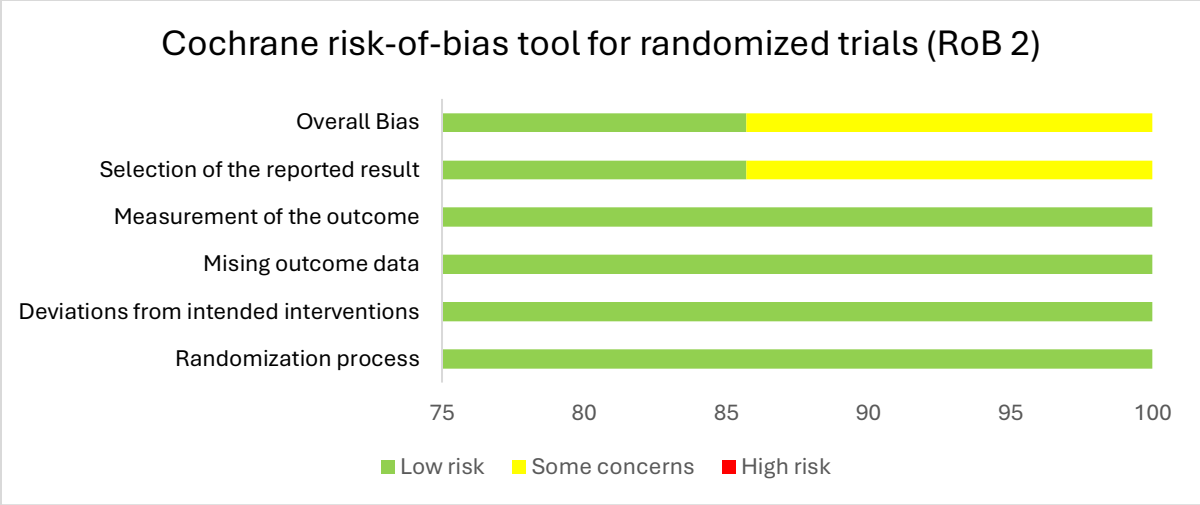


Figure 3 Summary of risk-of-bias judgments using the Cochrane RoB 2 tool for randomized trials

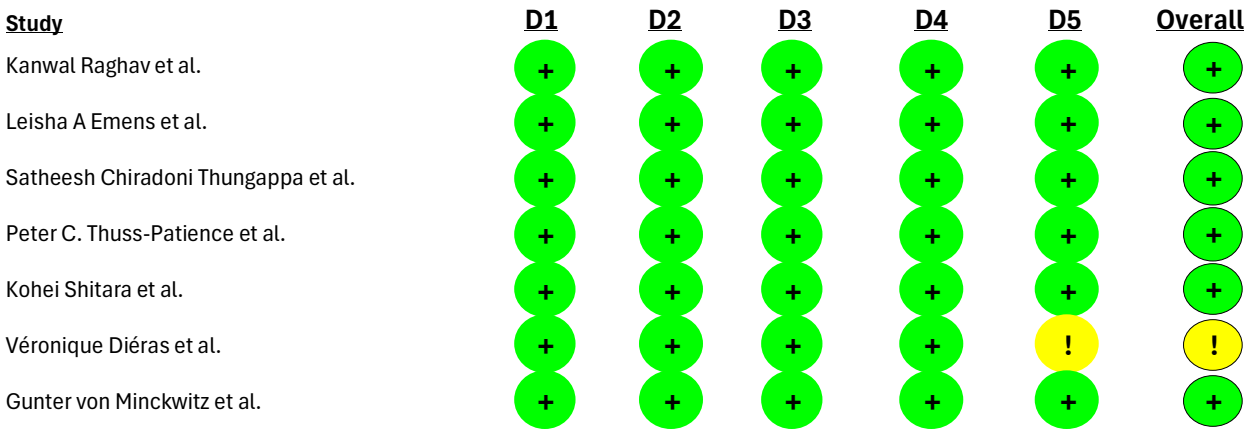
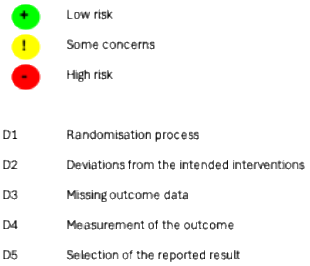


Figure 4 Domain-level assessment of risk of bias using the Cochrane RoB 2 tool for each randomized controlled trial.



Study	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	Total score
Harukaze Yamamoto et al.	2	0	2	2	0	0	2	0	8
Junji Tsurutani et al.	2	2	2	2	0	2	2	1	13
Adaaki Nishikawa et al.	2	2	2	2	0	2	1	1	12
Eric Van Cutsem et al.	2	2	2	2	1	2	1	2	14
Toshihiko Doi et al.	2	2	2	2	0	2	1	2	13
Akihiro Ohba et al.	2	2	2	2	2	2	1	2	15
Manish Gupta et al.	2	1	2	2	0	2	1	1	11
Rupert Bartsch et al.	2	2	1	2	1	2	1	0	11
M. Vaz Batista et al.	2	2	2	2	0	2	2	1	13
Shanu Modi et al.	2	2	2	2	1	2	2	2	15
Shanu Modi et al.	2	0	2	2	2	1	1	0	10
Dongmei Ji et al.	2	2	2	2	0	2	1	0	11
Beeram et al.	2	0	2	2	0	1	1	0	8
Masahiro Kashiwaba et al.	2	0	2	2	1	2	1	1	11
F. Montemurro et al.	2	0	2	2	0	2	1	1	10
Bob T Li et al.	2	2	2	2	1	2	0	2	13
Ian E. Krop et al	2	1	2	2	1	2	1	2	13
Ian E. Krop et al.	2	1	2	2	1	1	1	0	10
Akihiko Shimomura et al	2	2	2	2	1	2	1	1	13
K. L. Jhaveri et al.	2	2	2	2	0	1	1	1	11
Egbert F Smit et al.	2	1	2	2	1	2	1	2	13
Kenji Tamura et al.	2	2	2	2	0	2	2	1	13
Kensei Yamaguchi et al.	2	1	2	2	0	0	2	1	10

Figure 5 Methodological quality assessment of non-randomized studies using MINORS criteria, scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate), with total scores reflecting overall quality (15–16: good; 9–14: moderate; ≤8: poor). Green indicates adequate reporting, yellow indicate inadequate reporting, and red indicates items not reported or inadequately addressed.

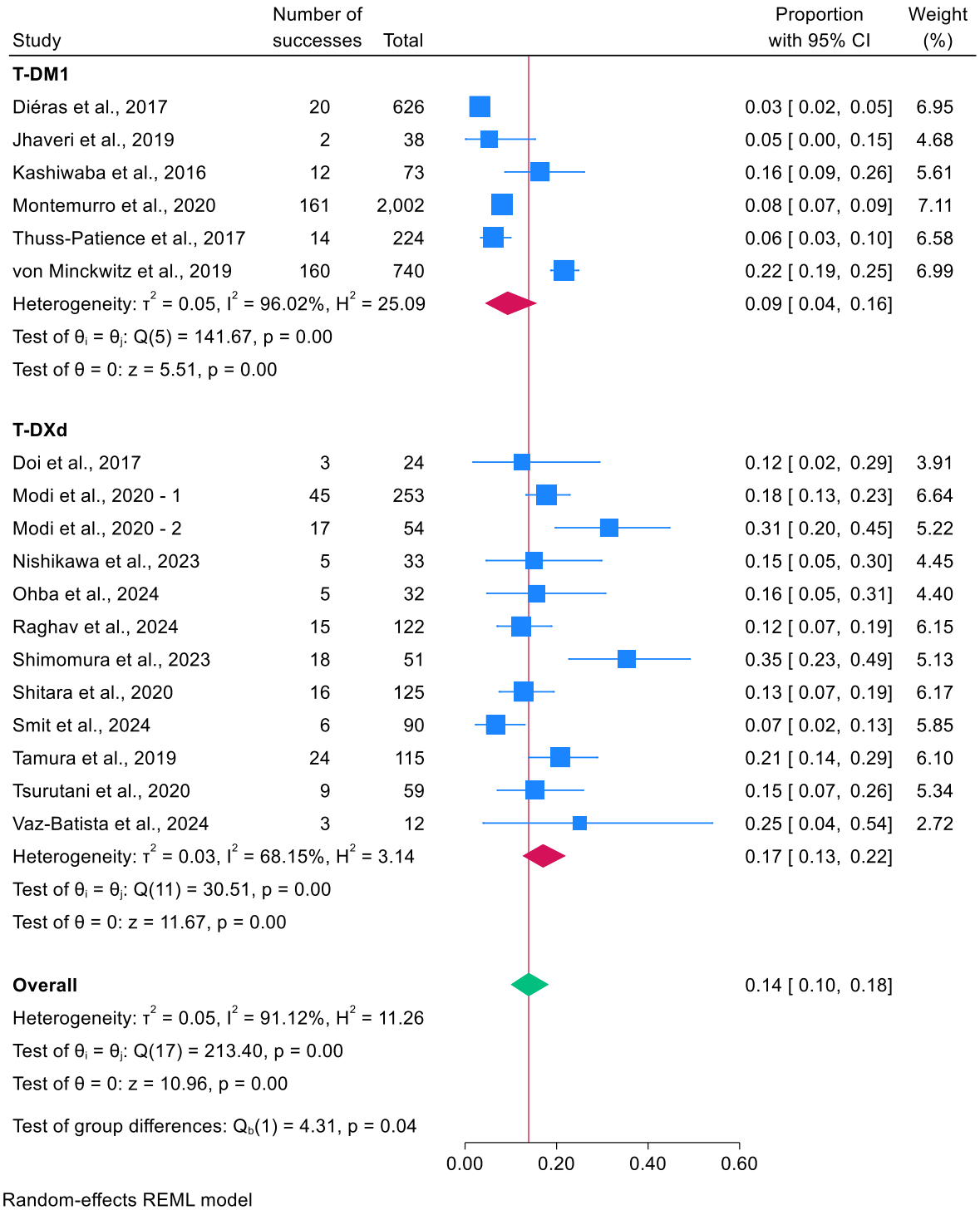


Figure 6 Forest plot illustrating the pooled prevalence of oral mucositis associated with HER2-targeted ADCs (T-DM1 and T-DXd). Squares represent the prevalence estimate for each study, with their size indicating study weight. Horizontal lines depict 95% confidence intervals. Diamonds represent pooled prevalence estimates for each medication subgroup and overall combined analysis. Heterogeneity was assessed using the I^2 statistic, and subgroup differences were tested using the Q-test. A random-effects REML model was used.

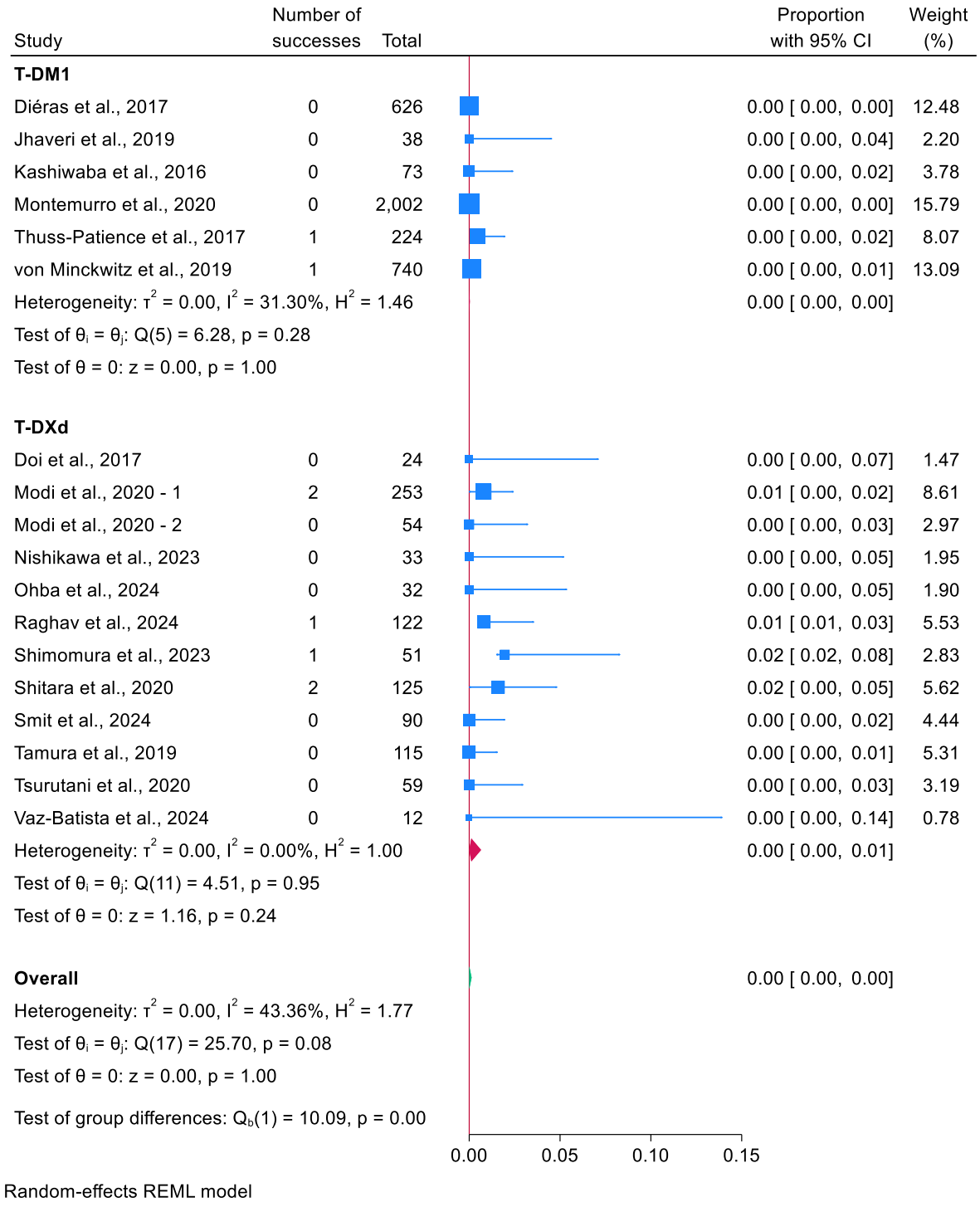


Figure 7 Forest plot showing pooled prevalence of Grade 3 or higher oral mucositis associated with HER2-targeted ADCs (T-DM1 and T-DXd). Squares represent the prevalence from individual studies, with their size proportional to study weight. Horizontal lines indicate the 95% confidence intervals (CIs). Diamonds represent the pooled prevalence estimates for each medication subgroup and the overall combined analysis. Heterogeneity was assessed using the I^2 statistic, and subgroup differences were evaluated using the Q-test. Analysis was performed using a random-effects REML model.

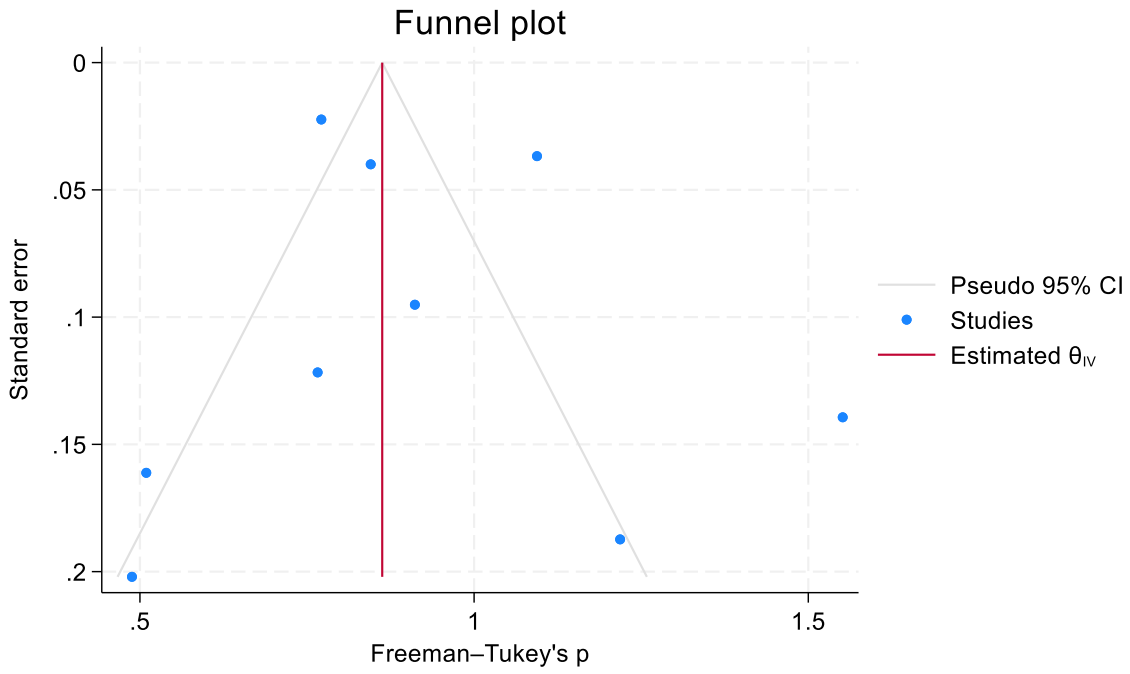


Figure 9 Funnel plot illustrating the publication bias assessment for oral mucositis prevalence among HER2-Targeted ADC studies.

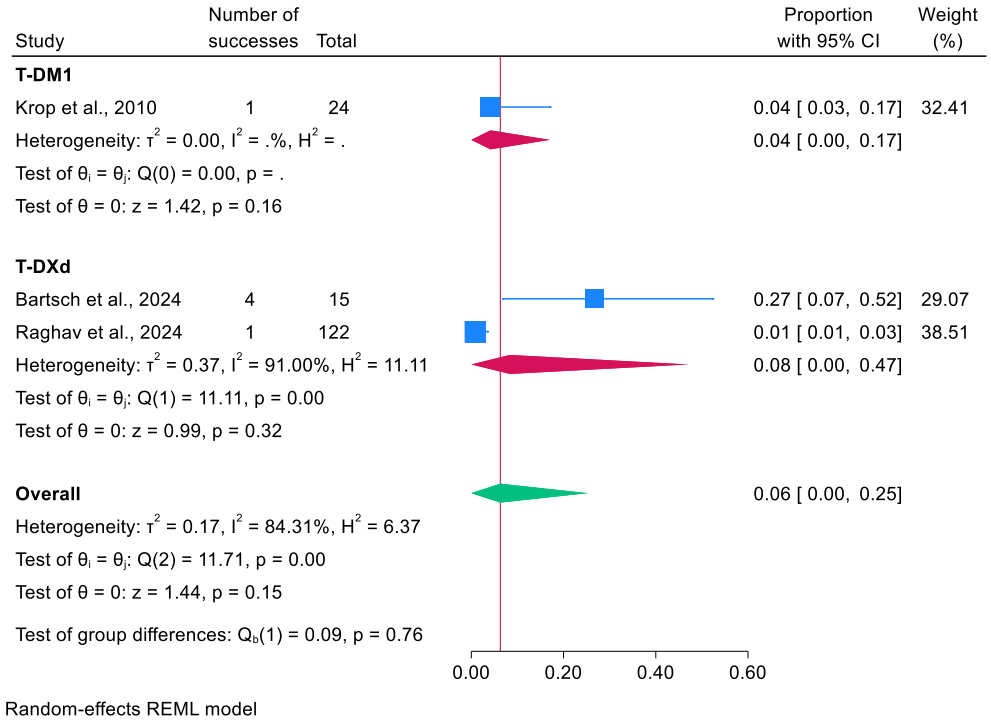


Figure 8 Forest plot illustrating the pooled prevalence of thrush among patients treated with HER2-targeted ADCs (T-DM1 and T-DXd). Squares represent the prevalence estimates of individual studies, with their sizes reflecting study weights. Horizontal lines indicate 95% confidence intervals (CIs). Diamonds depict subgroup and overall pooled prevalence estimates.

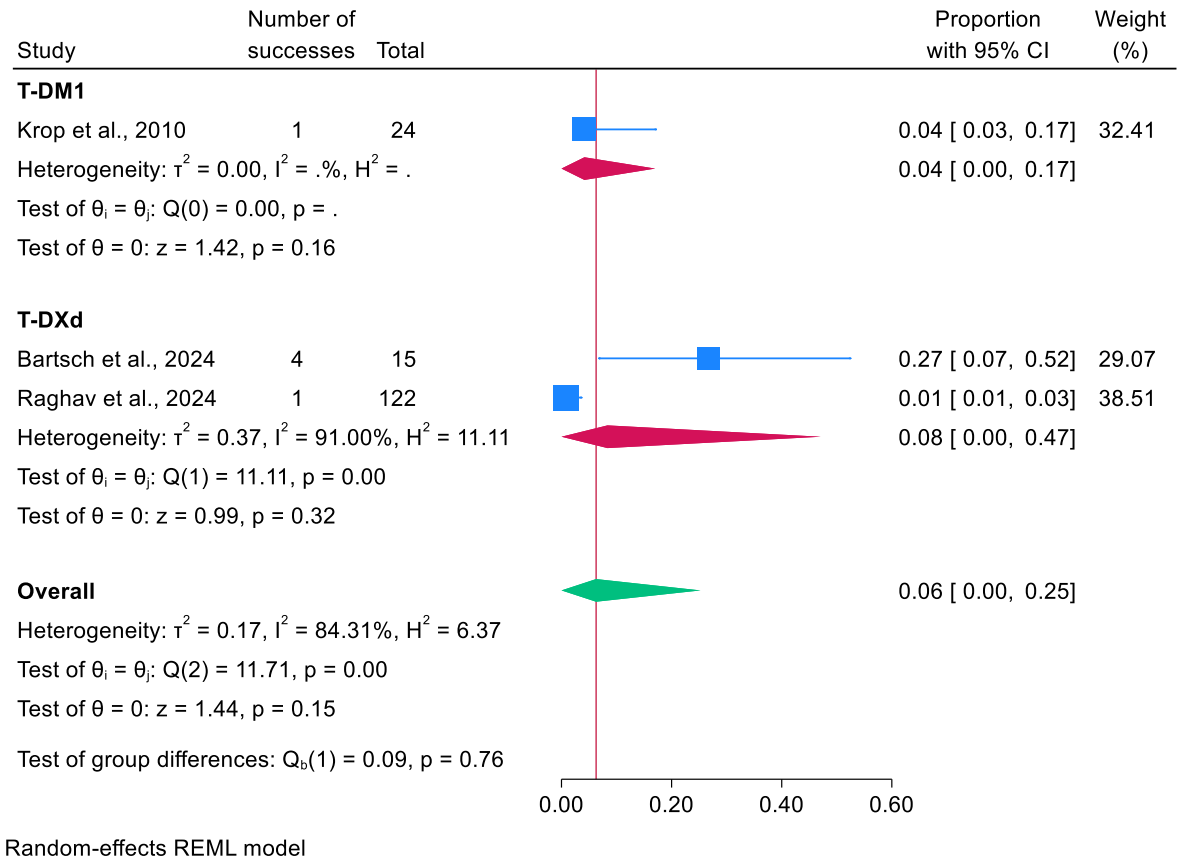


Figure 10 Forest plot depicting pooled prevalence of Grade 3 or higher thrush associated with HER2-targeted ADCs (T-DM1 and T-DXd). Squares represent individual study prevalence estimates, with their size proportional to the weight of the study. Horizontal lines indicate 95% confidence intervals (CIs). Diamonds illustrate subgroup and overall pooled prevalence using a random-effects REML model.

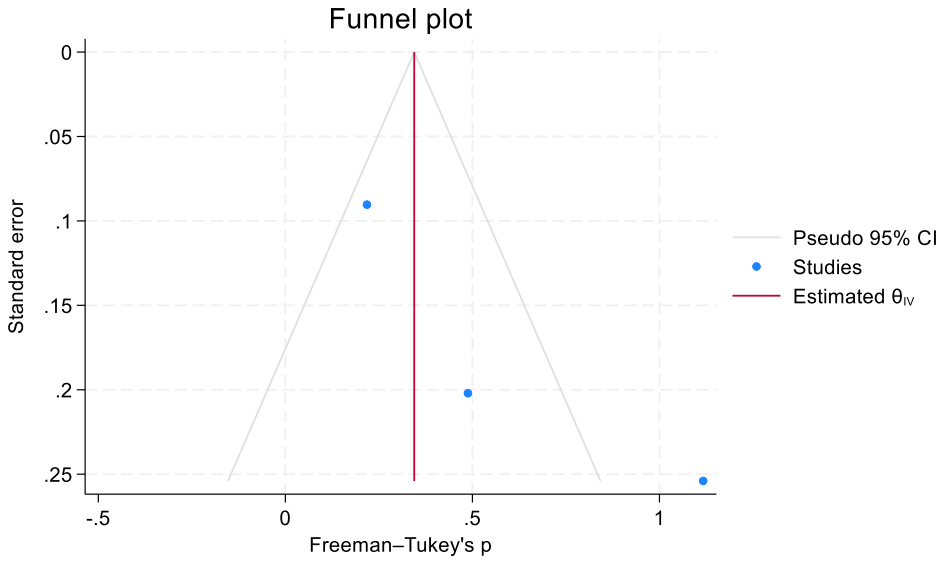


Figure 11 Funnel plot illustrating publication bias assessment for thrush prevalence among studies involving HER2-targeted ADCs.

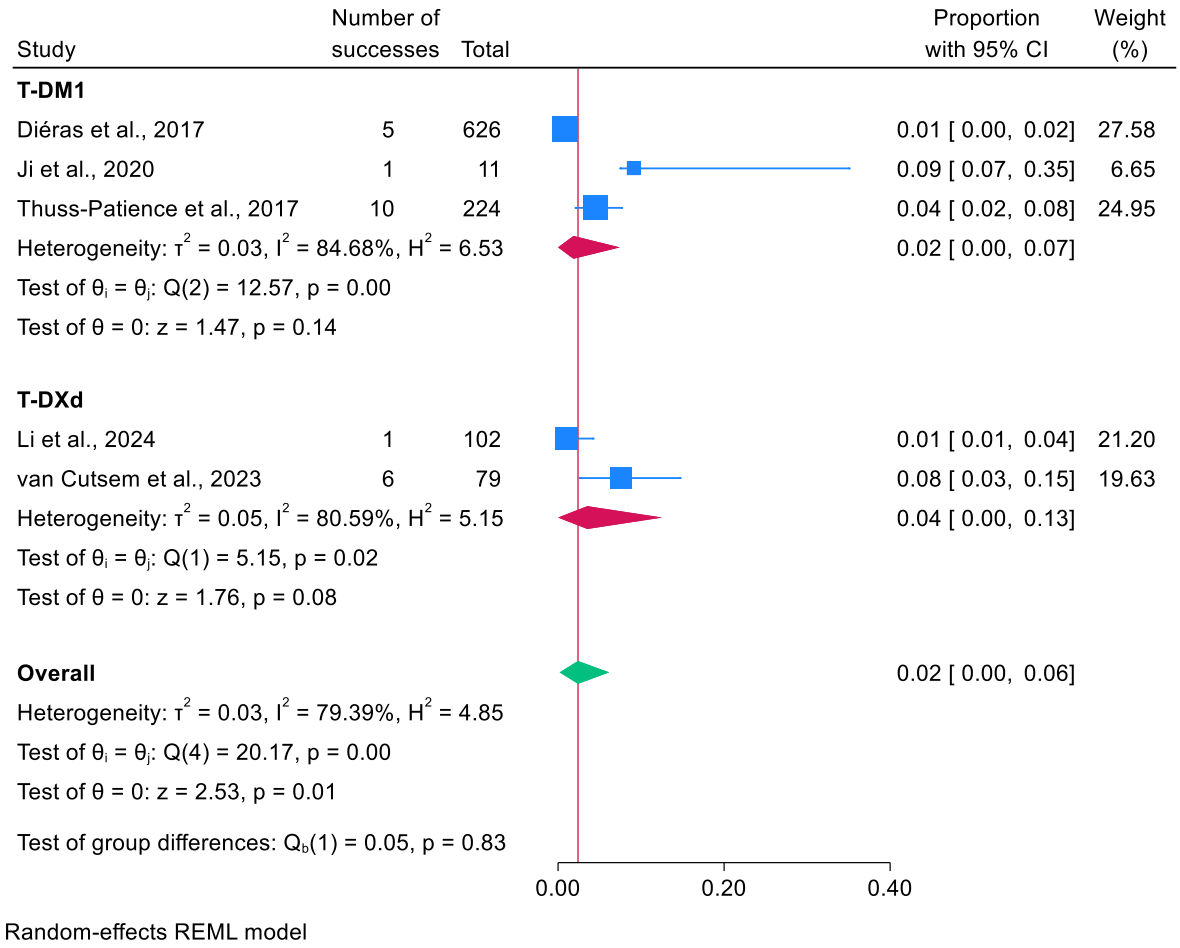


Figure 12 Forest plot illustrating the pooled prevalence of dysphagia among patients treated with HER2-targeted ADCs (T-DM1 and T-DXd). Squares represent individual study prevalence estimates, with size indicating relative study weight. Horizontal lines depict 95% confidence intervals (CIs). Diamonds show subgroup and overall pooled prevalence estimates derived from a random-effects REML model.

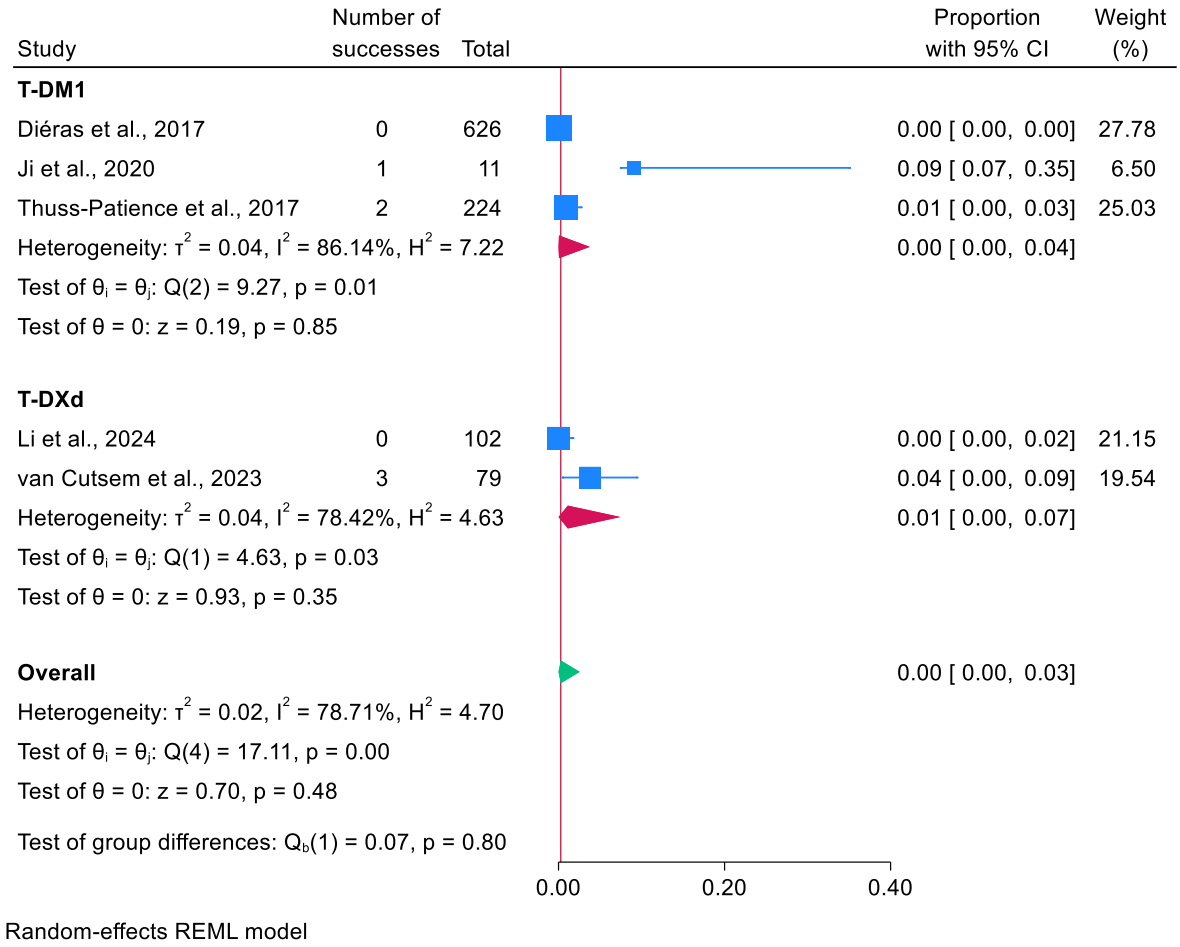


Figure 13 Forest plot showing pooled prevalence of Grade 3 or higher dysphagia associated with HER2-targeted ADCs (T-DM1 and T-DXd). Squares indicate prevalence estimates from individual studies, with size proportional to study weight. Horizontal lines represent 95% CIs. Diamonds indicate subgroup and overall pooled prevalences calculated using a random-effects REML model.

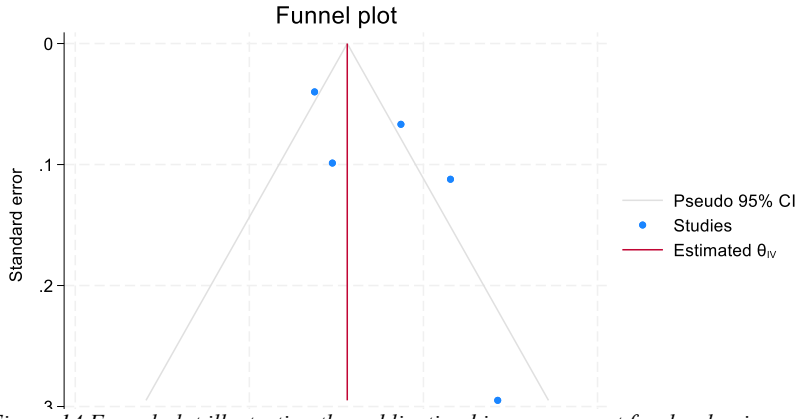


Figure 14 Funnel plot illustrating the publication bias assessment for dysphagia prevalence among studies involving HER2-targeted ADCs

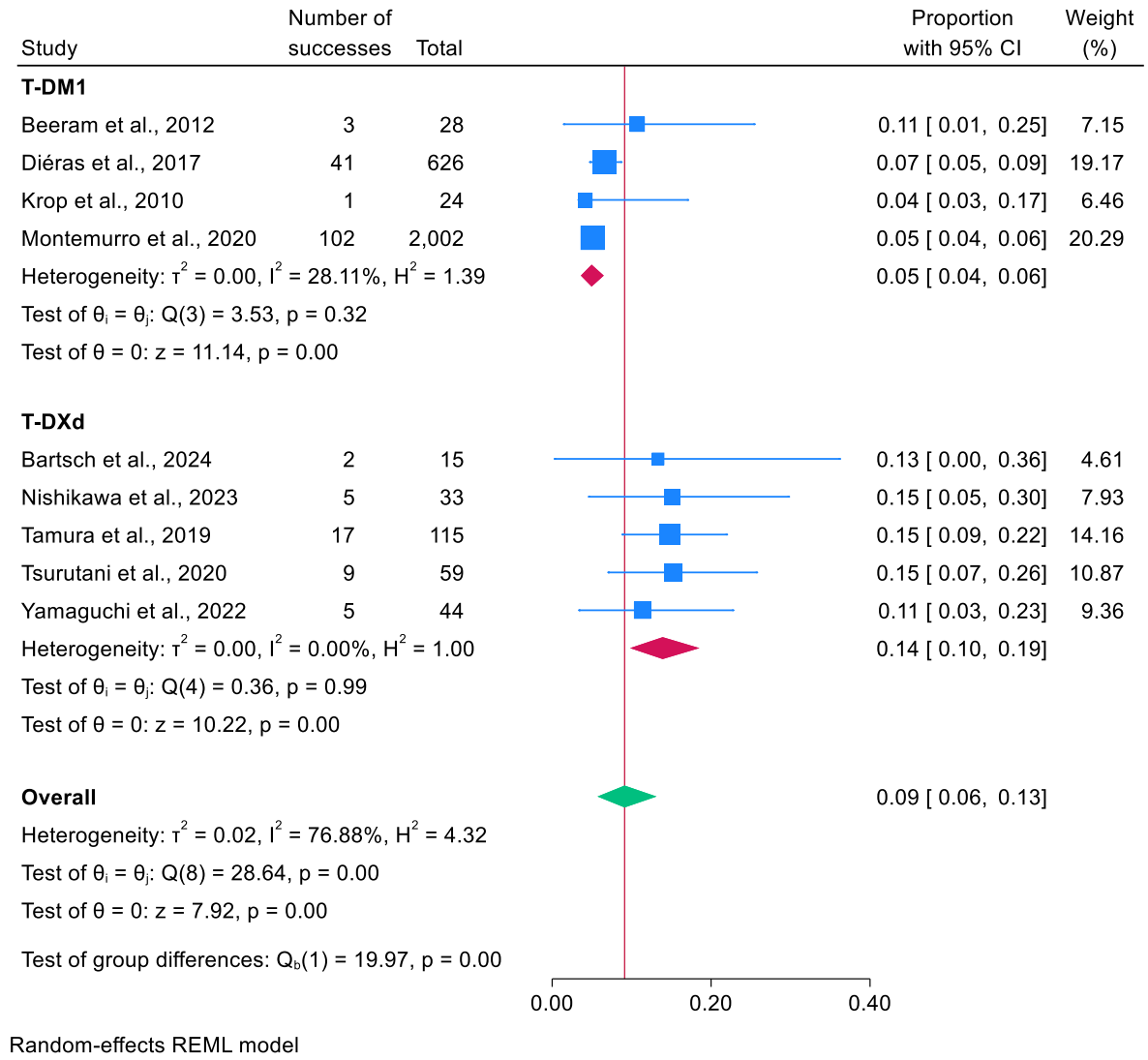


Figure 15 Forest plot illustrating the pooled prevalence of dysgeusia in patients treated with HER2-targeted ADCs (T-DM1 and T-DXd). Squares represent prevalence estimates from individual studies, with their size proportional to the study weight. Horizontal lines depict 95% confidence intervals (CIs). Diamonds indicate subgroup and overall pooled prevalence estimates obtained from a random-effects REML model.

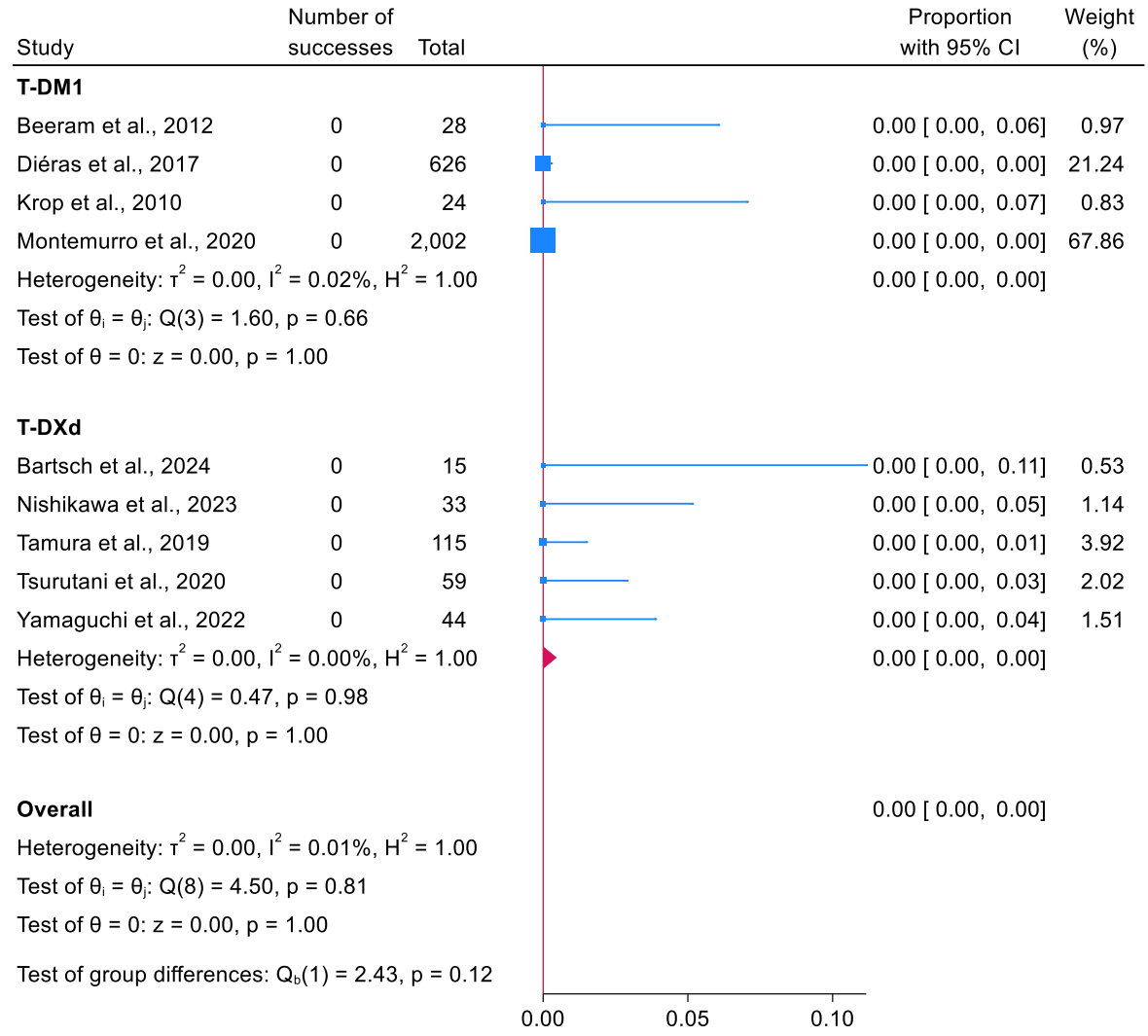


Figure 16 Forest plot showing pooled prevalence of Grade 3 or higher dysgeusia in patients receiving HER2-targeted ADCs (T-DM1 and T-DXd). Squares indicate individual study prevalence estimates with size proportional to their study weight. Horizontal lines represent 95% confidence intervals (CIs). Diamonds illustrate subgroup and overall pooled prevalence estimates using a random-effects REML model.

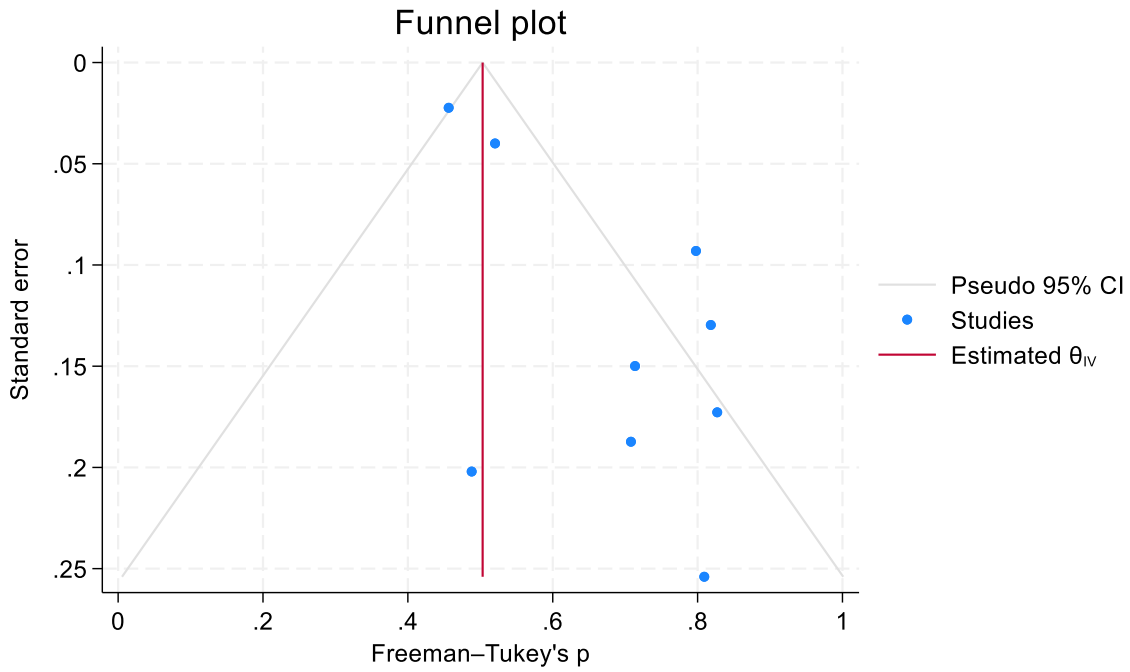


Figure 17 Funnel plot displaying the assessment of publication bias for dysgeusia prevalence among studies involving HER2-targeted ADCs.

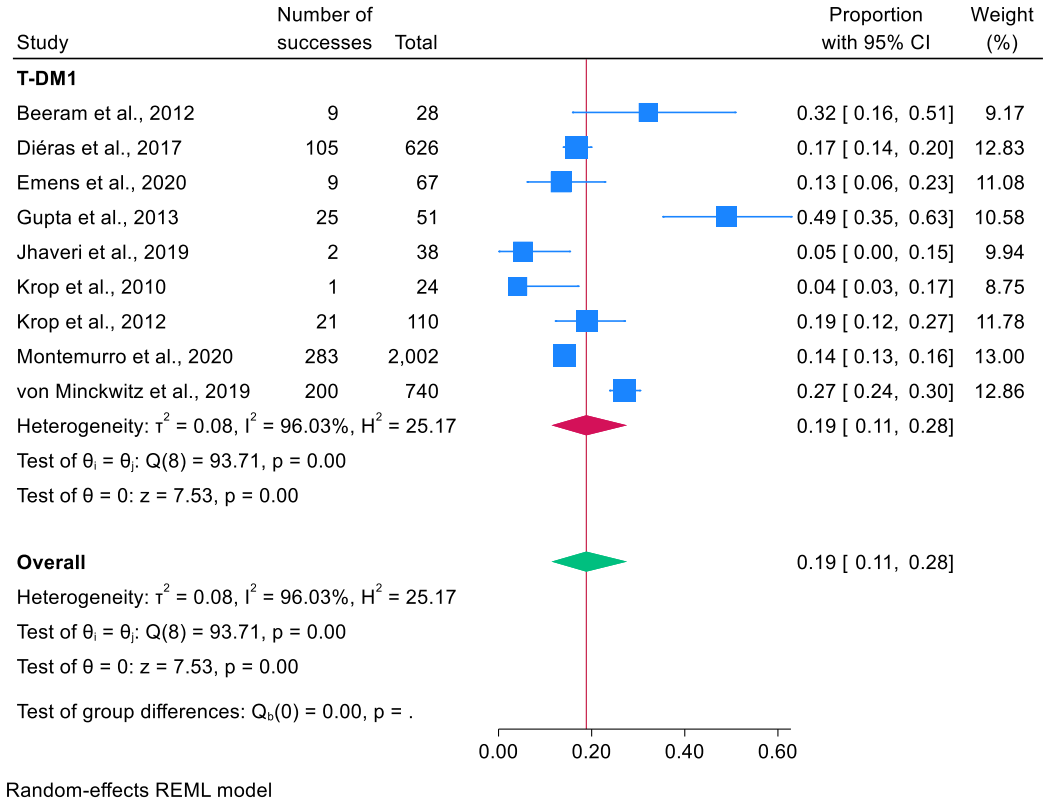


Figure 18 Forest plot showing pooled prevalence of dry mouth in patients receiving T-DM1.

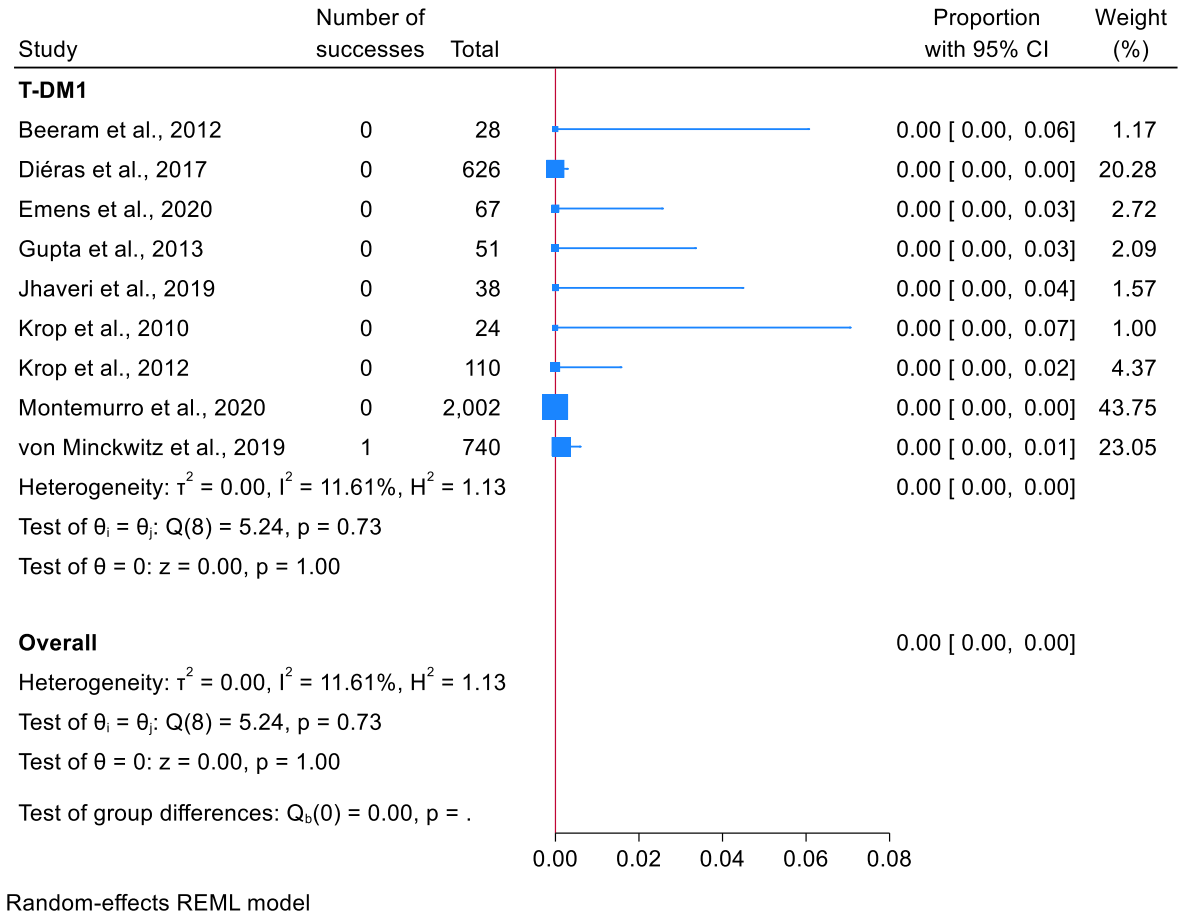


Figure 19 Forest plot illustrating Grade 3 or higher dry mouth prevalence in patients treated with T-DM1.

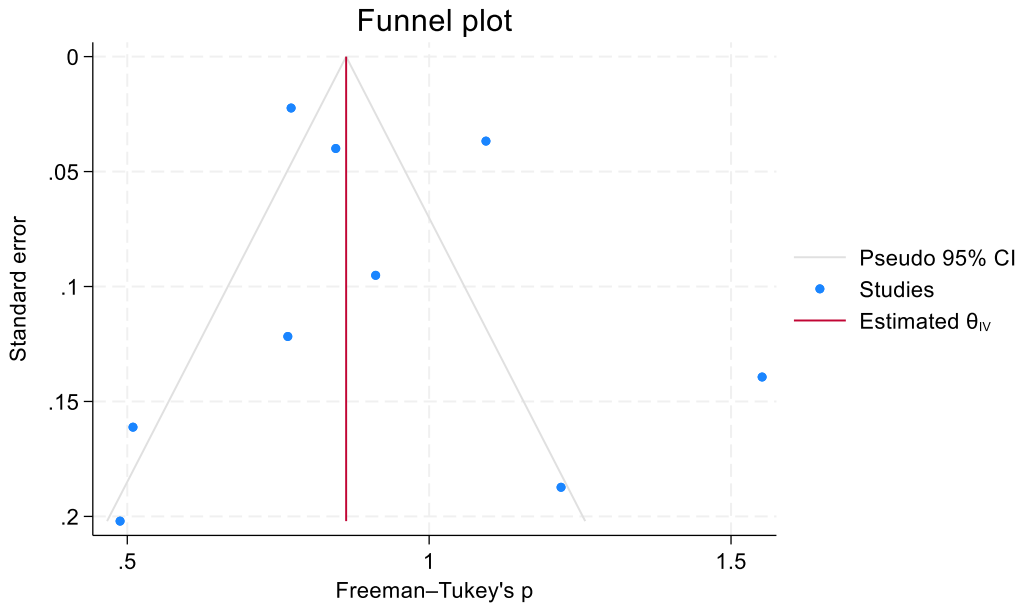


Figure 20 Funnel plot assessing potential publication bias in studies reporting dry mouth prevalence among patients treated with T-DM1.

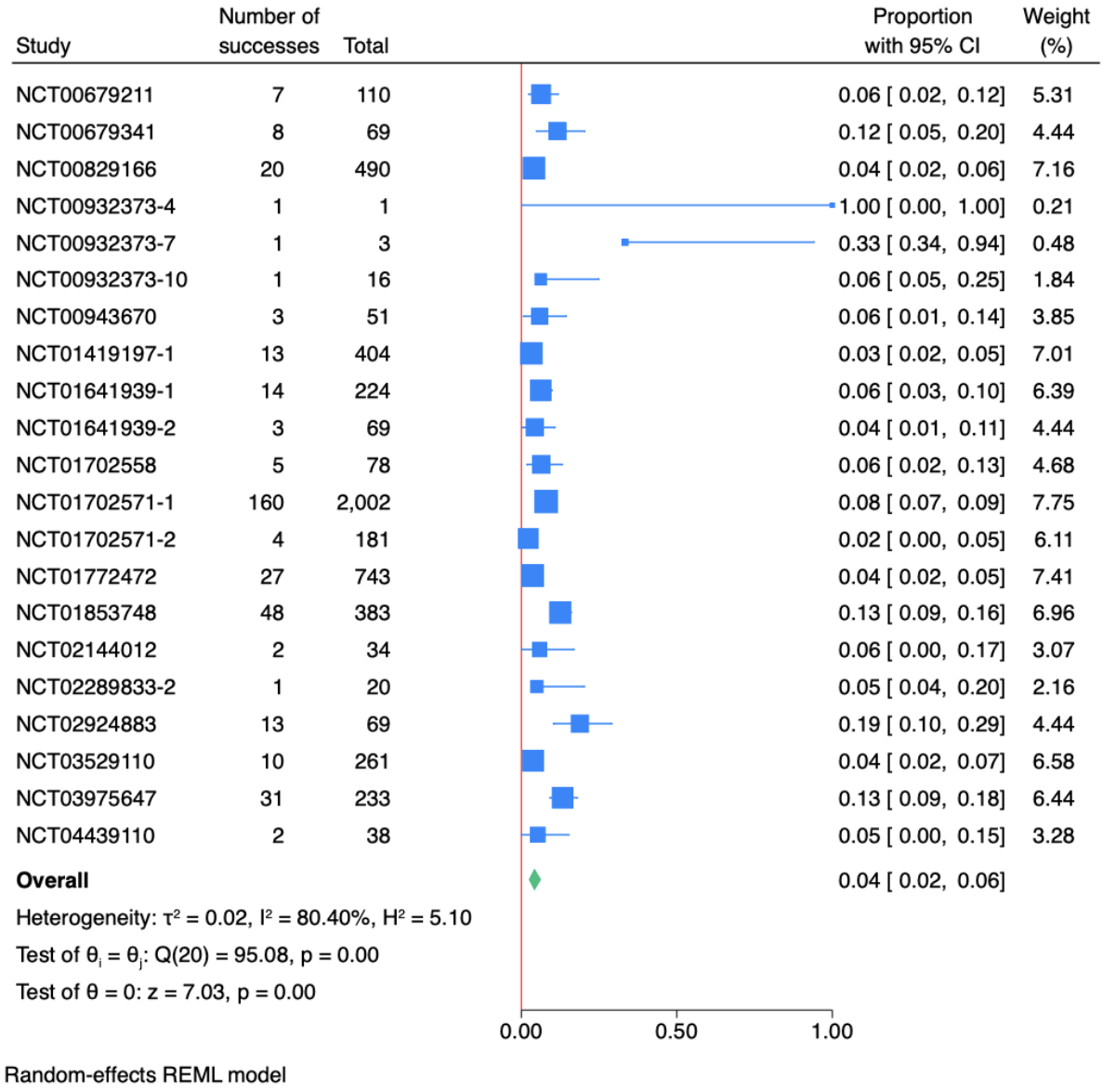


Figure 21 Forest plot showing the pooled prevalence of oral mucositis in T-DM1 clinical trials, with funnel plot and Egger's test assessing publication bias.

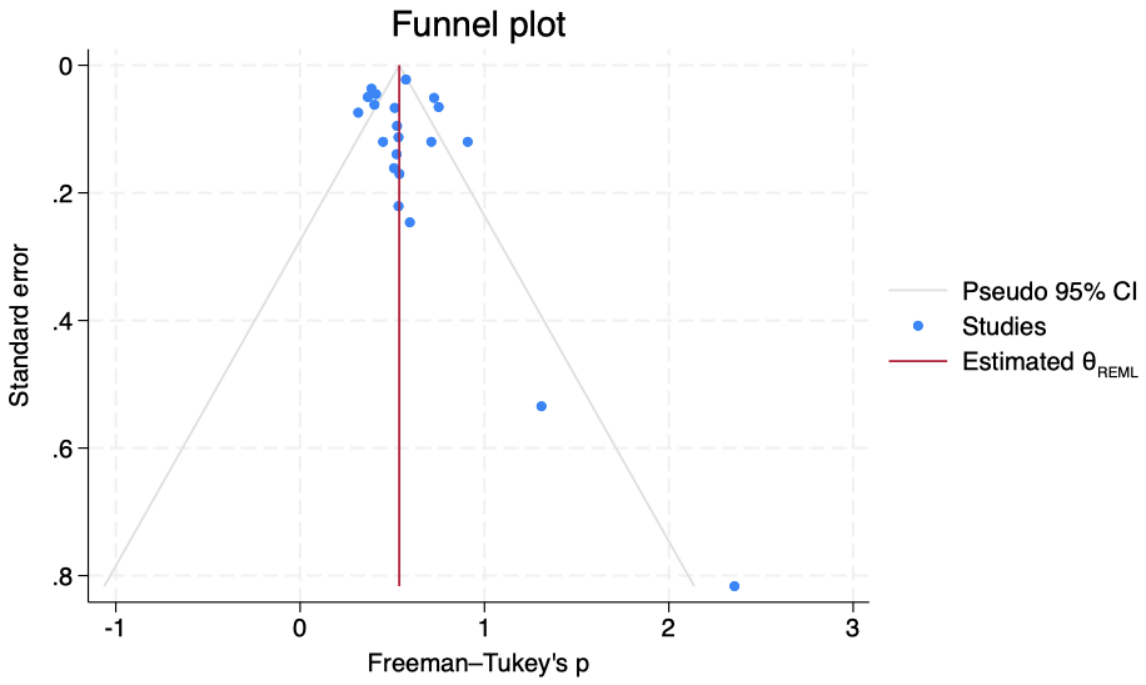


Figure 22 Funnel plot evaluating potential publication bias in the meta-analysis assessing oral mucositis prevalence among patients treated with T-DM1 in clinical trials. The suggested asymmetry and significant Egger's test (p = 0.0184) suggest possible small-study effects or publication bias.

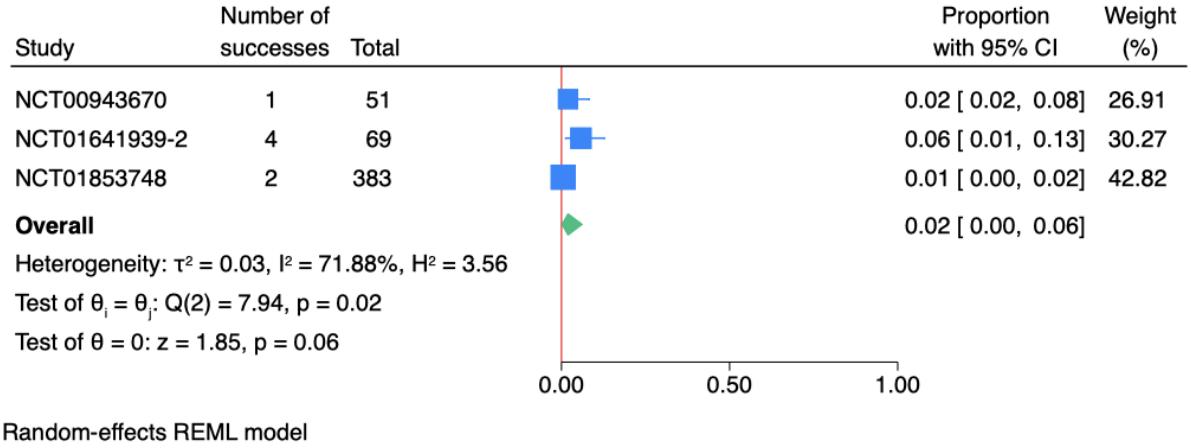


Figure 23 Forest plot illustrating the pooled prevalence of dysphagia reported in T-DM1 clinical trials. The analysis utilized a random-effects model. Each square represents the prevalence in an individual study, with its size corresponding to the study's weight in the meta-analysis. The diamond indicates the overall pooled prevalence.

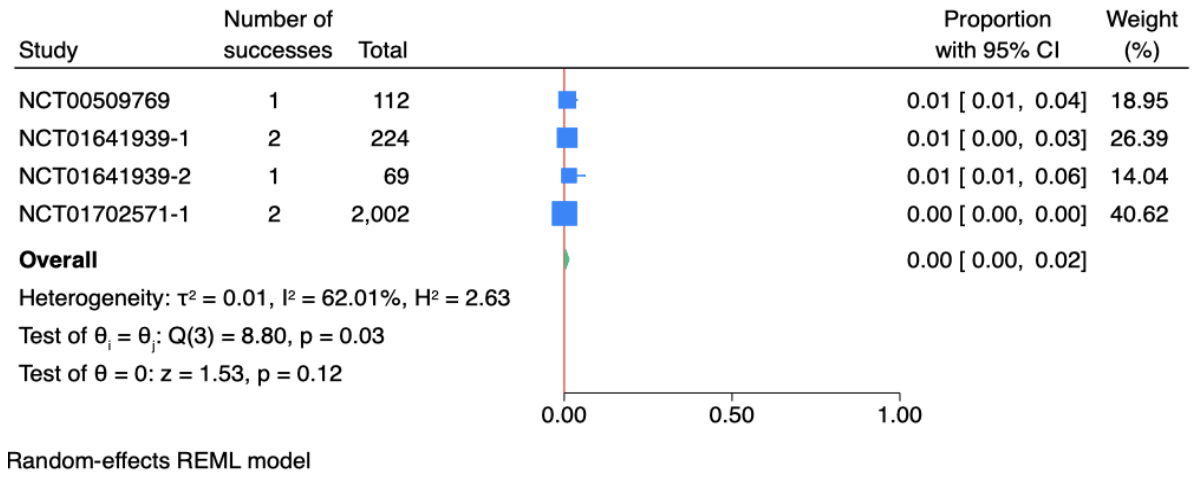


Figure 24 Forest plot displaying the pooled prevalence of serious dysphagia (Grade ≥3) among patients receiving T-DM1 in clinical trials.

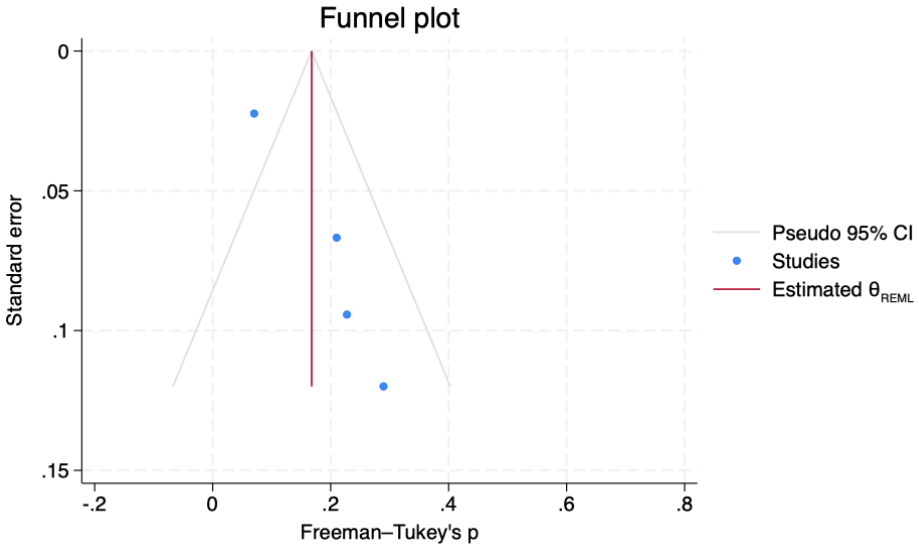


Figure 25 Forest plot assessing potential publication bias for the prevalence of dysphagia in T-DM1 clinical trials. The asymmetry noted visually was statistically confirmed by Egger's regression test (p = 0.0035), suggesting a potential small-study effect

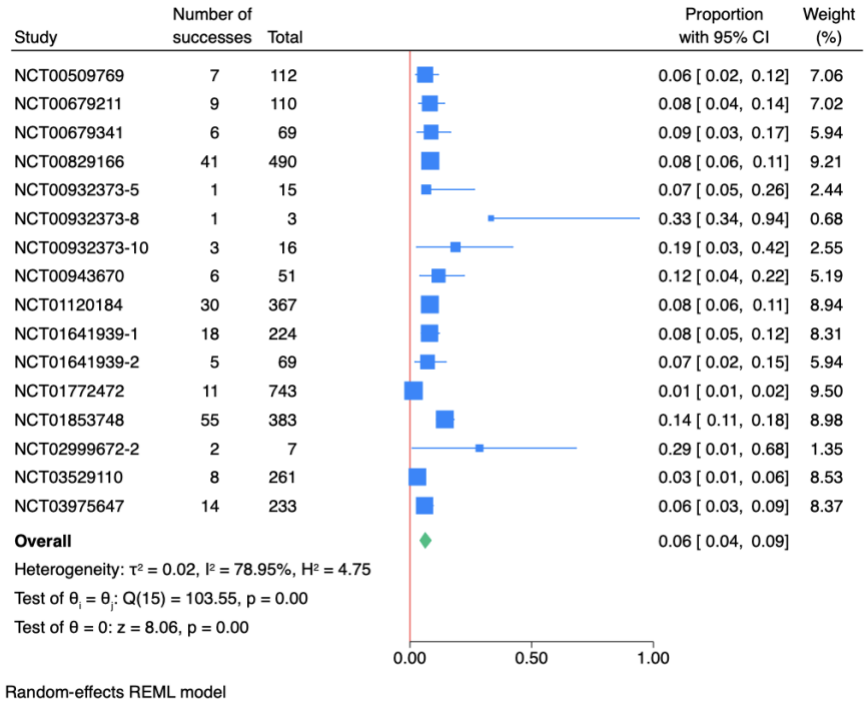


Figure 26 Forest plot depicting the pooled prevalence of dysgeusia in T-DM1 clinical trials.

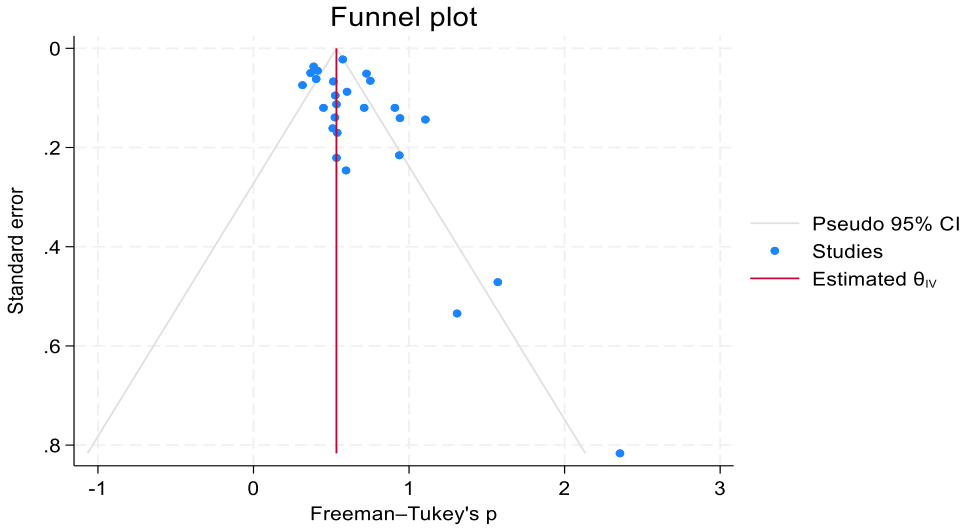


Figure 27 Funnel plot assessing publication bias for dysgeusia prevalence in T-DM1 clinical trials.

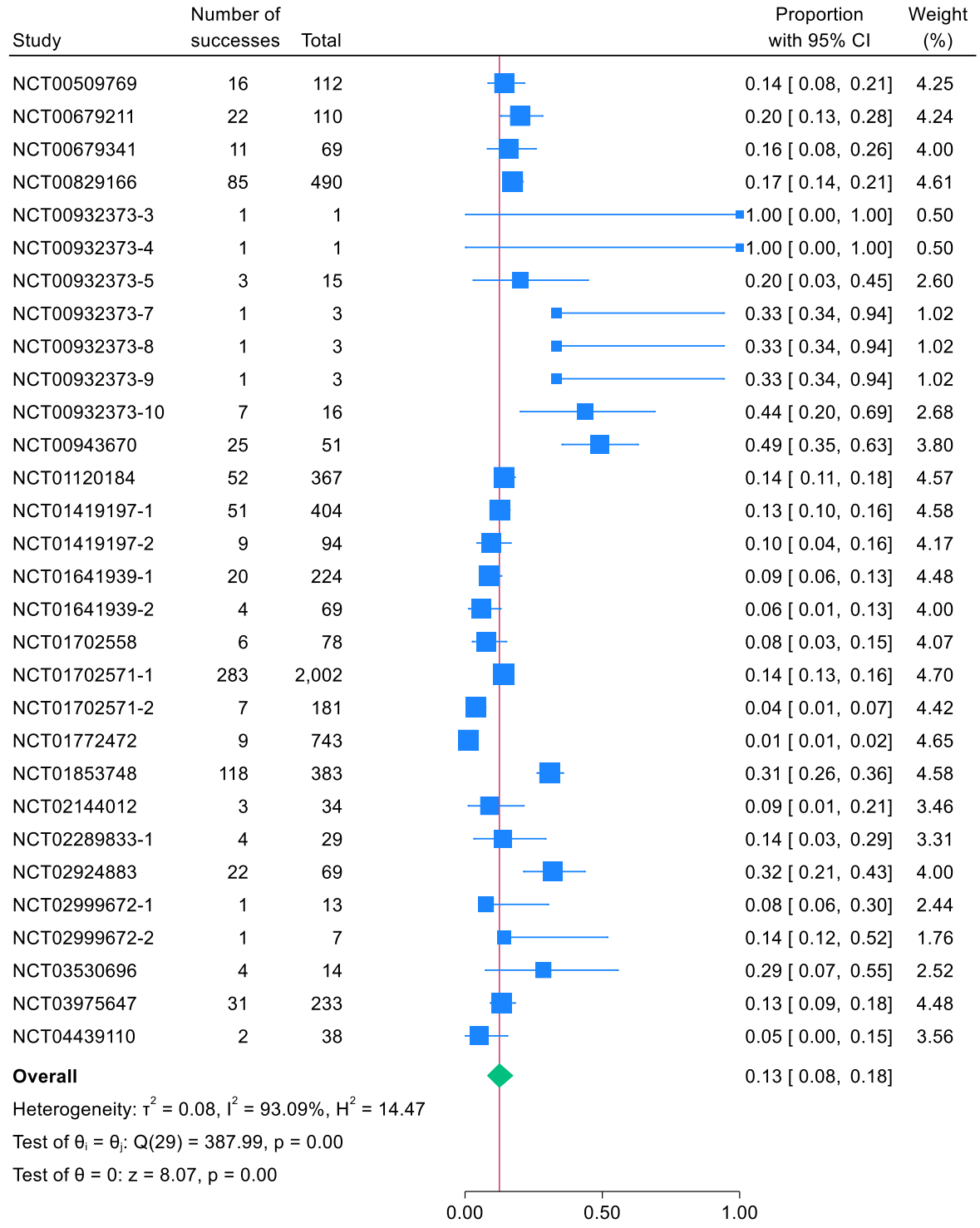


Figure 28 Forest plot demonstrating the pooled prevalence of dry mouth among patients treated with T-DM1 across clinical trials. The pooled prevalence was 13% (95% CI: 8–18%), indicating considerable heterogeneity (I^2 = 93.09%, $p < 0.01$).

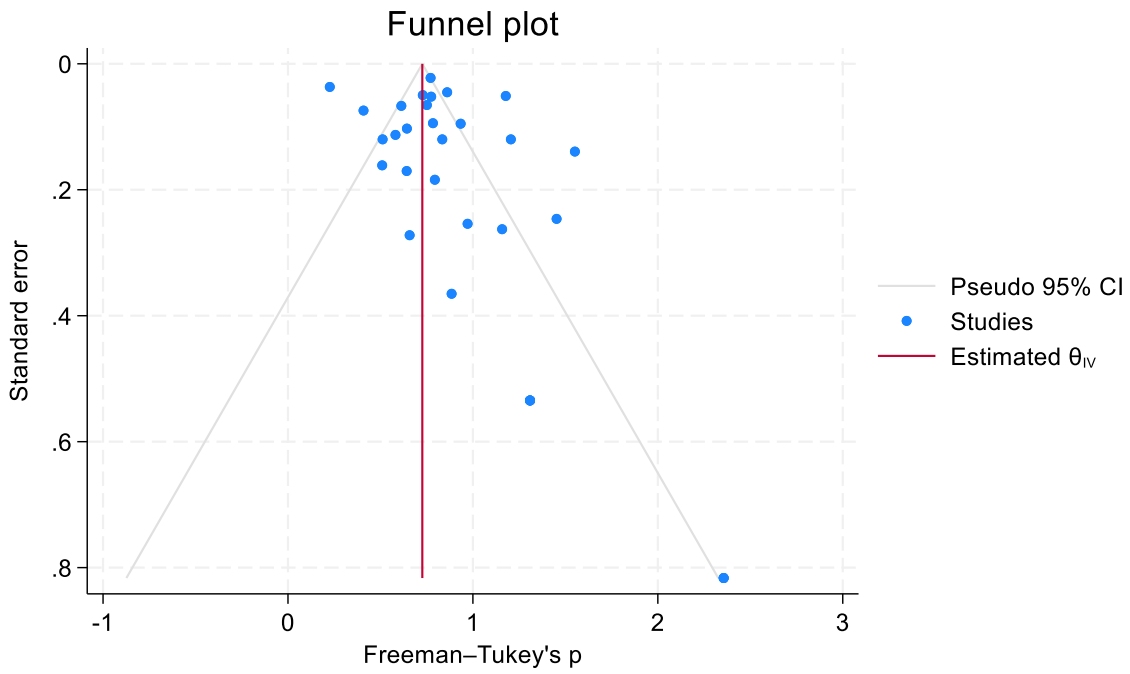


Figure 29 Funnel plot for dry mouth prevalence in T-DM1 clinical trials, showing visual asymmetry indicative of possible publication bias. Egger's test statistically confirmed significant evidence of small-study effects (p = 0.0016).

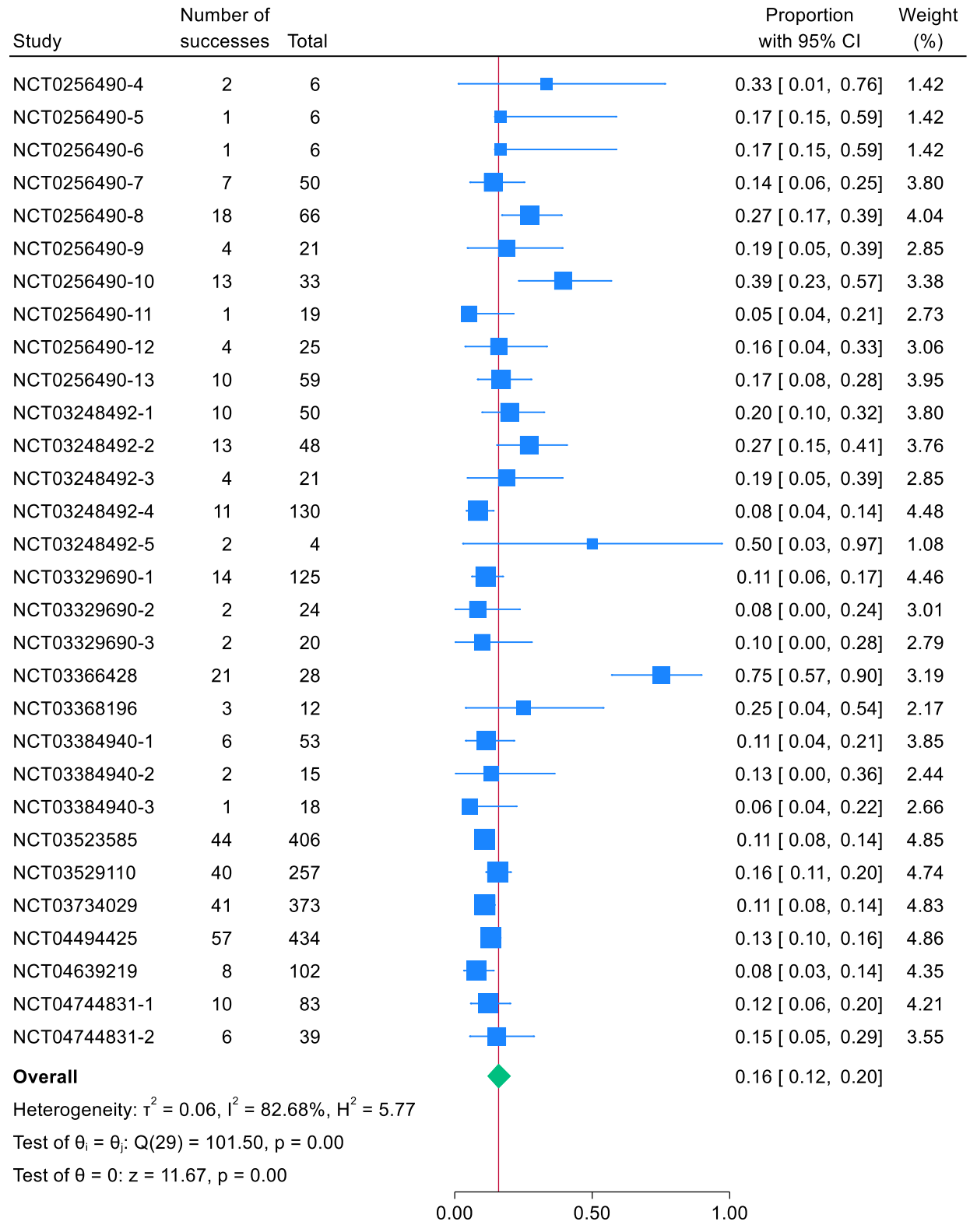


Figure 30 Forest plot showing the pooled prevalence of oral mucositis among patients treated with T-DXd in clinical trials, analyzed using a random-effects REML model.

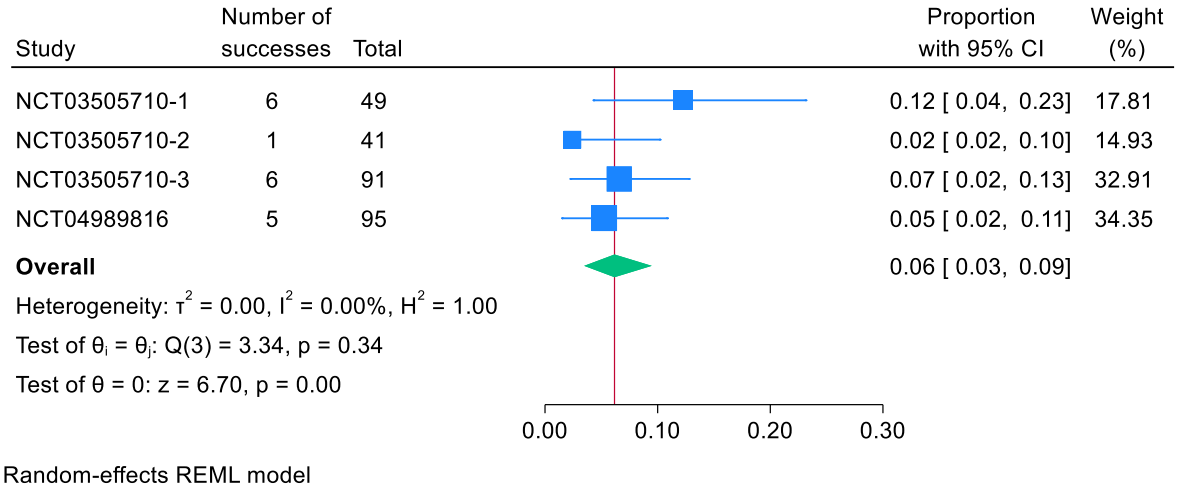


Figure 31 Forest plot illustrating the pooled prevalence of serious oral mucositis in patients treated with T-DXd across included clinical trials. The pooled prevalence was 6% (95% CI: 3–9%), with no significant heterogeneity observed among the included studies (I^2 = 0.00%, p = 0.34). Estimates were calculated using a random-effects REML.

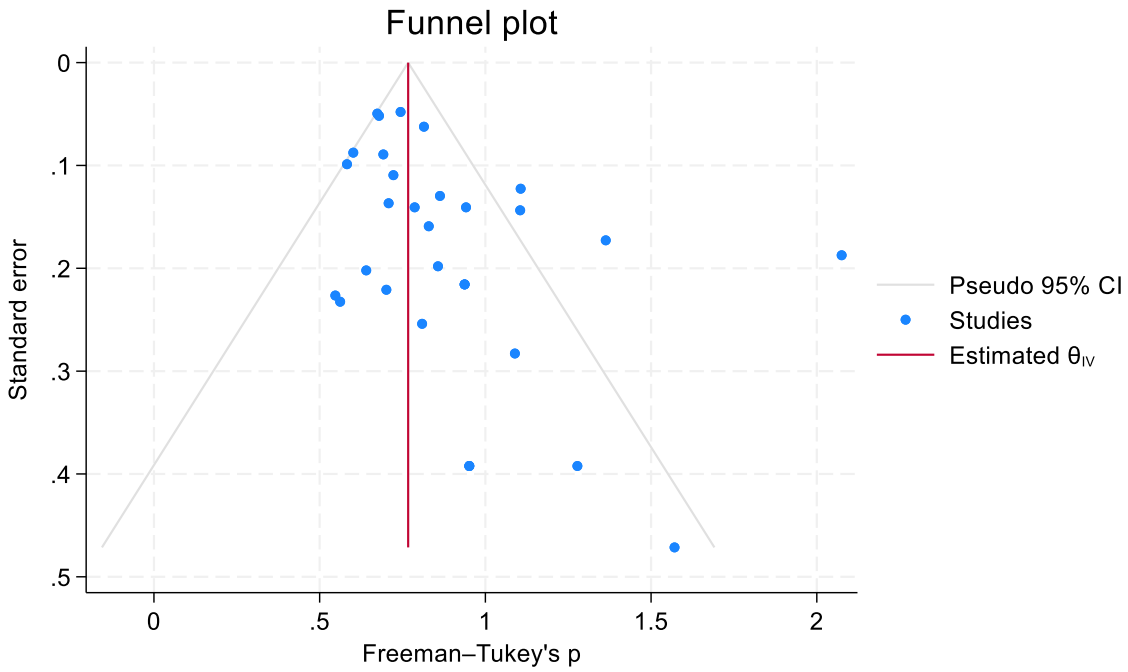


Figure 32 Funnel plot assessing potential publication bias for oral mucositis prevalence among patients treated with T-DXd in clinical trials. The Egger's test indicated statistically significant small-study effects (Egger's test, p = 0.0347).

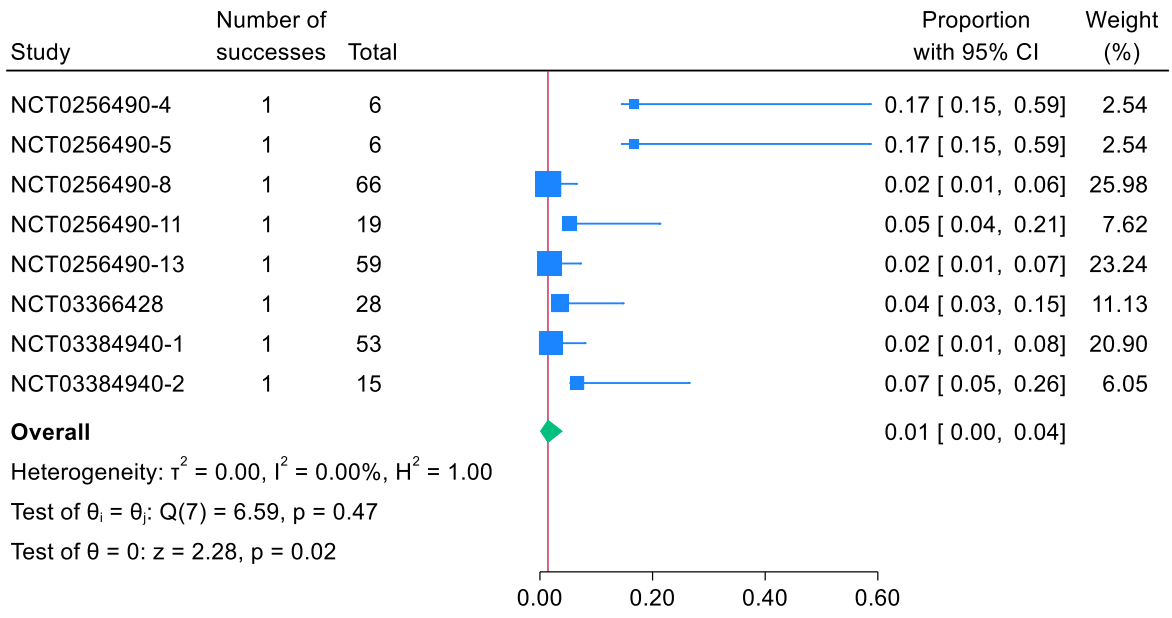


Figure 33 Forest plot showing the pooled prevalence of thrush (oral candidiasis) among patients treated with T-DXd across clinical trials.

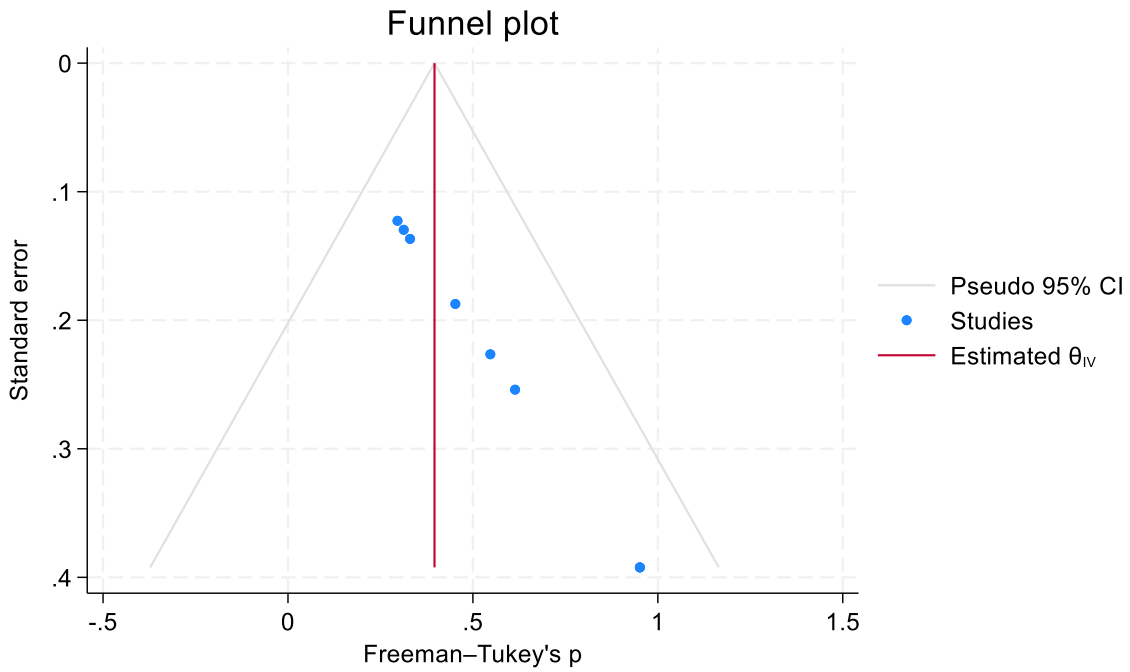


Figure 34 Funnel plot assessing potential publication bias for the prevalence of thrush (oral candidiasis) among patients treated with T-DXd across clinical trials.

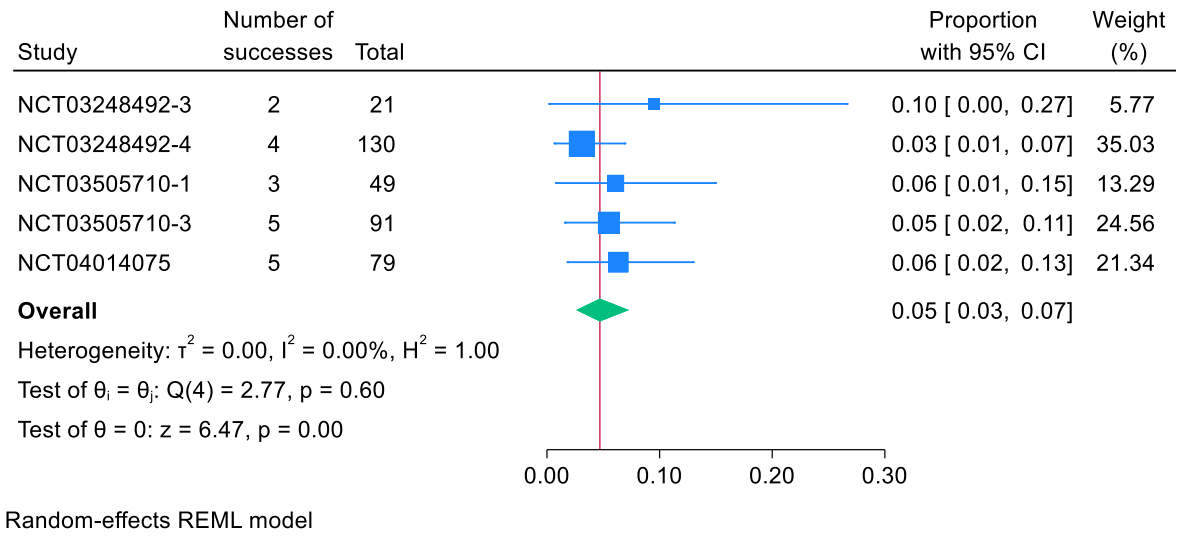


Figure 35 Forest plot showing the pooled prevalence of overall Dysphagia among patients treated with T-DXd across clinical trials.

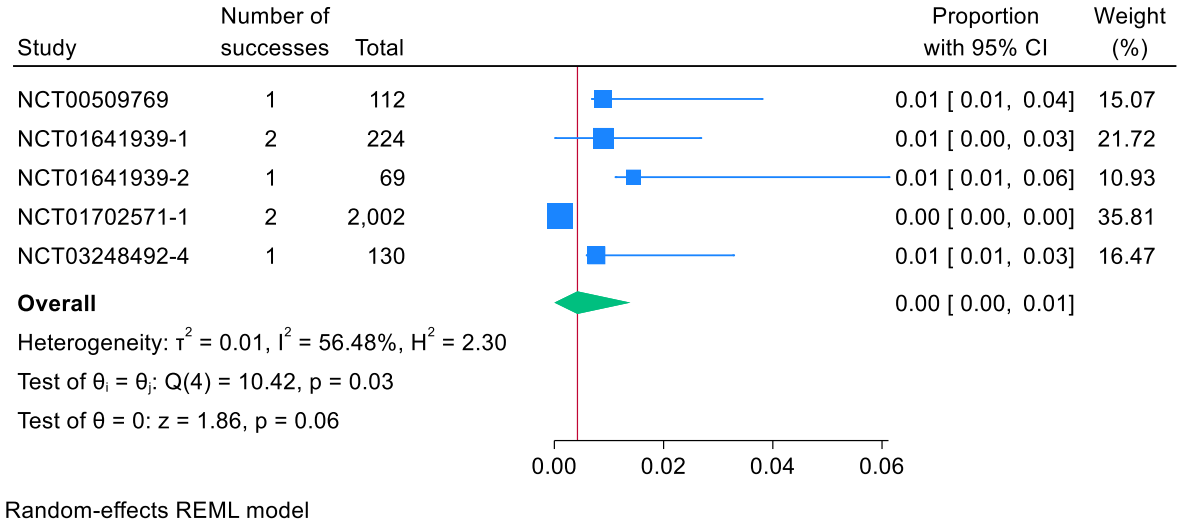


Figure 36 Forest plot showing the pooled prevalence of Serious Dysphagia among patients treated with T-DXd across clinical trials.

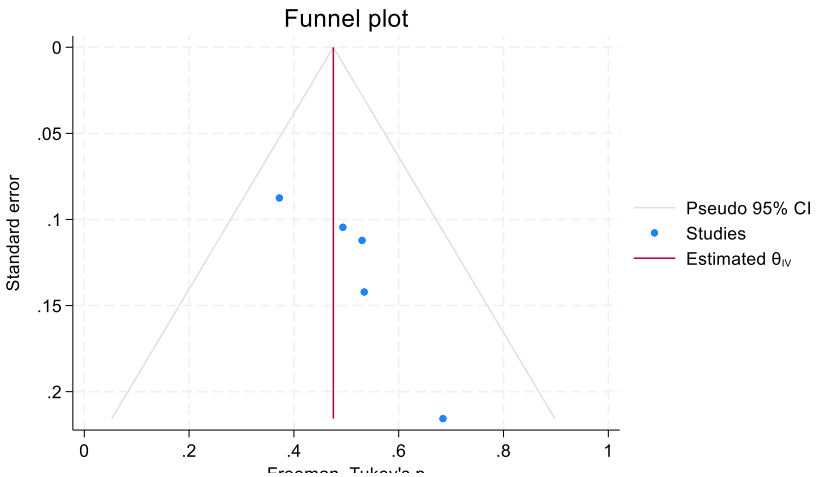


Figure 37 Forest plot depicting the pooled prevalence of dysgeusia among patients receiving T-DXd across clinical trials. Squares represent individual study prevalence estimates, with horizontal lines indicating 95% confidence intervals (CIs). The diamond represents the pooled prevalence estimate (6%; 95% CI: 4–8%), calculated using a random-effects model.

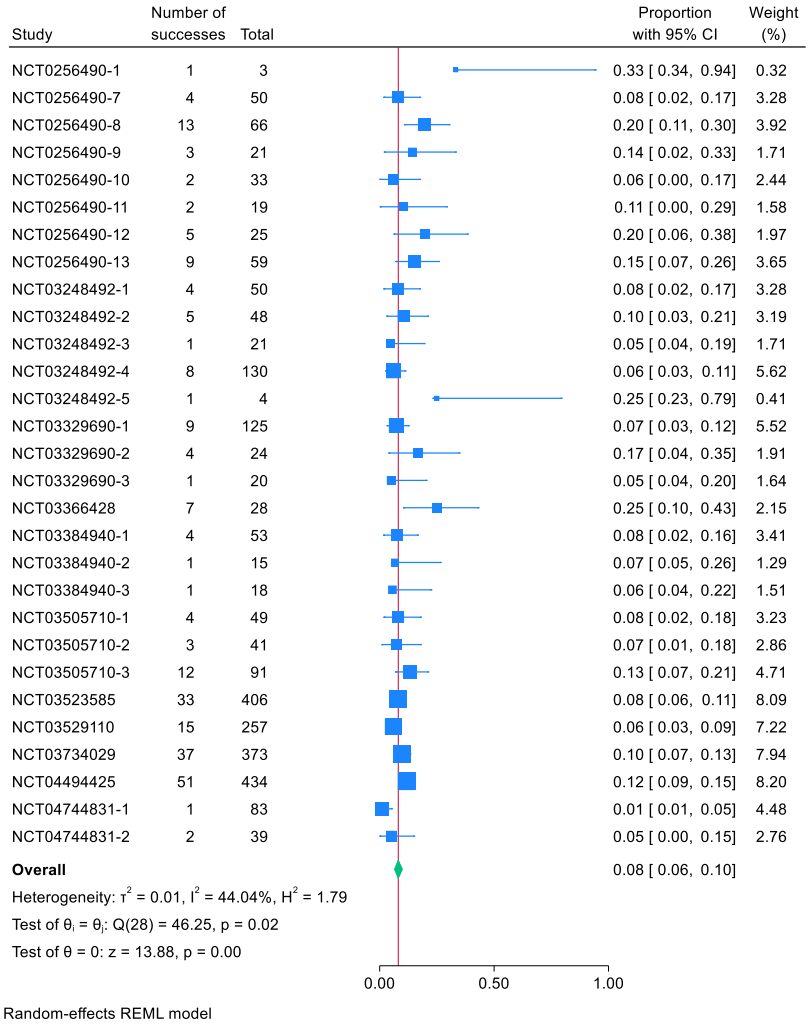


Figure 38 Funnel plot assessing potential publication bias in the reporting of dysphagia across clinical trials involving T-DXd.

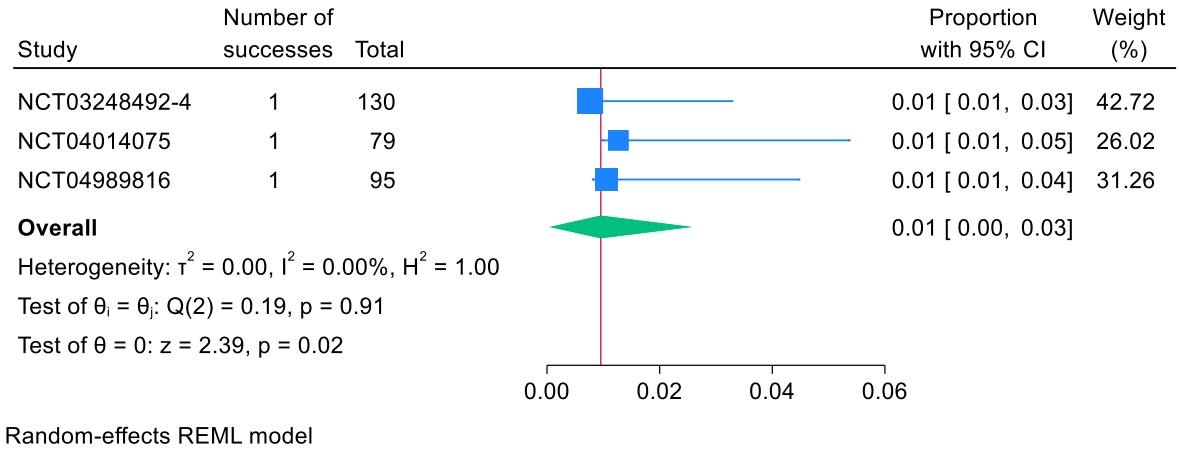


Figure 39 Forest plot illustrating the pooled prevalence of serious (Grade ≥3) dysgeusia among patients receiving T-DXd across included clinical trials. The pooled prevalence was low at 1% (95% CI: 0–3%), showing no observed heterogeneity ($I^2 = 0.00\%$, $p = 0.91$).

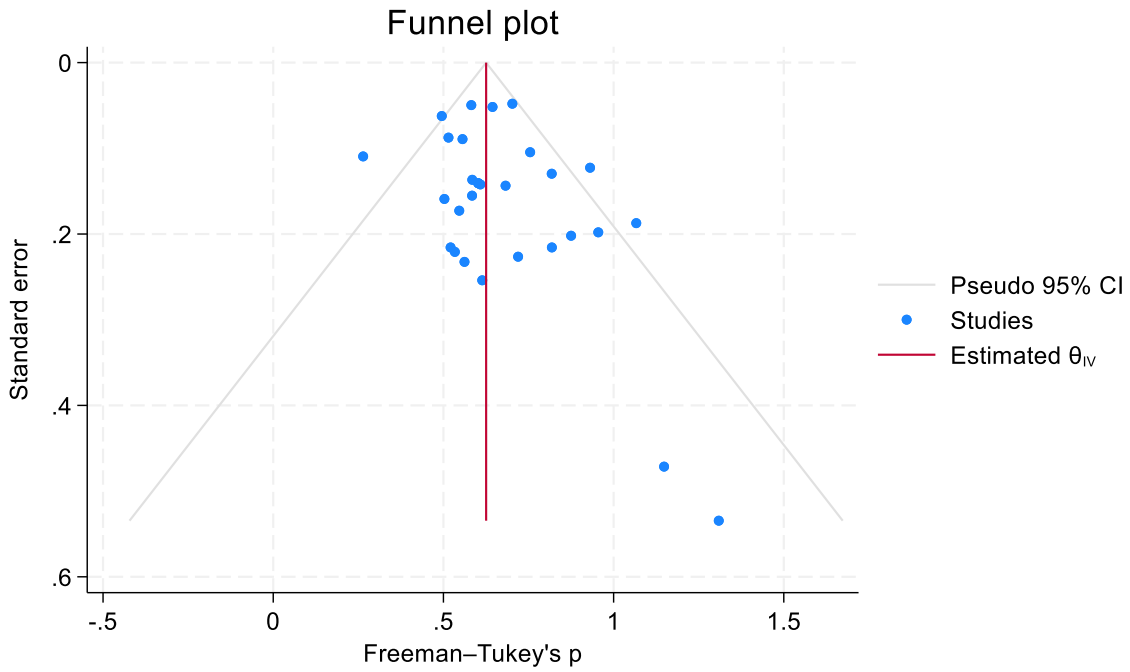


Figure 40 Funnel plot assessing publication bias for studies reporting dysgeusia among patients receiving T-DXd. Egger's test confirmed significant small-study effects ($p = 0.0046$), suggesting potential publication bias

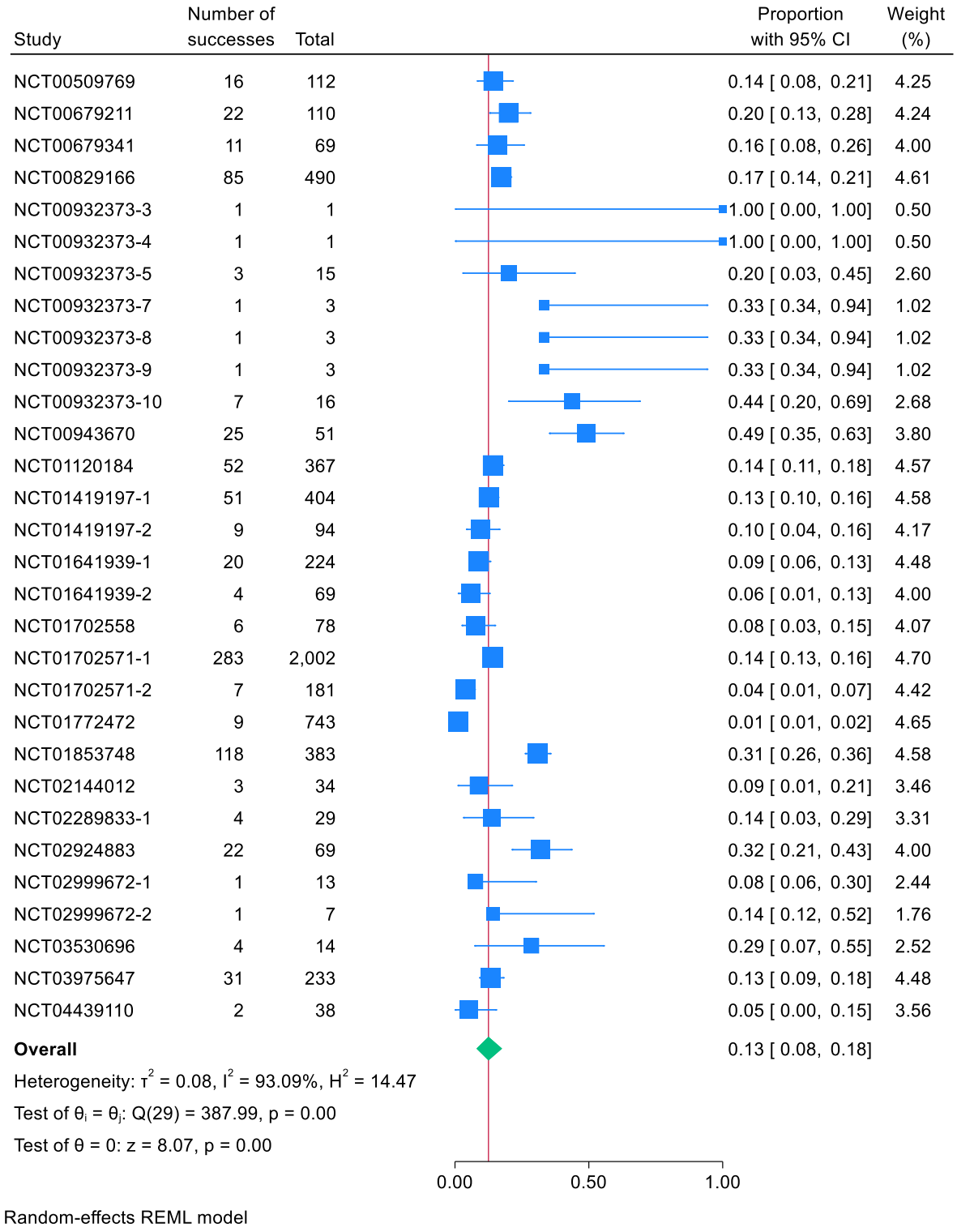


Figure 41 Prevalence of Dry Mouth in T-DXd Clinical Trials. Forest plot illustrating the pooled prevalence of dry mouth reported across clinical trials involving T-DXd. Individual studies are represented by squares proportional to their weight in the meta-analysis. The overall pooled prevalence is depicted by a green diamond, indicating a pooled estimate of 13% (95% CI: 8–18%), with substantial heterogeneity (I^2 = 93.09%, $p < 0.01$).

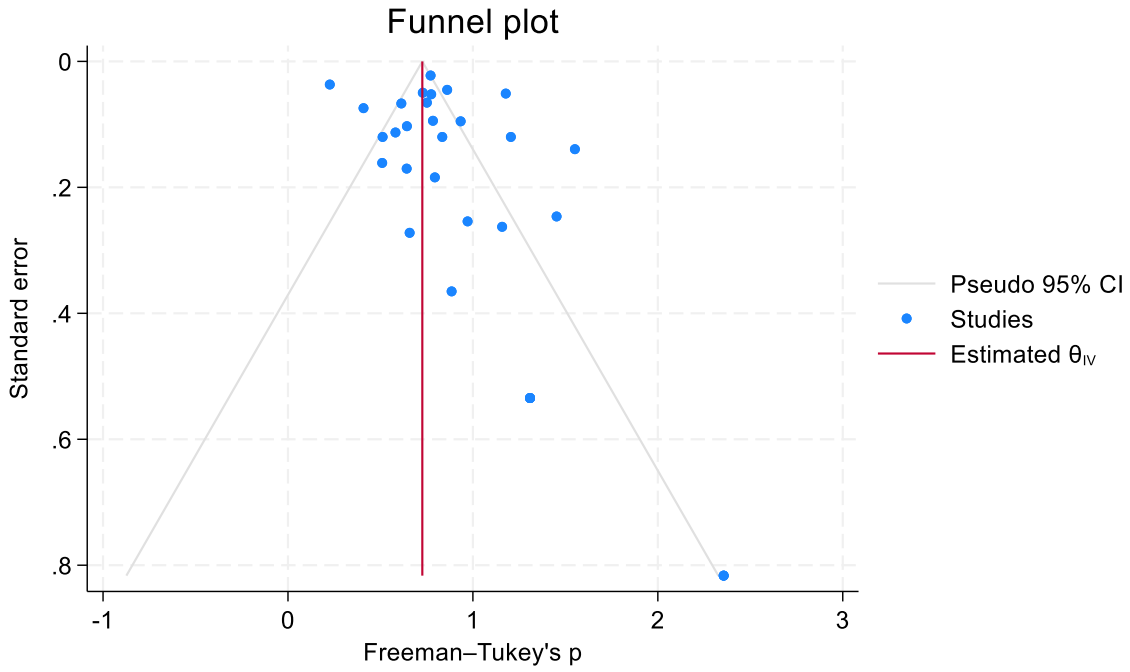


Figure 42 Funnel Plot for Publication Bias Dry Mouth in T-DXd Trials. Funnel plot assessing publication bias or small-study effects for the prevalence of dry mouth in T-DXd clinical trials. Points represent individual studies plotted according to their Freeman–Tukey transformed proportions and standard errors. Visual asymmetry suggests potential publication bias, statistically confirmed by Egger's test (p = 0.0016), indicating significant small-study effects.

APPENDIX B

Table 1 Characteristics of the included studies from the literature search

Authors	Year	Study	NCT NO	Other Registration ID	Phase	Cancer types	Study type	ADC drug	ADC dosage and frequency	Total number subjects of received at least one dose of ADC	Number of subjects with ≥ 1 general AE	AEs % threshold
Ian E. Krop et al.	2010	NA	NA	NA	1	BC	Single arm	T-DM1	0.3-4.8 mg/kg q3w	24	22	NA
Beeram et al.	2012	TDM3569g	NCT00932373	NA	1	BC	Single arm	T-DM1	1.2 - 2.9 mg/kg weekly	28	25	G1-4: ≥10%
Ian E. Krop et al.	2012	TDM4374g	NA	NA	2	BC	Single arm	T-DM1	3.6 mg/kg q3w	110	NA	G1-2: ≥ 10%, G≥3: 2%
Manish Gupta et al.	2013	TDM4688g	NCT00943670	NA	2	BC	Single arm	T-DM1	3.6 mg/kg q3w	51	51	NA
Harukaze Yamamoto et al.	2015	NA	NA	NA	1	BC	Single arm	T-DM1	1.8-3.6 mg/kg q3w	10	10	NA
Masahiro Kashiwaba et al.	2016	JO22997	NA	JAPIC CTI-101277	2	BC	Single arm	T-DM1	3.6 mg/kg q3w	73	70	G1-2 : ≥ 10%, G≥3 : ≥ 2%
Peter C. Thuss-Patience et al.	2017	GATSBY	NCT01641939	NA	2 and 3	GC and GOJC	RCT	T-DM1	2.4 mg/kg q3w	224	218	G1-2: ≥ 10% , G≥3: ≥ 1%
Véronique Diéras et al.	2017	EMILIA	NCT00829166	NA	3	BC	RCT	T-DM1	3.6 mg/kg q3w	136	478	G1-4: ≥ 10%
Toshihiko Doi et al.	2017	NA	NCT02564900	NA	1	BC, GC, GOC	Single arm	T-DXd	0.8- 8mg/kg	24	24	G1-4: ≥5%
K. L. Jhaveri et al.	2019	NCI-MATCH (EAY131) subprotocol Q.	NCT02465060	NA	2	HER2 solid tumor excluding BC and GC	Single arm	T-DM1	3.6 mg/kg q3w	38	N/A	NA
Gunter von Minckwitz et al.	2019	KATHERINE	NCT01772472	NA	3	BC	RCT	T-DM1	3.6 mg/kg q3w	740	731	G1-3 ≥ 10% G≥4: ≥ 2%
Kenji Tamura et al.	2019	NA	NCT02564900	JapicCTI-152978	1	BC	Single arm	T-DXd	5·4 mg/kg q3w	115	115	G1-2: ≥10% , G≥3: ≥ 2%
Leisha A. Emens et al.	2020	KATE2	NCT02924883	NA	2	BC	RCT	T-DM1	3.6 mg/kg q3w	67	65	G1-4: ≥10%
Dongmei Ji et al.	2020	NA	NCT03153163	NA	1	BC	Single arm	T-DM1	3.6 mg/kg q3w	11	11	NA
F. Montemurro et al.	2020	KAMILLA	NCT01702571	JAPIC CTI-101277	3b	BC	Single arm	T-DM1	3.6 mg/kg q3w	2002	1862	G1-2: ≥5% , G≥3 : ≥ 1%
Junji Tsurutani et al.	2020	NA	NCT02564900	NA	1	Advanced solid HER2 cancer excluding BC and GC	Single arm	T-DXd	6.4 mg/kg q3w	59	59	G1-4: >10%
Kohei Shitara et al.	2020	DESTINY-Gastric01	NCT03329690	NA	2	GC	RCT	T-DXd	6.4 mg/kg	125	125	G1-4: ≥ 10%
Shanu Modi et al.	2020	DESTINY-Breast01	NCT03248492	NA	2	BC	Single arm	T-DXd	5.4, 6.4, 7.4 mg/kg q3w	253	253	G1-4: ≥ 10%
Shanu Modi et al.	2020	NA	NCT02564900	NA	1	BC	Single arm	T-DXd	5.4-6.4 mg/kg q3w	54	53	G1-4: ≥ 10%
Satheesh Chiradoni Thungappa et al.	2021	NA	NA	CTRI/2018/07/014881	3	BC	RCT	T-DM1*	3.6 mg/kg q3w	168	132	NA

Kensei Yamaguchi et al.	2022	DESTINY-Gastric01	NCT03329690	NA	2	GC	Single arm	T-DXd	6.4 mg/kg q3w	44	44	G1-4: ≥ 20%
Adaaki Nishikawa et al.	2023	STATICE	NA	UMIN000029506	2	Uterine carcinosarcoma	Single arm	T-DXd	5.4-6.4 mg/kg q3w	33	33	G1-4: ≥ 10%
Eric Van Cutsem et al.	2023	DESTINY-Gastric02	NCT04014075	NA	2	GC or GJC	Single arm	T-DXd	6.4 mg/kg q3w	79	79	G1-4: ≥ 10%
Akihiko Shimomura et al.	2023	DS8201-A-J102	NA	NA	1	BC	Single arm	T-DXd	6.4 mg/kg q3w	51	51	G1-4: ≥ 20%
Kanwal Raghav et al.	2024	DESTINY-CRC02	NCT04744831	NA	2	CC	RCT	T-DXd	5.4-6.4 mg/kg q3w	122	121	G1-G2: ≥10%
Akihiro Ohba et al.	2024	HERB	NA	jRCT2091220423	2	BTC	Single arm	T-DXd	5.4 mg/kg q3w	32	32	G1-G4: ≥10%
Rupert Bartsch et al.	2024	TUXEDO-1	NCT04752059	EudraCT Number: 2020-000981-41	2	BC	Single arm	T-DXd	5.4 mg/kg q3w	15	15	NA
M. Vaz Batista et al.	2024	DEBBRAH	NCT04420598	NA	2	BC	Single arm	T-DXd	5.4 mg/kg q3w	12	12	G1-G4= ≥15%
Bob T. Li et al.	2024	DESTINY-PanTumor01	NCT04639219	NA	2	HER2 solid tumors	Single arm	T-DXd	5.4 mg/kg q3w	102	102	G1-2 ≥ 10% , G≥3 = Any
Egbert F. Smit et al.	2024	DESTINY-Lung01	NCT03505710	NA	2	NSCLC	Single arm	T-DXd	5.4-6.4 mg/kg q3w	90	82	G1-2: ≥ 5% , G≥3: ≥ 1%

Abbreviations: *BC, breast cancer; GC, gastric cancer; CC, colorectal cancer; BTC, biliary tract cancer; GJC, gastroesophageal junction cancer; GOC, gastric-oesophageal cancer; GOJC, gastro-oesophageal junction cancer; NSCLC, non-small cell lung cancer. (*) indicates the study comparing two formulations of T-DM1: Kadcyla and ZRC-3256.*

Table 2 Characteristics of clinical trials from ClinicalTrials.gov

NCT Number	Conditions	Phases	Study Design	Study Status	Enrollment	ADC types	Dosage and Frequency	Subjects Received ADC
NCT03530696	BC/mBC	2	RCT	C	55	T-DM1	3.6 mg/kg q3w	14
NCT00932373	mBC	1	Single Arm	C	3	T-DM1	0.3 mg/kg q3w	3
					1	T-DM1	0.6 mg/kg q3w	1
					1	T-DM1	1.2 mg/kg q3w	1
					1	T-DM1	2.4 mg/kg q3w	1
					15	T-DM1	3.6 mg/kg q3w	15
					3	T-DM1	4.8 mg/kg q3w	3
					3	T-DM1	1.2 mg/kg qw	3
					3	T-DM1	1.6 mg/kg qw	3
					3	T-DM1	2 mg/kg qw	3
					16	T-DM1	2.4 mg/kg qw	16
					3	T-DM1	2.9 mg/kg qw	3
NCT00509769	mBC	2	Single Arm	C	112	T-DM1	3.6 mg/kg q3w	112
NCT03975647	BC	3	RCT	ANR	466	T-DM1	3.6 mg/kg q3w	233
NCT00679211	mBC	2	Single Arm	C	110	T-DM1	3.6 mg/kg q3w	110
NCT04439110	HER2 solid cancer except BC, GC GEJC	2	Single Arm	ANR	38	T-DM1	3.6 mg/kg q3w	38
NCT01702558	BC and GC	2	Single Arm	T	182	T-DM1	3.6 mg/kg q3w	78
NCT03529110	BC	3	RCT	ANR	524	T-DM1	3.6 mg/kg q3w	261
NCT00943670	mBC	2	Single Arm	C	51	T-DM1	3.6 mg/kg q3w	51
NCT00679341	BC	2	RCT	C	137	T-DM1	3.6 mg/kg q3w	69
NCT01853748	BC	2	RCT	ANR	512	T-DM1	3.6 mg/kg q3w	383
NCT01702571	BC	3	Single Arm	C	2185	T-DM1	3.6 mg/kg q3w	2002
						T-DM1	3.6 mg/kg q3w	181
NCT02289833	NSCLC	2	Single Arm	C	49	T-DM1	3.6 mg/kg q3w	29
						T-DM1	3.6 mg/kg q3w	20
NCT01196052	BC	2	Single Arm	C	153	T-DM1	3.6 mg/kg q3w	
NCT01641939	GC	2 to 3	RCT	T	415	T-DM1	2.4 mg/kg q3w	224
						T-DM1	3.6 mg/kg q3w	69
NCT02999672	BLC, PC, CCC	2	Single Arm	C	20	T-DM1	2.4 mg/kg q3w	13
						T-DM1	2.4 mg/kg q3w	7
NCT00829166	BC	3	RCT	C	991	T-DM1	3.6 mg/kg q3w	490
NCT01419197	BC	3	RCT	C	602	T-DM1	3.6 mg/kg q3w	404

						T-DM1	3.6 mg/kg q3w	94
NCT02924883	mBC	2	RCT	C	202	T-DM1	3.6 mg/kg q3w	69
NCT01772472	BC	3	RCT	C	1487	T-DM1	3.6 mg/kg q3w	743
NCT02144012	mBC	3	RCT	T	49	T-DM1	3.6 mg/kg q3w	34
NCT03248492	BC	2	RCT	C	253	T-DM1	5.4 mg/kg q3w	50
						T-DM1	6.4 mg/kg q3w	48
						T-DM1	7.4 mg/kg q3w	21
						T-DM1	5.4 mg/kg q3w	130
						T-DM1	5.4 mg/kg q3w	4
NCT01120184	BC	3	RCT	C	1095	T-DM1	3.6 mg/kg q3w	367
NCT04744831	Advanced CC	2	RCT	C	122	T-DXd	5.4 mg/kg q3w	83
						T-DXd	6.4 mg/kg q3w	39
NCT04639219	Advanced Solid Tumors solid cancer with HER2	2	Single Arm	ANR	102	T-DXd	5.4 mg/kg q3w	102
NCT03529110	BC	3	RCT	ANR	524	T-DXd	5.4 mg/kg q3w	257
NCT05246514	NSCLC	2	Single Arm	C	72	T-DXd	5.4 mg/kg q3w	72
NCT04989816	GC or GEJC	2	Single Arm	C	95	T-DXd	6.4 mg/kg q3w	95
NCT04494425	Advanced or mBC	3	RCT	ANR	866	T-DXd	5.4 mg/kg q3w	434
NCT03523585	BC	3	RCT	ANR	608	T-DXd	5.4 mg/kg q3w	406
NCT02564900	Advanced Solid Tumors	Phase 1	RCT	C	292	T-DXd	0.8 mg/kg q3w	3
						T-DXd	1.6 mg/kg q3w	3
						T-DXd	3.2 mg/kg q3w	3
						T-DXd	5.4 mg/kg q3w	6
						T-DXd	6.4 mg/kg q3w	6
						T-DXd	8 mg/kg q3w	6
						T-DXd	5.4 mg/kg q3w	50
						T-DXd	6.4 mg/kg q3w	66
						T-DXd	5.4 mg/kg q3w	21
						T-DXd	6.4 mg/kg q3w	33
						T-DXd	5.4 mg/kg q3w	19
						T-DXd	6.4 mg/kg q3w	25
						T-DXd	6.4 mg/kg q3w	59
NCT03384940	Colorectal Neoplasm	2	Single Arm	C	86	T-DXd	6.4 mg*/kg q3w	53
						T-DXd	6.4 mg/kg q3w	15
						T-DXd	6.4 mg*/kg q3w	18
NCT03329690	Neoplasm, Gastrointestinal	2	RCT	C	233	T-DXd	6.4 mg*/kg q3w	125
						T-DXd	6.4 mg*/kg q3w	24
						T-DXd	6.4 mg*/kg q3w	20
NCT03366428	Malignant Neoplasm of Breast	1	Single Arm	C	51	T-DXd	6.4 mg/kg q3w	28

NCT03368196	Adenocarcinoma, Gastric Neoplasm, Breast	1	Single Arm	C	12	T-DXd	6.4 mg/kg q3w	12
NCT03505710	Non-Small Cell Lung Cancer	2	Single Arm	C	181	T-DXd	6.4 mg/kg q3w	49
						T-DXd	5.4 mg/kg q3w	41
						T-DXd	6.4 mg/kg q3w	91
NCT03734029	BC	3	RCT	ANR	557	T-DXd	5.4 mg/kg q3w	373
NCT04014075	Adenocarcinoma Gastric Stage IV With Metastases Adenocarcinoma - GEJ	2	Single Arm	C	79	T-DXd	6.4 mg/kg q3w	79
NCT03248492	BC	2	RCT	C	253	T-DXd	5.4 mg/kg q3w	50
						T-DXd	6.4 mg/kg q3w	48
						T-DXd	7.4 mg/kg q3w	21
						T-DXd	5.4 mg/kg q3w	130
						T-DXd	5.4 mg/kg q3w	4

Abbreviations: *BC, breast cancer; mBC, metastatic breast cancer; GC, gastric cancer; GEJC, gastroesophageal junction cancer; CC, colorectal cancer; BLC, bladder cancer; PC, pancreatic cancer; CCC, cholangiocarcinoma; NSCLC, non-small cell lung cancer; RCT, randomized controlled trial; ANR, active not recruiting; C, completed; T, terminated*

Table 3 Comparison of orofacial AEs between two methodologies

	SystemicReview					ClinicalTrials.gov			
AEs	**T-DM1 Study count (n=14)**	**T-DM1 Prevalence, CI 95%**	**T-DXd Study Count (n=16)**	**T-DXd Prevalence, CI 95%**	**Overall Prevalence, CI 95%**	**T-DM1 Trials count n=23)**	**T-DM1 prevalence, CI 95%**	**T-DXd Trials Count (n=16)**	**T-DXd prevalence, CI 95%**
Oral Mucositis	6	0.09 (0.05, 0.15)	11	0.17 (0.13, 0.22)	0.14 (0.10, 0.18)	17	0.04 (0.02, 0.06)	12	0.16(0.12, 0.20)
Oral Candidiasis	1	0.04 (0.00-0.17)	2	0.08 (0.00-0.47)	0.06 (0.00, 0.25)	N/A	N/A	2	0.06(0.03, 0.09)
Dysphagia	3	0.02 (0.00, 0.07)	2	0.04 (0.00, 0.13)	0.02 (0.00, 0.06)	3	0.02(0.00, 0.06)	3	0.05 (0.03, 0.07)
Dysgeusia	4	0.05 (0.04, 0.06)	5	0.14(0.10, 0.19)	0.09 (0.06, 0.13)	17	0.04(0.02, 0.06)	11	0.08(0.06, 0.10)
Dry Mouth	9	0.19 (0.11, 0.28)	N/A	N/A	N/A	20	0.13(0.08, 0.18)	4	0.04(0.03, 0.06)

REFERENCES

(1) Institute, N. C. *Common Cancer Sites*. 2025. https://seer.cancer.gov/statfacts/html/common.html (accessed.

(2) Cocco, E.; Lopez, S.; Santin, A. D.; Scaltriti, M. Prevalence and role of HER2 mutations in cancer. *Pharmacol Ther* 2019, *199*, 188-196. DOI: 10.1016/j.pharmthera.2019.03.010 From NLM.

(3) Pahuja, K. B.; Nguyen, T. T.; Jaiswal, B. S.; Prabhash, K.; Thaker, T. M.; Senger, K.; Chaudhuri, S.; Kljavin, N. M.; Antony, A.; Phalke, S.; et al. Actionable Activating Oncogenic ERBB2/HER2 Transmembrane and Juxtamembrane Domain Mutations. *Cancer Cell* 2018, *34* (5), 792-806.e795. DOI: 10.1016/j.ccell.2018.09.010 From NLM.

(4) Liu, K.; Li, M.; Li, Y.; Li, Y.; Chen, Z.; Tang, Y.; Yang, M.; Deng, G.; Liu, H. A review of the clinical efficacy of FDA-approved antibody–drug conjugates in human cancers. *Molecular Cancer* 2024, *23* (1), 62. DOI: 10.1186/s12943-024-01963-7.

(5) Gogia, P.; Ashraf, H.; Bhasin, S.; Xu, Y. Antibody-Drug Conjugates: A Review of Approved Drugs and Their Clinical Level of Evidence. *Cancers (Basel)* 2023, *15* (15). DOI: 10.3390/cancers15153886 From NLM.

(6) Fu, Z.; Li, S.; Han, S.; Shi, C.; Zhang, Y. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. *Signal Transduct Target Ther* 2022, *7* (1), 93. DOI: 10.1038/s41392-022-00947-7 From NLM.

(7) Strebhardt, K.; Ullrich, A. Paul Ehrlich's magic bullet concept: 100 years of progress. *Nature Reviews Cancer* 2008, *8* (6), 473-480. DOI: 10.1038/nrc2394.

(8) Tarantino, P.; Carmagnani Pestana, R.; Corti, C.; Modi, S.; Bardia, A.; Tolaney, S. M.; Cortes, J.; Soria, J. C.; Curigliano, G. Antibody-drug conjugates: Smart chemotherapy delivery

across tumor histologies. *CA Cancer J Clin* 2022, *72* (2), 165-182. DOI: 10.3322/caac.21705 From NLM.

(9) Takakura, T.; Shimizu, T.; Yamamoto, N. Antibody-drug conjugates in solid tumors; new strategy for cancer therapy. *Jpn J Clin Oncol* 2024, *54* (8), 837-846. DOI: 10.1093/jjco/hyae054 From NLM.

(10) De Cecco, M.; Galbraith, D. N.; McDermott, L. L. What makes a good antibody-drug conjugate? *Expert Opin Biol Ther* 2021, *21* (7), 841-847. DOI: 10.1080/14712598.2021.1880562 From NLM.

(11) Verdin, P. FDA new drug approvals in Q1 2025. *Nat Rev Drug Discov* 2025. DOI: 10.1038/d41573-025-00071-5 From NLM.

(12) Flynn, P.; Suryaprakash, S.; Grossman, D.; Panier, V.; Wu, J. The antibody-drug conjugate landscape. *Nat Rev Drug Discov* 2024, *23* (8), 577-578. DOI: 10.1038/d41573-024-00064-w From NLM.

(13) Criscitiello, C.; Morganti, S.; Curigliano, G. Antibody-drug conjugates in solid tumors: a look into novel targets. *J Hematol Oncol* 2021, *14* (1), 20. DOI: 10.1186/s13045-021-01035-z From NLM.

(14) Wolska-Washer, A.; Robak, T. Safety and Tolerability of Antibody-Drug Conjugates in Cancer. *Drug Saf* 2019, *42* (2), 295-314. DOI: 10.1007/s40264-018-0775-7 From NLM.

(15) Ceci, C.; Lacal, P. M.; Graziani, G. Antibody-drug conjugates: Resurgent anticancer agents with multi-targeted therapeutic potential. *Pharmacol Ther* 2022, *236*, 108106. DOI: 10.1016/j.pharmthera.2021.108106 From NLM.

(16) Mehta, G. U.; Vellanki, P. J.; Ren, Y.; Amatya, A. K.; Mishra-Kalyani, P. S.; Pan, L.; Zirkelbach, J. F.; Pan, Y.; Liu, J.; Aungst, S. L.; et al. FDA approval summary: fam-trastuzumab deruxtecan-nxki for unresectable or metastatic non-small cell lung cancer with activating HER2 mutations. *The Oncologist* 2024, *29* (8), 667-671. DOI: 10.1093/oncolo/oyae151 (acccessed 11/8/2024).

(17) Tarantino, P.; Ricciuti, B.; Pradhan, S. M.; Tolaney, S. M. Optimizing the safety of antibody–drug conjugates for patients with solid tumours. *Nature Reviews Clinical Oncology* 2023, *20* (8), 558-576. DOI: 10.1038/s41571-023-00783-w.

(18) Zhu, Y.; Liu, K.; Wang, K.; Zhu, H. Treatment-related adverse events of antibody-drug conjugates in clinical trials: A systematic review and meta-analysis. *Cancer* 2023, *129* (2), 283-295. DOI: 10.1002/cncr.34507 From NLM.

(19) Fu, Z.; Liu, J.; Li, S.; Shi, C.; Zhang, Y. Treatment-related adverse events associated with HER2-Targeted antibody-drug conjugates in clinical trials: a systematic review and meta-analysis. *EClinicalMedicine* 2023, *55*, 101795. DOI: 10.1016/j.eclinm.2022.101795 From NLM.

(20) Institute, N. C. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0: Quick Reference

. U.S. Department of Health and Human Services: 2017.

(21) D'Arienzo, A.; Verrazzo, A.; Pagliuca, M.; Napolitano, F.; Parola, S.; Viggiani, M.; Caputo, R.; Puglisi, F.; Giuliano, M.; Del Mastro, L.; et al. Toxicity profile of antibody-drug conjugates in breast cancer: practical considerations. *EClinicalMedicine* 2023, *62*, 102113. DOI: 10.1016/j.eclinm.2023.102113 From NLM.

(22) Hagiwara, Y.; Shiroiwa, T.; Shimozuma, K.; Kawahara, T.; Uemura, Y.; Watanabe, T.; Taira, N.; Fukuda, T.; Ohashi, Y.; Mukai, H. Impact of Adverse Events on Health Utility and Health-Related Quality of Life in Patients Receiving First-Line Chemotherapy for Metastatic Breast Cancer: Results from the SELECT BC Study. *Pharmacoeconomics* 2017, *36*, 215-223. DOI: 10.1007/s40273-017-0580-7.

(23) Alsheyyab, F.; Al-Momani, D.; Kasht, R.; Kamal, A.; Abusalem, D.; Al-Qasem, W. Impact of severe oral mucositis in pediatric cancer patients on resource utilization and cancer treatment plans. *Int J Clin Pharm* 2021, *43* (5), 1322-1326. DOI: 10.1007/s11096-021-01253-y From NLM.

(24) Higgins JPT, T. J., Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.3* Cochrane, 2022.

(25) Golder, S.; Loke, Y. K.; Wright, K.; Norman, G. Reporting of Adverse Events in Published and Unpublished Studies of Health Care Interventions: A Systematic Review. *PLoS Med* 2016, *13* (9), e1002127. DOI: 10.1371/journal.pmed.1002127 From NLM.

(26) Pranić, S.; Marušić, A. Changes to registration elements and results in a cohort of Clinicaltrials.gov trials were not reflected in published articles. *J Clin Epidemiol* 2016, *70*, 26-37. DOI: 10.1016/j.jclinepi.2015.07.007 From NLM.

(27) Hartung, D. M.; Zarin, D. A.; Guise, J. M.; McDonagh, M.; Paynter, R.; Helfand, M. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. *Ann Intern Med* 2014, *160* (7), 477-483. DOI: 10.7326/m13-0480 From NLM.

(28) Sterne JAC, S. J., Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. *RoB 2: A revised tool for assessing risk of bias in randomized trials*; Cochrane, London, UK, 2019. https://www.riskofbias.info/welcome/rob-2-0-tool.

(29) Slim K, N. E., Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological Index for Non-Randomized Studies (MINORS): development and validation of a new instrument. *ANZ Journal of Surgery* 2003, *73* (9), 712–716. DOI: 10.1046/j.1445-2197.2003.02748.x.

(30) Mercadante, S.; Aielli, F.; Adile, C.; Ferrera, P.; Valle, A.; Fusco, F.; Caruselli, A.; Cartoni, C.; Massimo, P.; Masedu, F.; et al. Prevalence of oral mucositis, dry mouth, and dysphagia in advanced cancer patients. *Support Care Cancer* 2015, *23* (11), 3249-3255. DOI: 10.1007/s00520-015-2720-y From NLM.

(31) Carneiro, B. A.; Papadopoulos, K. P.; Strickler, J. H.; Lassman, A. B.; Waqar, S. N.; Chae, Y. K.; Patel, J. D.; Shacham-Shmueli, E.; Kelly, K.; Khasraw, M.; et al. Phase I study of anti-epidermal growth factor receptor antibody-drug conjugate serclutamab talirine: Safety, pharmacokinetics, and antitumor activity in advanced glioblastoma. *Neurooncol Adv* 2023, *5* (1), vdac183. DOI: 10.1093/noajnl/vdac183 From NLM.

(32) Garrido-Laguna, I.; Krop, I.; Burris, H. A., 3rd; Hamilton, E.; Braiteh, F.; Weise, A. M.; Abu-Khalaf, M.; Werner, T. L.; Pirie-Shepherd, S.; Zopf, C. J.; et al. First-in-human, phase I study of PF-06647263, an anti-EFNA4 calicheamicin antibody-drug conjugate, in patients with advanced solid tumors. *Int J Cancer* 2019, *145* (7), 1798-1808. DOI: 10.1002/ijc.32154 From NLM.

(33) Suzuki, Y.; Zhou, S.; Ota, Y.; Harrington, M.; Miyagi, E.; Takagi, H.; Kuno, T.; Wright, J. D. Toxicity profiles of antibody-drug conjugates for anticancer treatment: a systematic review and meta-analysis. *JNCI Cancer Spectr* 2023, *7* (5). DOI: 10.1093/jncics/pkad069 From NLM.

(34) Imai, H.; Soeda, H.; Komine, K.; Otsuka, K.; Shibata, H. Preliminary estimation of the prevalence of chemotherapy-induced dysgeusia in Japanese patients with cancer. *BMC Palliative Care* 2013, *12* (1), 38. DOI: 10.1186/1472-684X-12-38.

(35) Hosseini, M.-S.; Sanaie, S.; Mahmoodpoor, A.; Jabbari Beyrami, S.; Jabbari Beyrami, H.; Fattahi, S.; Jahanshahlou, F.; Zarei, M.; Rahimi Mamaghani, A.; Kuchaki Rafsanjani, M. Cancer treatment-related xerostomia: basics, therapeutics, and future perspectives. *European Journal of Medical Research* 2024, *29* (1), 571. DOI: 10.1186/s40001-024-02167-x.