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SYSTEMATIC REVIEW

RAPID SYSTEMATIC REVIEW OF CLINICAL TRIALS ON PHARMACOLOGICAL THERAPIES FOR RARE GYNECOLOGICAL CANCERS

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ABSTRACT: The purpose of this study is to systematically review clinical trials on pharmacological therapies for rare gynecological cancers and analyze their characteristics. The PRISMA guidelines for systematic reviews were followed and two databases were searched (WHO´s International Clinical Trials Registry Platform and clinicaltrials.gov). The Jadad score was used to assess the methodological quality of completed clinical trials. A total of 212 records, covering trials from 1993 to 2022, were included in the final review. More than half were phase II trials (110; 51.89%) and the status of recruiting was mainly completed (80; 37.74%). There were 26 (12.26%) terminated or withdrawn clinical trials. Just 42.45% of the trials were specific only for rare types of gynecological cancers. The most common type of investigated therapy was chemotherapy (89; 41.98%), followed by targeted therapy (64; 30.19%) and a combination of therapies (23.11%). However, in the last five years there was an increase in trials investigating targeted therapies such as immunotherapy, overgrowth-related and angiogenesis-related therapies. All completed trials except one, had a Jadad score 0-2, indicating low-quality. Thirty-six (45.00%) completed clinical trials had neither posted results, nor publications. Higher quality clinical trials with better reporting of results are needed for rare gynecological cancers

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Impact statement: Despite the increase over the years in the number of trials investigating pharmacological therapies (especially targeted therapies) for rare gynecological cancers, higher quality clinical trials and better reporting of results are needed.

Key words: *rare gynecological cancer; clinical trials; chemotherapy; targeted therapy; immunotherapy.*

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INTRODUCTION

Currently, it is estimated that about 50% of gynecological cancers are rare (annual incidence of less than 6 per 100.000) (1). Nevertheless, they account for more than 80,000 new cases per year in Europe. Based on the 2020 WHO classification of female genital tumors, gynecological rare cancers include more than 30 histologic entities, located in different sites (vulva-vagina, uterine cervix, uterine corpus, fallopian tube, ovary etc.) and of different morphology (epithelial, germ cell, sex cord stromal, trophoblastic, mixed *etc*.) (2). As with most rare diseases, these types of cancers share similar challenges: poor diagnosis, scarce research opportunities, insufficient expertise, few clinical trials, and limited treatment options (3). Initial treatment for almost all rare gynecological cancers involves surgery, however systemic treatment is also part of the standard of care, including hormonal therapy, chemotherapy, immunotherapy and targeted therapies (4).

Randomized clinical trials are considered as the gold standard in epidemiological research, however due to poor accrual rates and ethical reasons this study design is generally not applied to rare diseases (5).

Over the last decade, there has been a significant increase in biomarker-based studies, clinical trials for immuno-oncology treatments and targeted therapies (6). The development and clinical use of new drugs that target gene alterations regardless of the tumor´s site and morphology has led to a new era of precision cancer medicine. Clinical trials design has notably evolved, especially in the first phase. For example, rapid phase I dose-escalation clinical trials are succeeded by large expansion cohorts. Novel clinical trials with more complex design include adaptive platform trials, basket trials, and umbrella trials. Adaptive platform trials comprise planned opportunities to adjust or adapt specific elements of the design according to the analysis of data acquired from patients, thus increasing the trials´ efficiency (7). In an oncology basket trial, one targeted treatment is simultaneously evaluated for a variety of cancers that share a common genetic alteration or molecular defect (one targeted treatment in a basket with several types of cancers). In an umbrella trial, multiple targeted treatments in different treatment arms are evaluated for one type of cancer stratified by molecular defects or genetic alterations (an umbrella with several treatments assigned according to the molecular characteristics targeting one type of cancer) (8, 9). Among the factors associated with problematic clinical trials are poor study design, poor recruitment, ineffective site selection, patient burden, and poor trial execution (10). The integration of artificial intelligence and mobile health technology (such as wearables and sensors) has the potential to transform and optimize clinical trials, particularly in oncology (11). Patients´ participation in clinical trials and their overall engagement is crucial to speed up funding and support research on rare gynecological cancers. Initiatives including the European Network of Gynecological Cancer Advocacy Groups (ENGAGE) are being implemented to promote patients´ involvement and collaboration in research (12). However, there is an underrepresentation of specific population groups in oncology clinical trials in general, such as children, adolescents and young adults, adults lacking the capacity to consent, older adults, as well as racial and ethnic minorities (13-16). This is particularly important in the case of rare gynecological cancers, which are prevalent among girls and young women. Addressing the under-representation of such groups and promoting inclusion is important to have more accurate and representative outcomes and expand access to new cancer treatments. Moreover, one recent study found that patients with rare cancers are significantly less willing to participate in clinical trials compared to patients with common cancers (17).

Despite the challenges, clinical trials on common and rare gynecological cancers have advanced in investigating targeted therapies including antiangiogenic agents, PARP inhibitors, tumor-intrinsic signaling pathway inhibitors, selective estrogen receptor down-regulators, and immune checkpoint inhibitors. This has led to several drugs recently approved by the FDA for these malignancies, such as bevacizumab (target: VEGFR), olaparib, rucaparib and niraparib (target: PARP), pembrolizumab (target: Anti PD-1) and pembrolizumab + lenvatinib (targets: anti PD-1 + VEGFR) (18). Higher benefits and lower grade 5 risk seem to occur in phase I oncology clinical trials which target only one tumor type and incorporate biomarkers among the eligibility criteria (19).

The vast variability in the different types of rare gynecological cancers poses a challenge to fully comprehend the trends on therapies investigated as part of clinical trials for these particular malignancies. Therefore, it is of utmost importance to synthesize the evidence from clinical trials, elucidate their characteristics and explore the type of therapies involved. A multidisciplinary approach, international consortia and increased resources are indispensable to harmonize research, improve diagnosis, and design suitable clinical trials, thus leading to better treatments and patients´ outcomes (20). When searching the Cochrane library for previously published systematic reviews on therapies for rare gynecologic cancers, only one systematic review had been carried out on a specific type of rare gynecological cancer, namely malignant germ cell ovarian tumor. The authors reported that the small number of included studies (one RCT and one retrospective) and of patients (32 women) were insufficient to give conclusions on the effectiveness and safety of chemotherapy (21). Among the most active current international projects on the topic, the COST Action CA-18117 GYNOCARE has established a multidisciplinary European network for Gynecological Rare Cancer research: from concept to cure. Members from Working Group 5 "Coordination of interactions between clinical trials, translational research, and basic research" have focused on developing a clinical trial reference depository and systematically

reviewing clinical trials for rare gynecological malignancies (22). As members of this Working Group, the objective of our study is to comprehensively analyze the characteristics of clinical trials (finalized and ongoing) on pharmacological therapies for rare gynecological cancers.

MATERIALS AND METHODS

The PRISMA 2020 guidelines for systematic reviews and meta-analysis (23) were followed and two different databases were searched. The WHO´s International Clinical Trials Registry Platform (ICTRP) and the clinicaltrials.gov databases were consulted, as well as the articles published in PubMed/MEDLINE reporting on results of the included clinical trials on rare gynecological cancers. The WHO ICTRP is a platform that serves as a database collecting data from various clinical trial registries. Its mission is to enable complete access to research to everyone involved in health care decision making (24). Clinicaltrials.gov is the largest public registry of clinical trials offering information to diverse stakeholders (researchers, healthcare providers, patients, and their families) regarding ongoing and completed clinical trials (25). The protocol for the systematic review has been registered in PROSPERO.

A full list of search terms for each database is provided in **Appendix 1**.

Inclusion criteria included, regarding the type of study, only interventional, clinical trials that investigated pharmacological therapies for at least one rare gynecological cancer, from inception till June 2022, with primary purpose treatment. Exclusion criteria were: study designs different from clinical trials, observational studies and studies that did not include pharmacological therapies.

Rare gynecological cancer was defined based on the list of rare gynecological cancers as adapted from the WHO classification of tumors (26, 27).

Two researchers independently screened for clinical trials that reported on pharmacological therapies for at least one rare gynecological cancer (K.H. and A.L.). Screening of search results against eligibility criteria was performed from 07.26.2002 to 08.26.2022. Discrepancies were resolved by reassessment of the full record and discussion between reviewers (S.D., J.C.-A.).

The complete record of each clinical trial was reviewed and the following data were extracted: registration number (NCT), study name/official title, study type/design, funding/sponsor, research site/locations, research institute, stage, status, (estimated) start date, (estimated) completion date, population included, sample size (estimated), cancer/cancers type, recruitment period, intervention group measures, control group measures, outcome measures (primary and secondary), random methods, blind methods, distribution concealment, measurement indicators, results (published or not), publications.

The treatments in the clinical trials were classified according to the type of therapy: chemotherapy, hormonal therapy, targeted therapy, and mixed (more than one type of therapy). Drugs of targeted therapies were listed, classifying them into: 1) overgrowth-related (apoptosis induction and proliferative signaling), 2) angiogenesis-related, and 3) immunotherapy (28, 29).

A separate analysis was performed for completed clinical trials. The average length, type of therapies, drugs/treatments, and design characteristics were recorded. The Jadad score was used to assess the methodological quality of the clinical trials, with regards to masking, randomization, and accountability of all patients, including withdrawals. This validated score lies in the range 0-5, where scores of 3 or more indicate higher quality trials (30). Excel® (Microsoft, Redmond, Washington) was used for analysis of data. Results were presented as frequencies (%) or means with range and standard deviation (SD), as appropriate.

RESULTS

Overall, 779 records were identified in both databases (520 from clinicaltrials.gov and 259 from WHO ICTRP). After removing 85 duplications, 694 clinical trials were eligible for screening. A total of 482 records were excluded for the following reasons: not including rare gynecological cancers (327), studies on prevention or quality of life (61), medical procedures such as radiotherapy or diagnostic procedures (55), observational studies (24), and preventive vaccines (15). Finally, a total of 212 records, covering trials recorded during the period 1993 - 2022, were included in the final review.

Figure 1 shows the PRISMA 2020 flow diagram for the systematic review. **Supplementary material 1** provides the full list of the included clinical trials.

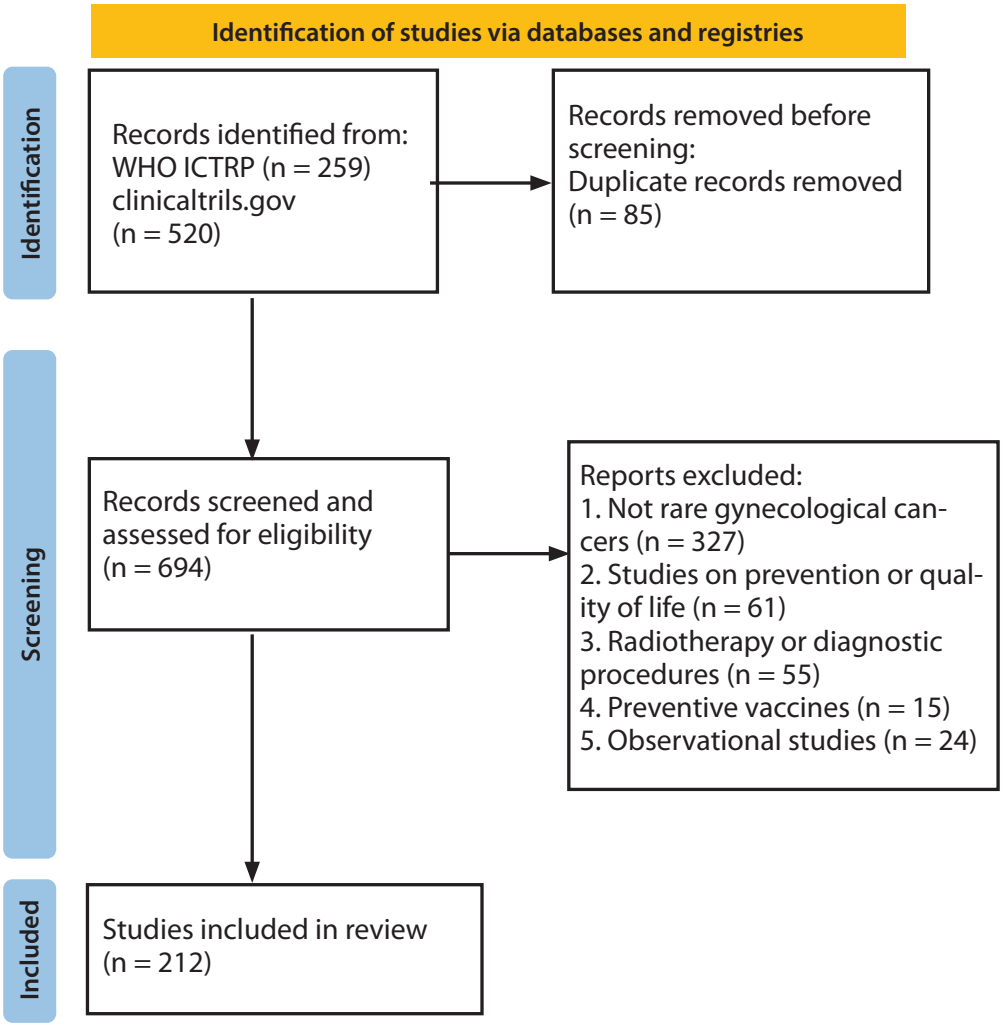

Figure 1. *PRISMA 2020 flow diagram for the systematic review.*

CHARACTERISTICS OF CLINICAL TRIALS

These interventional clinical trials included in the 212 records recruited, or estimated to recruit, a total of 30941 patients. Median number of patients included in the trials was 40, ranging from 0 (in seven withdrawn clinical trials) to 2059 (SD 299.73). Five clinical trials did not provide the number of patients. Most of the clinical trials included only female patients (145; 68.40% of the trials). This is because there were clinical trials which included men with testicular tumors, and other related tumors.Adult and older adult patients were eligible to be included in 99.06% and 95.75 % of the trials (210 and 203), respectively. There was a significantly lower number of clinical trials that included children (13.68%; 29 clinical trials).

Table I summarizes the characteristics of clinical trials for therapies on rare gynecological cancers included in our study.

More than half of the trials were phase II trials (110; 51.89%), followed by phase I (53; 25.00%), and phase III (32; 15.09%); the rest of them were phase I/II, phase II/III, phase III/IV and three reported not applicable (N/A). The status of recruiting was mainly completed (80; 37.74%), recruiting (59; 27.83%), and active, not recruiting (25; 11.79%). There were 26 (12.26%) terminated or withdrawn clinical trials due to various reasons such as low accrual (reported in 8 clinical trials), lack of approval by the ethics committee, sponsor decision to withdraw funding, principal investigator departure from institution or due to toxicity. Funding was public in 101 clinical trials (47.64%), private in 66 (31.13%), private, non-profit in 40 (18.87%), and the remaining (5; 2.36%) were mixed, unclear or not provided. Among the most frequent sponsors were: The National Cancer Institute (31) (45; 21.23%), universities or university hospitals (36; 16.98%) and the Gyne-

Table I. *Characteristics of clinical trials on pharmacological therapies for rare gynecological cancers.*

CLINICAL TRIAL CHARACTERISTIC	TYPE	NUMBER (%)
Status	Completed	80 (37.74)
	Recruiting	59 (27.83)
	Active, not recruiting	25 (11.79)
	Terminated or withdrawn	26 (12.26)
	Other (not yet recruiting, ongoing, suspended, unknown)	22 (10.38)
Phase	I	53 (25.00)
	I/II	11 (5.19)
	II	110 (51.89)
	III	32 (15.09)
	Other (II/III/IV/IV, not applicable	6 (2.83)
Funding	Public Private Private, non-profit Other (mixed, unclear, not provided)	101 (47.64) 66 (31.13) 40 (18.87) 5 (2.36)
Primary outcome measure	Efficacy Safety Both efficacy and safety Not provided	108 (50.94) 41 (19.34) 47 (22.17) 16 (7.55)
Therapy	Chemotherapy Hormonal therapy Targeted therapy Mixed Other	89 (41.98) 6 (2.83) 64 (30.19) 49 (23.11) 4 (1.89)

cologic Oncology Group (GOG foundation) (32) (25; 11.79%). The trials were mainly conducted in the USA: 142 or 66.98% of the trials, followed by Canada: 25 or 11.79%. One of the trials was carried out in Mexico. Study locations in Europe were distinctively fewer and placed mostly in the United Kingdom and France (both 15; 7.08%), followed by Italy (14), Germany (11), and Austria (6). Most of the clinical trials were international and multicenter, being carried out in multiple different countries.

Related to the type of cancer, 90 (42.45%) clinical trials including only patients with rare gynecological cancers were carried out, 67 (31.60%) clinical trials including patients with gynecological cancers encompassing at least one rare type, and 55 (25.94%) clinical trials including patients with various types of cancers, among them rare gynecological cancers. A vast heterogeneity was noted on the subtype of rare gynecological cancers included in clinical trials, comprising almost all sites, morphology, and types of malignancy. Some of the most prevalent were adenocarcinomas of the cervix, ovary, fallopian tube, and vulva-vagina, ovarian and uterine germ cell tumors, leiomyosarcomas, uterine carcinosarcomas, and uterine adenosarcomas.

We identified one basket trial, a multi-center phase II trial of nivolumab and ipilumab as dual anti-PD-1 and anti-CTLA-4 blockade in rare tumors (33).

Primary endpoints (outcome measures) of the clinical trials related largely to efficacy (50.94%), safety (19.34%) or both efficacy and safety (22.17%). Among the efficacy endpoints were: progression free survival (PFS), overall survival, objective response rate (ORR), and event-free survival (EFS). Safety endpoints were: frequency and severity of adverse events, dose-limiting toxicities (DLT), maximum tolerated dose (MDT).

PHARMACOLOGICAL THERAPIES INVESTIGATED IN THE INCLUDED CLINICAL TRIALS

The most common type of therapy investigated in clinical trials for rare gynecological cancers was chemotherapy (89; 41.98%), followed by targeted therapy (64; 30.19%), and mixed therapies (49; 23.11%), generally a combination of chemo-

therapy and targeted therapy. Hormonal therapy was rarely investigated (6; 2.83%), similarly to other therapies (4; 1.89%) such as propranolol, radiation modifier triapine and VCN-01 virus.

Table II and **table III** provide a complete overview of the therapies that were investigated in clinical trials on rare gynecological cancers (RGC) which were included in this review, classified by the type of therapy and group of drugs.

TRENDS OF CLINICAL TRIALS ON PHARMACOLOGICAL THERAPIES FOR RARE GYNECOLOGICAL CANCERS OVER TIME

The number of clinical trials investigating therapies for rare gynecological cancers (RGC) has steadily increased over the years, reaching 79 clinical trials initiated in the period from 2017 to 2022. **Figure 2** shows the number of clinical trials for these malignancies stratified by the type of therapy over the years. Moreover, the most evident finding is the increment in trials involving targeted therapies. Indeed, 35 new clinical trials on targeted therapies started in the last five years compared to just 26 from 2000 to 2016. Furthermore, during the last five years (2017-2022) there has been an increase in clinical trials investigating a combination of therapies (targeted therapies plus chemotherapy) and a decrease in clinical trials focused on chemotherapeutic agents only.

ANALYSIS OF COMPLETED CLINICAL TRIALS

A separate analysis was performed for the 80 completed clinical trials which were eligible for inclusion in this systematic review. The average length for these clinical trials was 59.77 months, median 53 months (SD 35.322). Indeed, the shortest trial lasted 9 months (34), investigating sunitinib in treating patients with recurrent or persistent leiomyosarcoma of the uterus, while the longest period was 17 years and 11 months (35), investigating combination chemotherapy plus peripheral stem cell transplantation in relapsed germ cell cancer.

Overall, 54 different drugs or treatments were included in the completed clinical trials. The type of therapy for rare gynecological cancers in these trials was mostly chemotherapy (43;

Table II. *Classification of chemotherapy and hormonal therapies in clinical trials on RGC.*

TYPE OF THERAPY/GROUP OF DRUGS	DRUGS, TREATMENTS
Chemotherapy	
Alkylating agents	
Nitrogen mustards	busulfan, melphalan
Platinum based	cisplatin, carboplatin, oxaliplatin, nedaplatin
Oxazaphosphorines	cyclophosphamide, ifosfamide, palifosfamide
Tetrazines	temozolomide
-	trabectedin, lurbinectedin
Purine analogs	dacarbazine
Antimetabolites	
Purine antagonists	fludarabine
Pyrimidine antagonists	5-fluorouracil, capecitabine, gemcitabine
Antifolates	pemetrexed
Mitotic spindle poisons	
Vinca alkaloids	vinorelbine
Taxans	paclitaxel, nab-paclitaxel, docetaxel
Microtubule inhibitors	ixabepilone, eribulin
Others	
Antibiotics	bleomycin, mitomycin C
Proteasome inhibitors	bortezomib
Topoisomerase I inhibitors	irinotecan, topotecan
Topoisomerase II inhibitors	etoposide, doxorubicin
Hormonal therapy	
Estrogen receptor antagonists	tamoxifen, fulvestrant
Progestin	levonorgestrel
Aromatase inhibitors	letrozole
Somatostatin analog therapies	177Lu-DOTATOC (177Lu-octreotate/octreotide)

Table III. *Classification of targeted therapies in clinical trials on RGC.*

TYPE OF THERAPY / GROUP OF DRUGS	DRUGS, TREATMENTS
Targeted therapies	
Overgrowth related targeted therapies (apoptosis induction and proliferative signaling)	
HER2 inhibitors	trastuzumab
mTOR inhibitors	everolimus, temsirolimus
PARP inhibitors	olaparib, rucaparib, niraparib, veliparib
MEK inhibitors	MEK162 or binimetinib, selumetinib, trametinib
MEK/RAF inhibitors	VS-6766
AKT inhibitors	ipatasertib
AKT/ERK Inhibitors	ONC201
ATR kinase inhibitors	AZD6738 or ceralasertib
Glutaminase inhibitors	IPN60090
BMI1 inhibitors	unesbulin
CDK4/6 inhibitors	palbociclib, ribociclib
CDK9 inhibitors	alvocidib
G2 checkpoint kinase (WEE1) inhibitors	ZN-c3
IDO1 inhibitor	epacadostat
FRα-binding antibody	mirvetuximab, STRO-002
HMT Inhibitor, EZH2-Inhibitor	tazemetostat
Gamma-secretase inhibitors	RO4929097
PDGFR-α inhibitor	olaratumab
Folate receptor targeted therapies	Folic-acid functionalized C'Dot-Drug-Conjugate (FA-CDC) ELU001
Angiogenesis related targeted therapies	
VEGF inhibitors	bevacizumab, sunitinib, cediranib
EGFR inhibitor	nimotuzumab, panitumumab, cetuximab
Tyrosine kinase inhibitors	imatinib, nintedanib, dasatinib, cabozantinib, tivozanib, brivanib, lenvatinib, vadalanib, pazopanib, anlotinib
Aurora A kinase inhibitors	alisertib
FAK inhibitors	defactinib
Immunotherapy	
Immune checkpoint inhibitors	
Inhibitor of CTLA-4	ipilimumab, tremelimumab, XmAb®22841 or bavunalimab
Inhibitor of PD-1	nivolumab, pembrolizumab, dostarlimab, PF-06801591 or sasanlimab
Inhibitors of both CTLA-4 and PD-1	XmAb20717 or vudalimab, lorigerlimab
Inhibitor of PD-L1	durvalumab, atezolizumab, avelumab
Inhibitor of TIGIT	etigilimab
Chimeric (human-mouse) monoclonal antibody	dinutuximab
Murine monoclonal antibody	oregovomab
Claudin 6-targeted half-life extended bispecific T-cell engager (HLE BITE®)	AMG794
CD47 blocker	TTI-622
Biological	Recombinant interleukin-12, GEN-1 IL 12
Tumor vaccines	pNGVL3-hICD vaccine pUMVC3-hIGFBP-2 multi-epitope plasmid DNA vaccine Attenuated Live Listeria Encoding HPV 16 E7 Vaccine ADXS11-001 DC-006 vaccine Personalized vaccine peptides
CAR T-cell therapy	huCART-meso Cells CAR.B7-H3 LCAR-M23 cells

HER2: human epidermal growth factor receptor 2; mTOR: mammalian target of rapamycin; PARP: poly ADP-ribose polymerases; MEK: mitogen-activated protein kinase; CDK: cyclin dependent kinases; FRα: Folate receptor alpha; HMT: Histone Methyltransferase; PDGFR-α: platelet-derived growth factor receptor alpha; VEGF: Vascular endothelial growth factor; EGFR: epidermal growth factor receptor; FAK: focal adhesion kinase; CTLA-4: cytotoxic T-lymphocyte associated protein 4; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; TIGIT: T cell immunoglobulin and ITIM domain; CAR: Chimeric antigen receptor.

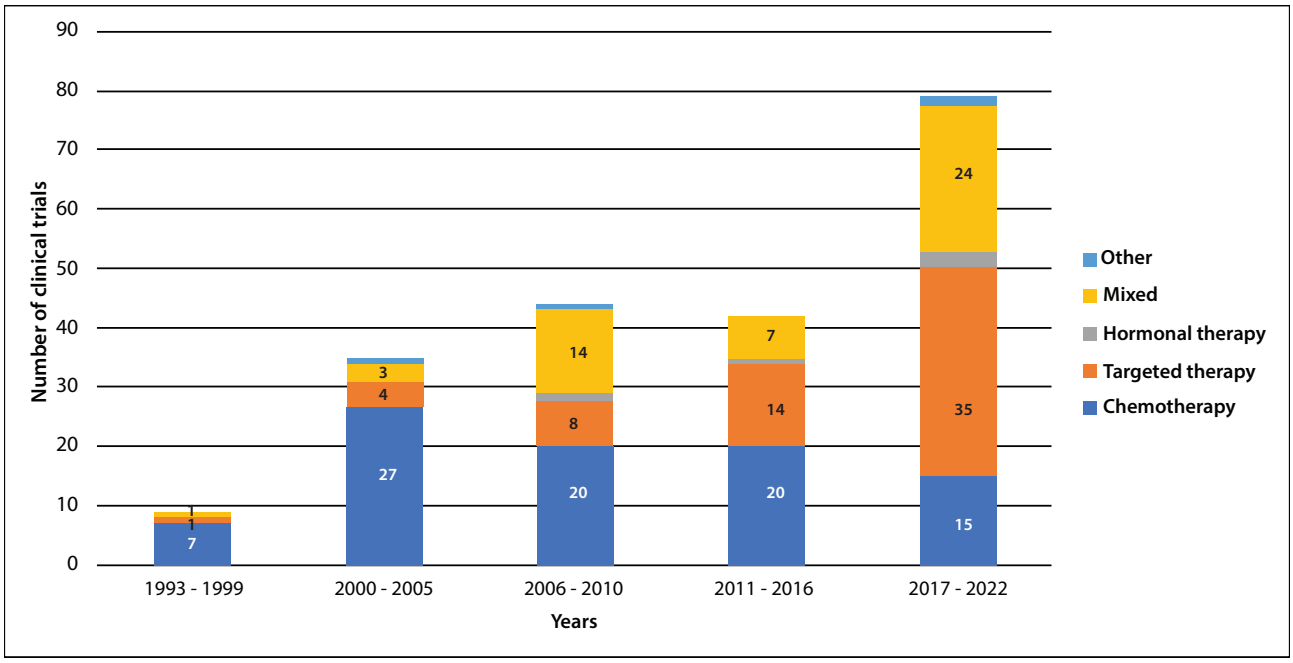

Figure 2. *Number of clinical trials on rare gynecological cancers and type of therapy over the years.*

53.75%), targeted therapy (19; 23.75%) and a combination of therapies (16; 20%). Out of 80 completed trials there was a predominance of phase II (47), phase I (20) and less often phase III (9). More than half (43; 53.75%) had public funding. The average number of patients enrolled in completed phase I clinical trials was 36.68 (ranging from a minimum of 11 to a maximum of 90 patients), for phase II clinical trials 131.35 (range 10-1873), and for phase III this figure was 304.89 (range 28-1520).

Regarding the study design, allocation was not applicable (49, 61.25%), non-randomized (10; 4.72%) and randomized (10; 4.72%), while for the remaining trials the information was not provided. Intervention model was mostly single group assignment (53; 66.25%), parallel assignment (8; 3.77%) or not provided (15; 7.08%). Masking was double (participant and investigator) in just two clinical trials, being the majority of clinical trials open label (69; 86.25%).

All completed trials except one (36), had a calculated Jadad score from 0 to two, indicating low-quality trials. Only 28 (35.00%) of the completed trials had posted results in the searched databases, and 30 (37.50%) had publications, either in databases or identified in Medline with the National Clinical Trial (NCT) number. Thirty-six (45.00%) completed clinical trials had neither posted results, nor publications.

DISCUSSION

This rapid systematic review provides valuable insight on the landscape and characteristics of clinical trials that investigate pharmacological therapies for patients with rare gynecological cancers. Just 42.45% of the 212 clinical trials were specific only for rare types of gynecological cancers. This implies that treatments for this group of cancers are more often studied together with other types of tumors. Phase II clinical trials predominated (51.89%), being more than all other phases together. We identified only one basket trial in our study. Basket trials enroll patients with the same genetic driver mutations, regardless of the tissue or organ of origin, including all types of cancer, both rare and common ones (37).

A considerable number of clinical trials for these rare malignancies (26; 12.26%) was withdrawn or terminated for various reasons, where the most common were related to slow accrual of patients, sponsor decisions, and limited funding. In the present review, funding was public in 47.64% of the trials. Despite hurdles concerning design and implementation, there is a growing need for first-in-human clinical trials for patients with rare gynecological cancers. These are imperative in the era of precision medicine to investigate appropriate novel treatments.

Closer cooperation between public and private institutions, and patients' organizations seems the best approach (38).

Our review revealed that overall, the majority of clinical trials included predominantly chemotherapy (41.98%), followed by targeted therapy (30.19%) and a combination of therapies (23.11%). In line with this finding, in a recent review on clinical trials for drug development in rare diseases, the authors found out that a small number of rare diseases (mostly cancer-related) contributed to the majority of trials and investigated drugs (39), hence, chemotherapeutic drugs were the most abundant in the top 20 tested drugs. In contrast, a study by Chen *et al.* on therapies for prostate cancer in China found that clinical trials were focused mainly on hormonal therapy (41.5%), chemotherapy (31.3%) and immunotherapy (20.7%) (40). This may be explained by the different types of treatment options due to different pathogenesis for these distinct cancers, which is reflected in the different profile of investigated therapies within clinical trials.

Not surprisingly, an evident increase was observed over the years in the total number of clinical trials investigating therapies for rare gynecologic cancers, particularly of those including targeted therapies such as immunotherapy (immune checkpoint inhibitors, tumor vaccines, CAR-T cells), overgrowth-related and angiogenesis-related targeted therapies. Indeed, 54 clinical trials investigating chemotherapy for these malignancies were initiated from 1993 to 2010, compared to 35 in the period from 2011 to 2022. Quite the opposite was observed for targeted therapy; 13 clinical trials from 1993 to 2010, compared to 49 that were initiated in the period from 2011 to 2022. This trend follows the same direction as in treatment regimens of other types of cancer, explained by the introduction of novel therapies with new mechanisms of actions. According to a report published by IQVIA, a paradigm shift in oncology drug expenditure from chemotherapy and hormonal therapy to targeted approaches has occurred over the past 25 years (41).

The heterogeneity of the subtype of rare gynecological cancer does make patient recruitment more challenging. The fact that these rare gynecological cancers can affect girls, adolescents and women of childbearing age is an added burden when planning these clinical trials and seeking ethics approval (42).

There was only little variation in the design of completed clinical trials, where most were open-label (no masking) with single group assignment and allocation was not applicable as they were single-arm trials. Only one completed clinical trial had a calculated Jadad score higher than 2 (Jadad score =3) which indicates higher quality. This phase III clinical trial of carboplatin and paclitaxel with or without bevacizumab in women with stage III or IV epithelial ovarian, primary peritoneal or Fallopian tube cancer was randomized, double blind and included a description of withdrawals and dropouts. (36). Results were unpublished in 65% of the completed clinical trials and 45% of them had neither publications, nor had posted any results. These findings highlight the need for higher-quality clinical trials and better reporting of data from the current ones.

LIMITATIONS OF THE STUDY

We did not include trials that investigated radiotherapy, surgery, or other procedures, as this particular review was focused on clinical trials comprising at least one pharmacological therapy. These could be studied in future systematic reviews to further shed light on existing literature. Our study may underestimate the number of basket trials, as they include many different types of cancer which exhibit the same biomarker or mutation, without specifying the site, morphology or histologic diagnosis. Furthermore, the majority of clinical trials lacked published results and/or publications, making it difficult to extract such information.

Clinical trials in rare gynecological cancers are a main research priority. "Smarter" and higher quality clinical trials are needed with the involvement of multiple centers in different countries. Patient engagement through advocacy groups is key in order to enhance education and awareness on current research. Examples include the European Network of Gynecological Cancer Advocacy Groups (ENGAGe) (43). More awareness about the importance of biobanking, particularly in the case of rare gynecological cancers, will hopefully increase patient participation, and thus lead to the design of better multicenter clinical trials. Establishing international networks focusing on rare gynecological research, from basic research to cure, such as GYNOCARE (44) needs to continue to be encouraged in order to reach out to the

key stakeholders. This will bring together experts in basic science research, pathology, oncology, surgery, gynecology, pharmacy, and other specialties together with lawyers, ethicists and data protection officers in order to help bridge the gap with pharmaceutical companies and industry, and lead to effective well-designed clinical trials which will start to address the lacunae in our current knowledge of how to best manage patients with rare gynecological cancers.

CONCLUSIONS

This systematic review gives a snapshot of clinical trials on pharmacological therapies for rare gynecologic cancers and their characteristics.

The paucity of high-quality trials limits evidence-based decisions in clinical care, therefore it is essential to design and implement novel trials with good quality and better reporting of results.

COMPLIANCE WITH ETHICAL STANDARDS

Fundings

This paper is based upon work from COST Action CA18117 – European network for Gynecological Rare Cancer research: From Concept to Cure (GYNOCARE), supported by COST (European Co-operation in Science and Technology). COST (European Cooperation in Science and Technology) is a funding agency for research and innovation networks. COST Actions help connect research initiatives across Europe and beyond to enable scientists to grow their ideas by sharing them with their peers. This boosts their research, career, and innovation (www.cost.eu). KH, NC, and AC are Action management committee members, and JA is the chairperson of this Action.

Conflicts of interests

The Authors have declared no conflict of interests.

Availability of data and materials

The data presented in this study are available in the **Supplementary Material 1** and Annex A. Further data is available on request from the Corresponding Author.

Code availability

N/A.

Authors' contributions

KH and JCA: conceptualization; KH: writing; KH, NC, SD, AC, MK, AL and JCA: writing-review and editing; JCA: funding acquisition. All Authors have read and agreed to the published version of the manuscript.

Ethical approval

Human studies and subjects

Since this study involved the review of exisiting published research, no new patients or study participants were recruited. Hence no ethical approval was needed.

Animal studies

Since this study involved the review of exisiting published research, no new animal studies were carried out. Hence no ethical approval was needed.

Publication ethics

Plagiarism

This is a review article and all original studies are cited as appropriate.

Data falsification and fabrication

N/A.

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APPENDIX 1

The complete list of search terms for each of the databases

1.1 Search terms in www.clinicaltrials.gov

gynecological tumors, rare
rare gynecological cancers, neuroendocrine
malignant female reproductive system neoplasm, rare
gynecological tumors, neuroendocrine
gynecological cancer, vaginal, vulvar
uterine adenosarcoma
rare gynecological cancer, ovarian cancer
ovarian clear cell carcinoma
germ cell tumors, gynecologic
ovarian sertoli-leydig cell tumor
ovarian germ cell tumors, neoplasm, cancer, malignancy
dysgerminoma
PARP-inhibitors, CD-4 inhibitors, MEK inhibitors, anti HER2

1.2 Search terms in WHO ICTRP https://www.who.int/clinical-trials-registry-platform

rare gynecological cancer
rare gynaecological cancer
rare gynecologic cancer
"gynecological cancer" and rare
rare diseases and orphan drugs "gynecological cancer"
"epithelial ovarian cancer" rare diseases and orphan drugs
low grade serous carcinoma
leiomyosarcoma
ovarian cancer, epithelial
vulvar cancer
vaginal cancer
uterine cervix cancer