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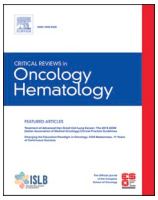

Clinical trials for patients with salivary gland cancers: A systematic review of worldwide registers and an evaluation of current challenges

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ABSTRACT

Background: Clinical trials (CT) are crucial for generating scientific evidence and improving clinical outcomes, but they can be challenging in the context of rare cancers. Salivary gland cancers (SGC) are rare and heterogeneous tumors, without standard-of-care approved systemic therapies. We analyzed completed and ongoing CTs to assess the current state of clinical research activity in the field.

Methods: ClinicalTrials.gov, WHO-ICTRP, HealthCanadaCT were searched for antineoplastic pharmacological and interventional CT involving patients with SGC from the trials database creation until August 6th, 2024. CT characteristics and status were collected.

Results: 134 clinical trials met inclusion criteria. Of these, 78 % were sponsored by non-industry entities. 49 % were conducted at only one site, and 61 % at up to five centers. Only 25 trials (19 %) were multinational, being 15 industry-sponsored, a significantly higher proportion compared to non-industry-sponsored trials($p < 0.01$). 16 % CTs were umbrella or basket, and 6 % were randomized, again predominantly industry-sponsored ($p < 0.01$). Regarding SGC-specific trials, 32 % were open to all patients with SGC, regardless of specific histology. Patients with adenoid cystic, salivary duct, and mucoepidermoid carcinoma had access to 92 %, 66 % and 62 % of trials, respectively. 88 % CT targeted palliative setting, and 38 % incorporated predictive biomarkers. Tyrosine kinase inhibitors were the most studied therapy(26 %), followed by immunotherapy(15 %), chemotherapy and antibody-drug conjugate(12 % each) and androgen-blockade(8 %), among others.

Conclusion: Clinical research for patients with SGC relies mainly in non-industry organisations, most of them limited to run trials in one to five sites, in a single country. Further collaboration between investigators is needed, as well as reconsidering inclusion criteria and trial designs.

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1. Introduction

Salivary gland tumors accounted for 6 % of neoplasms arising in the head and neck region worldwide in 2020, with 53,583 new cases (Sung et al., 2021; Cancer Facts & Figures, 2023), within the context of an expected increase in the elderly population over the next two decades (Colombo et al., 2022). However, under the term "Salivary Gland Cancers" (SGC), there is a highly heterogeneous group of tumors, which present a diagnostic challenge for pathologists, often necessitating subsequent histological reviews and complex molecular analysis (Xu et al., 2021). The World Health Organization classification has evolved significantly from 1972 to the latest edition in 2022, now recognizing 21 different histologies with distinct molecular biology and clinical behaviours, especially the distinction between Adenoid Cystic Carcinoma (ACC) and the other histologies (Żurek et al., 2023; Locati et al., 2023).

Half of cases are diagnosed at an early stage, with surgery being the primary curative option. In cases of unresectability or the presence of high-risk features for relapse in the surgical specimen, radiotherapy may be employed for local control (2024a). Despite these treatments, reported estimates for the risk of recurrence over 5 and 10 years vary from 17 % to 49 % and 22–55 % respectively (Carrillo et al., 2007).

Systemic therapies are frequently used in an attempt to improve outcomes. However, no neoadjuvant, concomitant, or adjuvant therapy has proven significantly to enhance the results of surgery or radiotherapy in the early disease setting with a high level of evidence (Geiger et al., 2021; van Herpen et al., 2022). Additionally, in cases of relapse or metastatic disease (R/M) not amenable to curative treatment, there remains a need to improve the 5-year overall survival rate of 43 % across histologies (SEER, 2023), as there is currently no clear standard-of-care for palliative systemic therapies in the existing guidelines (2024a). The available data show chemotherapy offers minimal tumor shrinkage while causing high levels of toxicity. On the other hand, targeted therapies have emerged as promising agents in specific setting, showing benefits in non-controlled studies where there is a clear and plausible target, such as with anti-HER2 therapies, androgen receptor inhibitors, NTRK and other tyrosine kinase inhibitors (Rached et al., 2024).

However, a significant portion of patients remain ineligible for any targeted therapy, and the benefits from some of these therapies might be minimal or short-lived even for patients whose disease demonstrates the target (Geiger et al., 2021; van Herpen et al., 2022). Even when a tumor is found to express a predictive biomarker, access to targeted therapies is often challenging since there is no specific indication for salivary gland cancer for drugs approved by the regulatory agencies and much variation across regulatory and funding jurisdictions. Instead, clinicians and patients must often rely on tumor-agnostic drug prescriptions, compassionate use, and early access, co-payment, or "pay-by-result" schemes which frequently do not cover the full cost of drugs (Polak et al., 2023; Bergmann et al., 2016; Michelsen et al., 2020). Clinical trials represent the gold-standard way to increase evidence in the field and provide access to therapies. Nevertheless, SGC- specific clinical trials have been in scant supply across the recent decades (Silva et al., 2024). This situation is exacerbated for patients with SGC in low- and middle-income countries. All these facts can result in a patient experience characterized by lack of support for those with rare, incurable, relapse or metastatic disease (Simons et al., 2024; Drabbe et al., 2021).

Overall, the low global and dispersed incidence of SGC, the unhelpful concept of considering these malignancies as one unique condition under the term SGC, and the sometimes-confusing histopathological diagnostic terms represent a significant barrier to establishing randomized and controlled clinical trials. Last but not least, the molecular biology of SGC can be frustrating because non-druggable gene fusions and mutations across the different histologies can be disheartening to patients and clinicians alike (Skálová et al., 2022; Rack et al., 2022). Silva et al. systematically reviewed clinical outcomes from the completed clinical trials involving patients with SGCs (Silva et al., 2024). However, there is a lack of a methodical and comprehensive review of the approaches and research strategies employed in past and ongoing clinical trials in this field. Reflecting on the trial designs and conduct of previous and current studies could help cooperative research groups and pharmaceutical companies in how planning future multi-center trials. It could also assist policymakers and funding bodies in understanding and utilizing evidence from underpowered and non-randomized trials for patients with rare conditions.

In this systematic review, we have conducted a methodical examination of the existing clinical trial registries to (a) identify and assess all the pharmacological interventional clinical trials for patients with SGC; (b) categorize their design characteristics, and (c) summarize their outcomes.

2. Methods

The study protocol was registered with PROSPERO (CRD42024531273) and was conducted following the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines (Page et al., 2021) and adhered to the "EQUATOR Reporting Guidelines"(Altman et al., 2008). Statements and checklist are provided in Supplementary Table S1.

Two independent researchers (P.J.L. and L.L) led a systematic search of the literature. Clinical trial databases (ClinicalTrials.gov, Health Canada's Clinical Trials Database, and World Health Organization International Clinical Trials Registry Platform which includes major registries from Europe, Asia, Oceania, South America and Africa) were searched for antineoplastic pharmacological and interventional clinical trials directed to patients with SGC from trial database creation until August 6th, 2024. The registries, countries included, and keywords for the search strategy can be found in Supplementary Table S2. Initially, potential trials were screened and those that did not meet inclusion and exclusion criteria were excluded.

Inclusion criteria for the systematic review were (a) registered clinical trials specifically targeting or particularly examining patients with SGC (major or minor glands, as well as those originating from outside the head and neck region); and (b) pharmacological prospective interventional studies. The exclusion criteria were: (a) pan-tumor trials without a specific cohort or sub analysis for SGC in their registry categorization, inclusion criteria or assessment, (b) those not properly registered with a specific codification; (c) non-anti-cancer-treatment-based clinical trials (e.g. supporting care treatments without cytotoxic or cytostatic effects), (d) protocols not published in English or Spanish, and (e) cases where the basic detailed protocol was unavailable. Duplicate records were identified by comparing trial identifiers, titles, and key study characteristics across databases, and were removed during the screening process to ensure each trial was represented only once.

Data from the included studies were independently extracted by two researchers (P.J. and L.L). The two databases were then cross-checked, and discrepancies were resolved through consensus under the supervision from the senior researchers (I.B and K.J.H). Reviewer agreement during the screening process was assessed using Cohen's kappa statistic, with a resulting inter-agreement of 0.92. A summary of the selected variables included: phase of study; type of drug; disease setting; eligible SGC histology subtypes to include; presence or absence of a control group; randomization; characteristics for enrolment (conventional [understood as testing a single treatment in a fixed group of patients] umbrella, basket or platform trial); estimated target sample size for recruitment, statistical design (% power, type of errors and hypothesis to test), year of study start; study status; sponsorship (non-industry sponsors [understood as academia, medical institutions or organizations] and pharmaceutical companies), enrolment sites (countries and number of centers [1, 1–5, 6–10, 11–20, >20]), primary endpoints and use of predictive biomarkers. Geographical categorization can be founded in Supplementary Table S3.

Studies categorized as active, completed, terminated, withdrawn or suspended were then searched via their full text in Core Collection,

BIOSIS Citation Index, KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index, in order to assess the grade of the publication, the accomplishment of primary endpoint and the risk of bias. Studies with a status of unknown, completed, withdrawn, terminated, or suspended in registries were considered as negative if their results were not published. The risk of bias was assessed using the ROBINS-I tool for non-randomized studies and the RoB2 tool for randomized studies (Sterne et al., 2016, 2019). The data gathered from the selected studies were methodically synthesized. Evidence was organized based on the therapeutic drugs and the types of tumors involved. Qualitative variables were correlated with each other using the Chi-square test, and quantitative variables were correlated using logistic regression. R software v4.4.1 was employed for all statistical analyses, with a statistically significant p-value set at < 0.05 (R, 2024).

3. Results

A total of 134 clinical trials were identified from 817 records (PRISMA diagram of selected databases and registers in Supplementary Figure S1). Among these, only 4 trials (3 %) were accessible for the paediatric and/or adolescent population, while the remainder were exclusively for adults.

One hundred and five trials (78.4 %) were sponsored by non-industry entities such as academic institutions, medical organizations, and single hospitals, while 29 trials (21.6 %) were driven by pharmaceutical companies. A list of sponsorships is given in Supplementary Table S4–5. Of the 134 clinical trials, 52.9 % (k [number of trials]=71) were based in North America, 25.3 % (k = 34) in Asia, 20.1 % (k = 27) in Europe, and 1.5 % (k = 2) in Australia and Oceania. Fig. 1 shows the sponsor's headquarter per country, and Supplementary Figure S2 per region. Clinical trials categorized by phase, design type, treatment setting, status, reporting of results, and achievement of primary endpoints are presented in Table 1, both overall and stratified by sponsorship (Park et al., 2024; Li et al., 2018; Dou et al., 2019; Adeberg et al., 2020; Locati et al., 2021, 2019; Honma et al., 2024; Pearson et al., 2024; Okano et al., 2023; Hotte et al., 2016; Van Boxtel et al., 2022; Burman et al., 2021; Kim et al., 2022; Locati et al., 2016; Jakob et al., 2015; Rodriguez et al., 2018; Chae et al., 2023; Guigay et al., 2016; Agulnik et al., 2007; Ji et al., 2024; Hernando-Calvo et al., 2023; Locati et al., 2020; Wong et al., 2016; Jiang et al., 2024; Li et al., 2019; Mohamadpour et al., 2023; van Ruitenbeek et al. 2024; Chau et al., 2012; Fayette et al., 2023; 2024b; Gilbert et al., 2006; Haddad et al., 2003; Pfeffer et al., 2007; Laurie et al., 2010; Kim et al., 2017; Lee et al., 2022; 2024c; Ho et al., 2024; Li et al., 2024; Meric-Bernstam et al., 2024; Abstract CT178, 2024; Zhang et al., 2023; Desai et al., 2022; Herpen et al., 2008; 2024d; Hanna et al., 2023; Thomson et al., 2015; Ferrarotto et al., 2022; Hanna et al., 2020; Hong et al., 2018; Fushimi et al., 2018; Hanna et al., 2021; Cohen et al., 2018; Schoenfeld et al., 2019; Keam et al., 2020; Zhu et al., 2021; Ho et al., 2016; Kang et al., 2021; Goncalves et al., 2017; Hoover et al., 2015; Tchekmedyian et al., 2019; 2024e; Ho et al., 2022; Ferrarotto et al., 2023; Kurzrock et al., 2020; Eigentler et al., 2022; Dillon et al., 2013; Keam et al., 2015; Even et al., 2020; Ferrarotto et al., 2018; 2024f; ICTRP, 2024).

The ongoing 5-year period from 2020 to 2024 has the most trials since registries' creation, with 47 trials, as is detailed in Fig. 2 and Supplementary Figure S3. The risk of bias in both non-randomized and randomized studies was moderate, as outlined in detail in Supplementary Table S6.

Regarding the inclusion criteria, 92 % of clinical trials were accessible to patients with ACC, 66 % for those with salivary duct carcinoma, 62 % for adenocarcinoma and mucoepidermoid carcinoma, 57 % for carcinoma ex pleomorphic adenoma, 56 % for acinic cell carcinoma, and 54 % for myoepithelial carcinoma. Overall, 43 trials were designed to enrol patients with all types of SGC histologies (32 %), 41 trials were exclusively dedicated to ACC (30.6 %), and 30 trials were pan-tumor trials with a specific cohort or sub-analysis for SGC histologies (22.4 %) among the entire trial cohort.

Across the 112 trials with a phase II design, 23 (20.5 %) reported using a two-stage Simon design. Of these, 7 trials utilized the Simon Minimax version, 5 trials employed the two-stage Simon optimal version, and 1 trial used a three-stage Gehan design. For trials with a two-stage design, the median and arithmetic mode response in the first stage were both one response out of 12 patients (0.08; k = 29). This criterion was used to determine whether to proceed to the second stage. The median predefined sample size for non-pantumor phase II trials was 33 patients (range 10–120; k = 95).

One hundred and twelve (83.6 %) predefined primary endpoints related to treatment efficacy. Disease-free survival (DFS) was the most

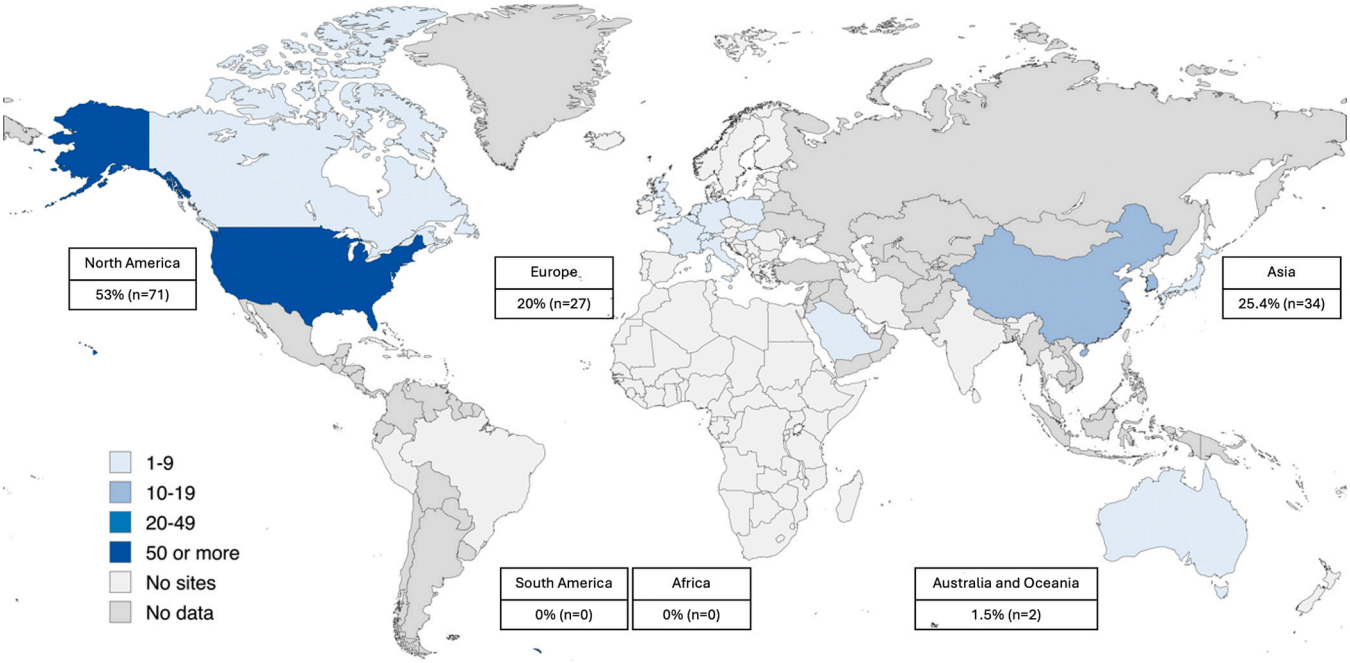

Fig. 1. Heatmap of Global Clinical Trial Distribution by Sponsor Site.

Table 1
Summary of included clinical trials for systematic review. Abbreviation: N/A: Not applicant; n: sample size; RT: Radiotherapy; *k*: number of trials; Ha: Alternative hypothesis; Ho: Null hypothesis. *points statistically significant values.

	Total number of trials (n, %)	Non-Industry-sponsored (n, %)	Industry-sponsored (n, %)	Chi-Square p-value
Clinical Trials	134 (100 %)	105 (78.36 %)	29 (21.64 %)	N/A
- Trials eligible for systematic review				
Clinical Trial Phase	23 (17.15 %)	9 (8.57 %)	14 (48.28 %)	31.75 (<0.01 *)
	6 (4.5 %)	2 (1.90 %)	4 (13.79 %)	
- Phase I	105 (78.35 %)	94 (89.52 %)	11 (37.93 %)	
- Combined Phase I/II	0 (0 %)	0 (0 %)	0 (0 %)	
- Phase II				
- Phase III				
Type of Clinical Trial	112 (83.58 %)	96 (91.43 %)	16 (55.17 %)	35.01 (<0.01 *)
	17 (12.69 %)	4 (3.81 %)	13 (44.83 %)	
- Conventional	5 (3.73 %)	5 (4.76 %)	0 (0 %)	
- Basket trial	0 (0 %)	0 (0 %)	0 (0 %)	
- Umbrella trial				
- Platform trial				
Trial Characteristics	9 (6.72 %)	8 (7.62 %)	1 (3.45 %)	0.14 (0.70)
	8 (6 %)	7 (6.67 %)	1 (3.45 %)	0.04 (0.83)
- Controlling (observation or control treatment arm)	0 (0 %)	0 (0 %)	0 (0 %)	N/A
- Randomization				
- Use of placebo or treatment-blinding				
Recruitment Sites Distribution	66 (49.25 %)	65 (61.90 %)	1 (3.45 %)	29.31 (<0.01 *)
	68 (50.75 %)	40 (38.10 %)	28 (96.55 %)	(Unicenter vs Multicenter[All])
- Unicenter	16 (11.94 %)	14 (13.33 %)	2 (6.90 %)	
- Multicenter (all)	12 (8.96 %)	8 (7.62 %)	4 (13.79 %)	
- Multicenter (1−5)	15 (11.19 %)	12 (11.43 %)	3 (10.34 %)	
- Multicenter (6−10)	25 (18.66 %)	10 (9.52 %)	15 (51.72 %)	
- Multcenter (11−20)				
- Multicenter (>20)				
Geographical Distribution	109 (81.34 %)	97 (92.38 %)	12 (41.38 %)	35.27 (<0.01 *)
	25 (18.66 %)	8 (7.62 %)	17 (58.62 %)	
- Single country				
- Multinational				
Clinical Trial Inclusion	74 (55.22 %)	51 (48.57 %)	23 (79.31 %)	7.72 (<0.01 *)
	60 (44.78 %)	54 (51.42 %)	6 (20.69 %)	
- All SGC histologies				
- Selected SGC histologies				
Treatment Setting	15 (11.19 %)	15 (14.29 %)	0 (0 %)	3.20 (0.07)
	6 (4.48 %)	6 (5.71 %)	0 (0 %)	(Curative[All] vs Palliative[All])
- Curative – Overall	1 (0.75 %)	1 (0.95 %)	0 (0 %)	
- Curative – Neoadjuvant	8 (5.97 %)	8 (7.62 %)	0 (0 %)	
- Curative – Concomitant with RT	118 (88.06 %)	89 (84.76 %)	29 (100 %)	
- Curative – Adjuvant	85 (63.43 %)	74 (70.48 %)	11 (37.93 %)	
- Palliative – Overall	113 (84.33 %)	85 (80.95 %)	28 (96.55 %)	
- Palliative – Accessible for first line				
- Palliative – Accessible for second line and beyond				
Use of Predictive Biomarkers	52 (38.81 %)	39 (37.14 %)	13 (44.83 %)	1.27 (0.73)
Clinical Trial Status	6 (4.48 %)	6 (5.71 %)	0 (0 %)	0.26 (0.61)
	2 (1.49 %)	2 (1.90 %)	0 (0 %)	(Active [All] & Completed vs Rest of
- Unknown	2 (1.49 %)	2 (1.90 %)	0 (0 %)	Studies[All])
- Withdrawn (removed before starting enrolment)	5 (3.73 %)	3 (2.86 %)	2 (6.9 %)	
- Suspended (possibly resuming later)	5 (3.73 %)	5 (4.76 %)	0 (0 %)	
- Terminated (stopped during enrolment)	34 (25.37 %)	23 (21.90 %)	11 (37.93 %)	
- Active – Not yet recruiting	17 (12.69 %)	11 (10.48 %)	6 (4.65 %)	
- Active – Currently recruiting	63 (47.01 %)	53 (50.48 %)	10 (7.75 %)	
- Active – Not recruiting				
- Completed				
Clinical Trial with Efficacy Primary Endpoint Results	83 (61.8 %)	70 (66.66 %)	13 (44.83 %)	0.31 (0.96)
	66 (49.25 %)	54 (51.4 %)	12 (41.38 %)	(Published vs Unpublished, $k = 83$)
- Completed, suspended, withdrawn, terminated, or published active clinical trials	17 (12.67 %)	16 (15.2 %)	1 (3.45 %)	
- Published interim or final results				
- Unpublished results				
Published Data from Clinical Trials with Efficacy Primary Endpoints	11 (8.2 %)	11 (10.47 %)	0 (0 %)	0.15 (0.70)
	6 (4.4 %)	5 (4.7 %)	1 (3.45 %)	(Ha Primary Efficacy Endpoint Reached
	7 (5.2 %)	5 (4.7 %)	2 (6.9 %)	vs Not Reached, $k = 74$)
- Trials with at least one primary efficacy endpoint which its Ha´was achieved (positive trial)				
- Trials with at least one primary efficacy endpoint which its Ho´threshold was surpassed, but not the Ha				
- Trials with primary efficacy endpoint committed in post-hoc sub-group analysis				

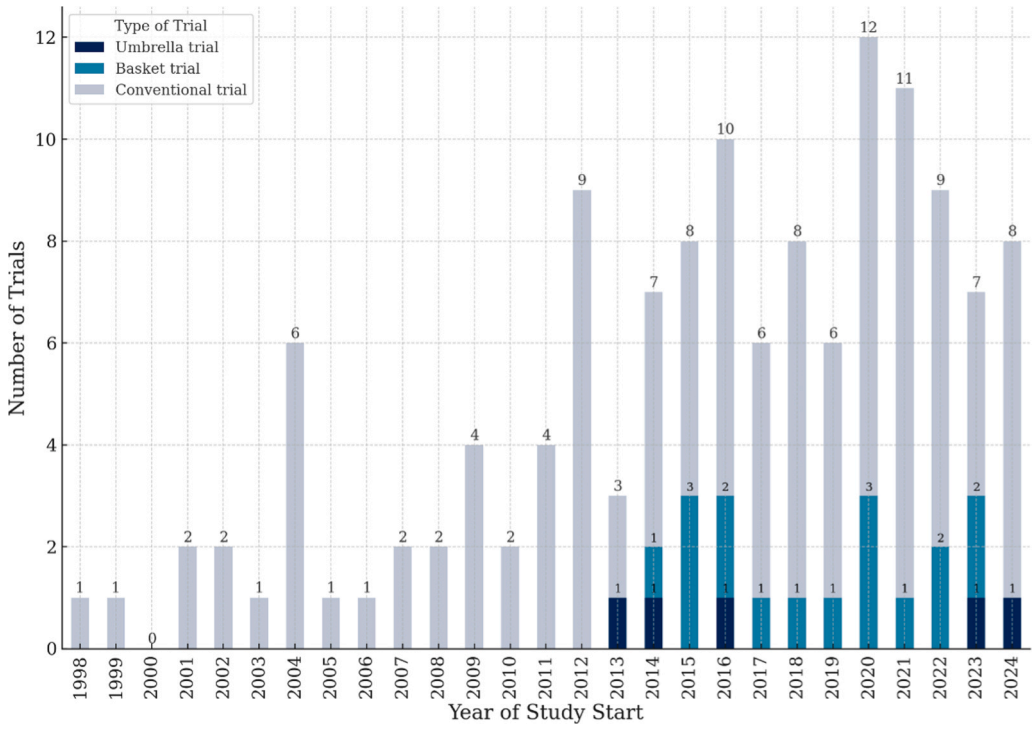

Fig. 2. Annual Distribution of Clinical Trials by Type (1998–2023).

selected primary efficacy endpoint in the curative setting, chosen in 7 out of 15 studies (46.7 %) followed by major pathological response in 3 studies (20 %) and overall response rate (ORR) in 1 study (6.6 %). In the metastatic setting, ORR was the primary efficacy endpoint in 87 out of 97 trials (91.6 %). Other endpoints included progression-free survival (PFS) in 4 trials (4.1 %), disease control rate in 3 trials (3 %), and non-progression rate, duration of response, tumor growth reduction (TGR), and overall survival, each in one trial (1 %). Of these 112 clinical trials

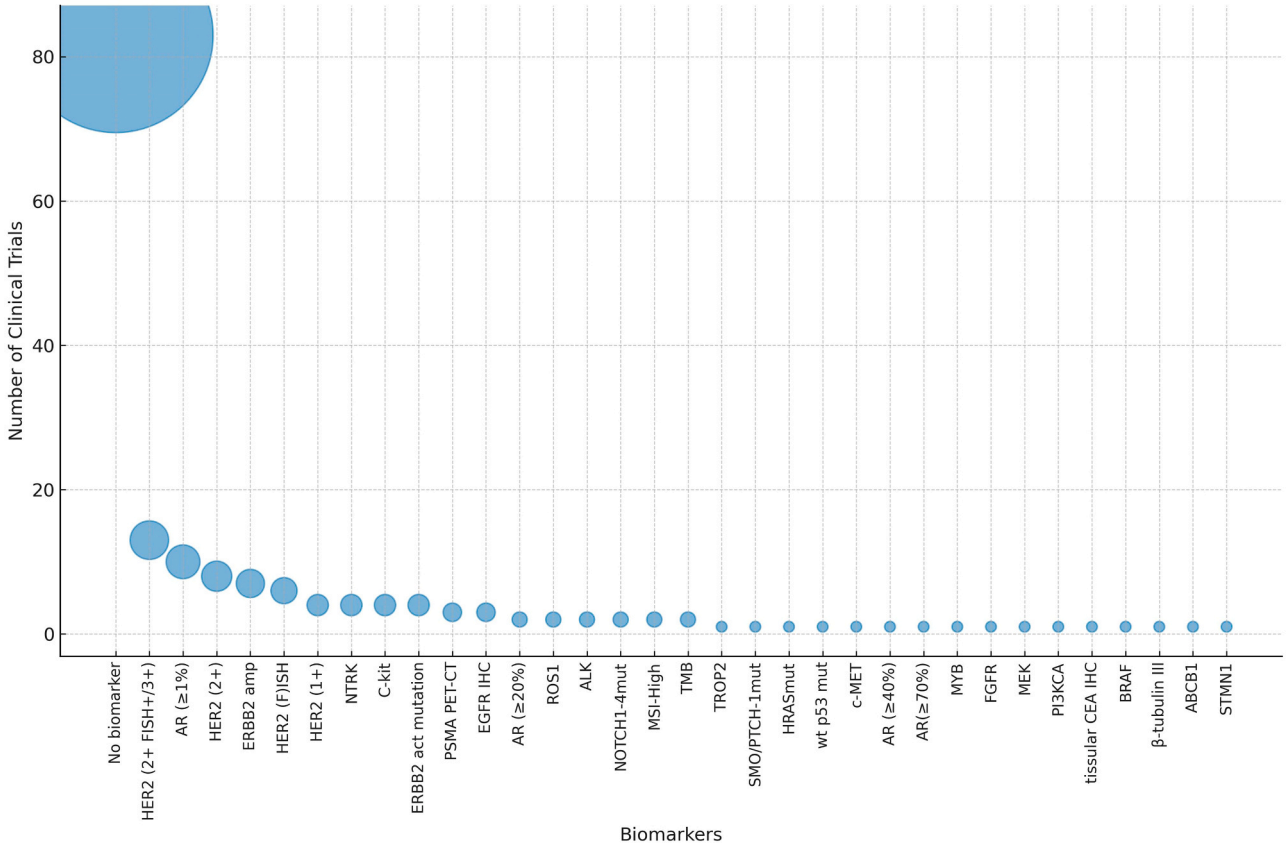

Fig. 3. Distribution of Clinical Trials by Predictive Biomarkers Used. Note: A single study may include more than one biomarker.

with predefined efficacy endpoints, only 14 trials (12.5 %) specified that efficacy assessments would be conducted by independent radiology teams, with 10 of these assessments being unblinded and 4 blinded. In 12 trials (10.7 %), the efficacy assessments were conducted by the same investigators who delivered the treatment, while the remaining 85 trials did not specify their assessment methods.

The median type I error rate selected across trials was 10 % (range 5–15 %, $k = 28$). The median type II error rate was 13.5 % (range 5–20 %, $k = 31$). The median ORR required to rule out the null hypothesis was 5 % (range 1–50 %, $k = 33$), and the ORR needed to confirm the alternative hypothesis had a median of 20 % (range 14–65 %, k = 37).

A total of 51 clinical trials (38.4 %) utilized predictive or selection biomarkers to guide their experimental treatments. The most common biomarker was HER2, with up to 13 trials (9.7 %) using HER2 immunohistochemistry (IHC)+ + combined with positive (F)ISH or IHC+ ++ alone. This was followed by androgen receptor (AR) positive staining (≥1 %) in 10 trials (7.5 %), HER2 IHC+ + irrespective of (F)ISH status in 8 trials (5.9 %), and ERBB2 gene amplifications identified through molecular testing, as well as HER2 (F)ISH positive status irrespective of IHC, among others. Detailed information on predictive biomarkers is represented in Fig. 3 and can be found in Supplementary Table S7.

Up to 35 trials assessed either as monotherapy, or in combination, tyrosine kinase inhibitors (TKI) (26.1 %), 20 evaluated on immunotherapy (15 %), 16 focused on both antibody-drug conjugates (ADC) and chemotherapy (12 % each), 13 studied non-ADC antibodies (9.7 %), 3 three on delivered radionuclides (2.2 %), and 2 two on tested cell therapies (1.5 %). Of note, 18 trials were based on HER2-and-*ERBB2*-blockade based (13.4 %), 11 trials assessed androgen -blockade based (8.3 %), 5 were on NOTCH-targeted therapies (3.7 %), and 3 assessed *MYB*-targeted therapies (2.2 %). Complete information about clinical trials selected can be found in Supplementary Tables S8–9.

A statistically significant proportion of the trials ($p < 0.01$; $k = 134$) were multicenter, and multinational studies, as well as basket trials, phase I or combined phase I/II, all conducted under industry sponsorship, as shown in Table 1. There was seen a trend for correlation between the likelihood of a trial being published and its having a positive result ($p = 0.07$; $k = 74$), suggesting a potential publication bias as is shown in Supplementary Table S10. Finally, the type of experimental drug significantly impacted the likelihood of publication ($p = 0.01$; $k = 83$), with trials involving TKI being twice as likely to be published compared as those involving other experimental drugs.

4. Discussion

To the best of the authors' knowledge, this is the first systematic review of SGC clinical trials from registries, examining their patient inclusion criteria, geographic distribution, and design characteristics as a means of highlighting key concepts.

Through our review, we have identified that four out of five trials have been developed by non-industry sponsors, with most involving some level of secondary collaboration from pharmaceutical companies, highlighting the scientific efforts from academia in the field of rare cancers in recent decades. However, the ability of universities, societies and single hospitals to sponsor and undertake multicenter and multinational studies is greatly limited in comparison with pharmaceutical companies. Approximately half of the studies were based in only one center, and 80 % in only one country. These facts highlight the need for stronger collaborations between investigators across district health areas and borders to achieve high levels of patient recruitment in such a low-incidence, heterogeneous disease as SGC (Komatsubara and Carvajal, 2016). Additionally, novel methods for enrolling more patients, rather than the low median number seen in the phase II trials collected, are needed to reach the thresholds required for phase III clinical trials and may allow for subgrouping patients based on histologies or predictive biomarkers. Decentralizing clinical trials has been postulated as one solution for rare cancer clinical trials, as many centers may not activate single-arm trials due to accrual concerns (2024g). This approach might involve patients in rural areas and decrease the burden of long and frequent medical journeys to highly specialized centers. Artificial intelligence tools for optimizing recruitment are also under investigation for accrual purposes, highly necessary for patients with rare conditions, spotlighting potential candidates through electronic health records (Lu et al., 2024).

In reference to the geographical distribution, USA and Canada showed the highest rate of clinical trials in this field. Alternatively, half of the SGC incidence occurs in Asia (Sung et al., 2021), which could explain a high concentration of trials in countries such as China, Japan and South Korea. On the other hand, low- and middle-income countries were under-represented in this specific area of clinical research, which may had an impact on patient treatment opportunities and the multicenter trials (Rubagumya et al., 2022).

Regarding inclusion, patients with specific histologies, such as ACC, are more likely to be eligible for enrollment in clinical trials compared to those with other histologies. This may be due to the postulated ACC sensitivity to TKIs and the extensive development of these treatments. Nonetheless, one out of three trials was designed to enroll patients with any SGC subtype, regardless of the specific histology. Ideally, treating SGC as a single disease entity in conventional trials should be avoided due to the diversity of clinical and molecular patterns of SGC. Nonetheless, this practice persists due to the previously discussed challenges in patient enrollment (Roland, 2022).

Therapeutic advances for patients with SGC have largely depended on, and continue to rely on, phase II clinical trials, as highlighted in this review. However, there is still room for improvement. Up to 80 % of these trials were designed as phase II, mostly without an internal control arm, but incorporating external controls may be an alternative (Casali et al., 2015). A strong preclinical background, phase I safety data, and studies conducted multicentrally are crucial for minimizing the risk of early termination, suspension, or withdrawal. In regards to efficacy assessment, ensuring independent central review of RECIST data is an important quality research factor (Ford et al., 2009). This was observed in only 12.6 % of screened trials.

Having a low enrolment capacity has tended to result in underpowered studies and, consequently, the probability of incorrectly rejecting the null hypothesis that the experimental drug is ineffective. This is also known as type I error, which is traditionally set at 5 % in oncology phase II trials, frequently based in highly heterogenous past trials. However, as shown in our data, SGC trials often accept a higher threshold, typically 10 %, to reduce the required sample size as described before in the literature (Bogaerts et al., 2015; Ashley et al., 2015).

The choice of endpoint is also under discussion and represents an area for improvement to enhance data harmonization in ongoing and future studies. ORR, disease control, or non-progression rate (response rate plus stable disease) have not always been found to correlate with overall survival across multiple oncology studies, yet they remain useful for assessing treatment efficacy in early phase clinical trials (Solomon et al., 2022). Additionally, the nature of most SGC tumors, which tend to be slow-growing, suggests that these outcomes may not be the most suitable to investigate on their own, depending on the treatment being assessed (Blagosklonny, 2005). For this reason, PFS or TGR have increasingly appeared as additional primary endpoints in recent years in the SGC field which could be encouraging for patient involvement in trials. Future trial designs could be improved following evidence-based methodological framework as the SPIRIT-Outcomes 2022 states, enhancing utility and replicability.

In recent years, research has increasingly shifted toward basket and umbrella trials, which may offer greater efficiency compared to conventional trials, that might involve often altered novel targets such as PI3K, BRAF, MSI or HRAS. These trial designs allow for the simultaneous

testing of multiple hypotheses in heterogeneous patient groups, maybe leading to faster and more actionable insights through genomic and transcriptomic testings. Wider use of next-generation sequencing is expected to identify rare but actionable mutations, supporting biomarker-driven enrolment. Liquid biopsies may enable real-time, non-invasive detection of tumor alterations, while artificial intelligence-driven models could help integrate data to improve trial matching and design (Li et al., 2024; Park et al., 2019). Based on our data, no platform trial has yet been conducted specifically in this field, although such an approach could be optimal for maintaining recruitment and testing different treatment sequences in rare cancers (Hau and Frühwald, 2024; Dhaenens et al., 2024), particularly in cases of progressive disease such as HER2-positive SGC, AR-positive SGC, or ACC treated with TKIs (Schettini et al., 2024; Home. STAMPEDE, 2024; Khosroyani et al., 2023). Although these different designs may involve distinct endpoints across arms, complicating both inter-arm comparisons and indirect comparisons with results from other trials.

Receptor tyrosine kinases, immune checkpoints, and the pathway from the gene ERBB2 to the surface protein HER2 have been among the most studied molecular pathways. Additionally, novel biomarkers that show characteristics of driving disease biology are beginning to be investigated with innovative targeted therapies as seen in our review. Alterations in the NOTCH signalling pathway, particularly NOTCH1 mutations, have been implicated in aggressive behaviour and poor prognosis in ACC. Targeting this pathway may provide new therapeutic strategies, as gamma secretase inhibitors, which are being explored in other solid tumors. Similarly, aberrant activation of the MYB–NFIB fusion gene is another hallmark of ACCs, driving tumor growth and survival. Brill et al. (2011) While direct targeting of MYB remains challenging, downstream effectors and synthetic lethality approaches are under investigation (Ferrarotto et al., 2017),. However, a significant number of patients with SGC lack druggable biomarkers, making them a sizable group in head and neck clinics (Rack et al., 2022). Notably, 20 % of the trials found were phase I in whole or in part of their design. In this context, addressing intractable proteins and other major molecular events remains a current challenge. This highlights the importance of incorporating early-phase clinical trial units, molecular tumor boards, parallel biomarker testing, and translational research from bench to bedside into the clinical trajectory of patients with SGC (Coleman and Rodon, 2021).

Lastly, timely publication of study results, including negative outcomes, remains crucial (Nardo et al., 2023). Our findings suggest that certain trial characteristics may influence the dissemination of results in SGC research. However, it is essential to stay on the right path to ensure the future approval of effective treatments.

This review has several limitations that should be considered. First, it does not include trials that are not listed in the selected registries. However, trial registration is a practice that has been common for most high-income countries since the early 2000s, and the included list of data sources is comprehensive. Additionally, pan-tumor clinical trials that did not specifically identify SGC tumors as a primary group were not included. Including such trials would have limited the ability to draw meaningful conclusions for this patient population. Lastly, not all published results were complete or peer reviewed.

In conclusion, the development of clinical trials for patients with SGC is highly dependent on non-industry entities. Multicentre and multinational collaboration is key to try to set up greater number of controlled clinical trials for this population in the hope that this will yield data to support phase III studies. Histologic-specific subtype designs and master trials, guided by predictive biomarkers, involving patients in their design and delivery, might reach higher evidence levels in international guidelines, hopefully leading to practice-changing studies.

Author Contribution

PJL (conceptualization, protocol writing – original draft, methodology, data curation, data extraction, systematic review search, writing-original draft), LL (conceptualization, protocol writing – original draft, methodology, data curation, data extraction, systematic review search, writing-original draft), CG (protocol review and editing, writing - review and editing), EK (writing - review and editing), SB (writing - review and editing), MF (protocol review and editing, writing - review and editing), RM (protocol review and editing, writing - review and editing), RF (protocol review and editing, writing - review and editing), PB (conceptualization, methodology, writing - review and editing, supervision), BO (conceptualization, methodology, writing - review and editing, supervision), GH (conceptualization, methodology, writing - review and editing, supervision), EF (conceptualization, methodology, writing - review and editing, supervision), IB (conceptualization, methodology, writing - review and editing, supervision), KJH (conceptualization, methodology, supervision). All authors contributed to manuscript revision, read, and approved the submitted version.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2025.104747.

Data availability

The data that support the findings of this study are available from the corresponding author, PJL, upon reasonable request.

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