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TRAIL receptors as prognostic markers and survival predictors in ovarian cancer: A systematic review of clinical studies and meta-analysis

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Summary

Introduction: TRAIL cytokine (TNF-Related Apoptosis-Inducing Ligand) interacts with five receptors, four of which are expressed at the plasma membrane (DR4, DR5, DcR1, DcR2), and the fifth is a soluble osteoprotegerin receptor (OPG). Only the death receptors DR4 and DR5 contain the cytoplasmic death domain (DD), which is involved in triggering the apoptotic cascade. These receptors are found in tumor cells of various types, including ovarian cancer cells. **Purpose:** The aim of this article is to describe in a systematic review the presence of death receptors in cancer cells of patients and to discuss the clinical implications of this approach on various signs and clinical mechanisms of cancer. **Method:** The systematic review was performed on June 1, 2022, using PubMed Central - PMC, SCOPUS (Elsevier), Web of Science, Cochrane Library, and Biblioteca Virtual em Saúde - BVS (BIREME). The data were summarized in tables and critically analyzed. After the database search, five relevant studies were identified for review. **Results:** Analysis of these studies revealed evidence of increased survival in patients with ovarian cancer who detected these receptors in cancer tissue. In addition, we seek to understand the biological mechanisms involved in the resistance of cancer cells to TRAIL-induced apoptosis.

Keywords: Ovarian cancer, Apoptosis-Inducing, TRAIL, DR4, DR5, Caspase.

Resumen

Receptores TRAIL como marcador de pronóstico y predictores de la supervivencia en el cáncer de ovario: una revisión sistemática de estudios clínicos y metanálisis

Introducción: La citocina TRAIL (Ligando inductor de apoptosis relacionado con TNF) interactúa con cinco receptores, cuatro de los cuales se expresan en la membrana plasmática (DR4, DR5, DcR1, DcR2), y el quinto es un receptor de osteoprotegerina soluble (OPG). Solo los receptores de muerte DR4 y DR5 contienen el dominio de muerte citoplasmático (DD), que está involucrado en el desencadenamiento de la cascada apoptótica. Estos receptores se encuentran en células tumorales de varios tipos, incluidas las células de cáncer de ovario. **Propósito:** El objetivo de este artículo es describir en una revisión sistemática la presencia de receptores de muerte en células cancerosas de pacientes y discutir las implicaciones clínicas de este enfoque en varios signos y mecanismos clínicos del cáncer. **Método:** La revisión sistemática se realizó el 1 de junio de 2022, utilizando PubMed Central - PMC, SCOPUS (Elsevier), Web of Science, Cochrane Library y Biblioteca Virtual em Saúde - BVS (BIREME). Los datos se resumieron en tablas y se analizaron críticamente. Después de la búsqueda en la base de datos, se identificaron 5 estudios relevantes para su revisión. **Resultados:** El análisis de estos estudios reveló evidencia de una mayor supervivencia en pacientes con cáncer de ovario en quienes se detectaron estos receptores en el tejido canceroso. Además, buscamos comprender los mecanismos biológicos involucrados en la resistencia de las células cancerosas a la apoptosis inducida por TRAIL.

Palabras clave: Cáncer de ovario, Inductor de apoptosis, TRAIL, DR4, DR5, Caspasa.

Resumo

Receptores TRAIL como marcadores de prognóstico e preditores da sobrevivência no câncer de ovário: uma revisão sistemática de estudos clínicos e metanálises

Introdução: A citocina TRAIL (TNF-*Related Apoptosis-Inducing Ligand*) interage com cinco receptores, quatro dos quais são expressos na membrana plasmática (DR4, DR5, DcR1, DcR2) e o quinto é um receptor solúvel de osteoprotegerina (OPG). Apenas os receptores de morte DR4 e DR5 contêm o domínio citoplasmático de

morte (DD), que está envolvido no desencadeamento da cascata apoptótica. Esses receptores são encontrados em células tumorais de vários tipos, incluindo células de câncer de ovário. **Propósito:** O objetivo deste artigo é descrever em uma revisão sistemática, a presença de receptores de morte em células cancerígenas de pacientes e discutir as implicações clínicas desta abordagem em vários sinais e mecanismos clínicos do câncer. **Método:** A revisão sistemática foi realizada em 1º de junho de 2022, utilizando PubMed Central - PMC, SCOPUS (Elsevier), *Web of Science*, *Cochrane Library* e Biblioteca Virtual em Saúde - BVS (BIREME). Os dados foram resumidos em tabelas e analisados criticamente. Após a busca nos bancos de dados, cinco estudos relevantes foram identificados para revisão. **Resultados:** A análise desses estudos revelou evidências de aumento da sobrevida em pacientes com câncer de ovário nos quais esses receptores foram detectados no tecido canceroso. Além disso, buscamos entender os mecanismos biológicos envolvidos na resistência das células cancerígenas à apoptose induzida por TRAIL.

Palavras chaves: Câncer de ovário, Indutor de apoptoses, TRAIL, DR4, DR5, Caspase.

Introduction

Despite remarkable progress in understanding the biology of cancer and the development of new diagnostic and therapeutic strategies, cancer remains one of the leading causes of death. Worldwide, 225,500 new cases of ovarian cancer are diagnosed each year, and 140,200 people die from this cancer [1, 2]. Although ovarian cancer was considered a single entity, it can be divided into different histological subtypes with different identifiable risk factors, cells of origin, molecular compositions, clinical features, and treatments [3].

Effective screening strategies for early detection of ovarian cancer do not exist, but individuals at high risk for developing ovarian cancer, such as those with germline mutations in BRCA1 or BRCA2 or other genes associated with high risk for developing ovarian cancer, can be identified [3, 4]. The discovery of this unique feature among members of the TNF superfamily has laid the foundation for testing the clinical potential of TRAIL-R targeted therapies in cancer clinics [5]. However, the efficacy of TRAIL-based cancer therapies has yet to be demonstrated, as most cancer cells are TRAIL-resistant or develop resistance after multiple treatments [6, 7].

TRAIL is a multifunctional cytokine produced and secreted by most normal tissue cells. It acts in the process of cellular apoptosis, mainly in tumor cells [8]. Targeting the

apoptosis death receptor pathway represents a promising approach for the development of new cancer therapies, as cell surface death receptors are directly linked to the apoptotic machinery, preferentially in cancer cells, while sparing non-malignant cells [9].

Therefore, in this study, we aim to summarize the currently available evidence on whether TRAIL receptors serve as prognostic markers and predict survival in ovarian cancer through a systematic review and meta-analysis, and to present the extent of clinical relevance of these genes.

This systematic review summarizes the mechanisms of TRAIL-induced apoptosis via extrinsic and intrinsic apoptotic signaling pathways. It also reviews the mechanisms of cancer cell resistance to TRAIL-induced apoptosis in ovarian cancer.

Methods

The presence of death receptors significantly correlated with cancer patient survival in experimental models was assessed by a systematic review and meta-analysis performed according to the principles described in the Cochrane Handbook [10]. The steps related to the search and selection of articles and the extraction, analysis, and interpretation of data of interest, were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11]. To identify studies of interest, we applied the **PEOS** strategy to the articles from the electronic search as follows: "population," patients with ovarian cancer; "exposure," presence or absence of death receptors; "outcomes," survival; "study design," clinical, observational, and epidemiologic hospital surveillance studies [12].

Search strategy

First, a systematic search was performed in five databases (PubMed Central, SCOPUS, Web of Science, Cochrane Library, and *Biblioteca Virtual em Saúde*) using the Medical Subject Heading (MeSH) term "TNFRSF10A" in conjunction with at least two of each of the following descriptors: "track R1," "TNFRSF10A," "death receptors," "cancer," "survival," "mortality." For the search, these descriptors were combined with the connector "AND" between them, as in the following example: "cancer" AND "track R1". The search was conducted through June 1, 2022, and was limited to studies written in English, with no date limit. A search for gray literature in theses and dissertations was also conducted through the Thesis and Dissertation Catalog of the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES) and the Digital Library of

Theses and Dissertations of the Universidade Federal de Minas Gerais (UFMG) and the Universidade de São Paulo (USP). In addition, the reference lists of all included articles and relevant narrative reviews in the field were reviewed for relevant articles.

Study selection

In addition to the electronic search, studies identified as review articles, notes, correspondence, editorials, and letters were excluded. Other studies were excluded based on the following criteria: (i) in silico and in vitro studies; (ii) studies in which the death receptor was not identified; (iii) studies in which ovarian cancer was not identified; (iv) studies in which none of the main outcomes (survival) were examined. In cases where the article met the inclusion criteria but the full text was not available, the corresponding author was contacted three times by e-mail (14 days apart), and articles were included if received by the last contact. The details of the search strategy for each database are provided in the supplementary files.

In the first phase of selection, two independent researchers (J.C.M.B. and P.C.) searched the databases. Duplicate records were deleted using Rayyan (a web and mobile app for systematic reviews) [13] and the titles and abstracts of the selected studies were reviewed according to PEOS eligibility criteria. Studies that examined cancer patient survival in the presence of death receptors were selected and subsequently assessed by full-text review.

Any disagreements were resolved through discussion with the other investigator (L.M.S), and the kappa coefficient (with a 95% confidence interval) was used to analyze the level of agreement between assessors [14].

Data extraction and statistical analysis

After a complete analytical reading, all data of interest were summarized in a table for further critical analysis and interpretation. Ovarian cancer patient mortality rates with death were analyzed by meta-analysis using RStudio® software, using the meta package and metaprop command. Heterogeneity of the primary data was determined using the I-squared index (I^2), were $I^2 > 50\%$ was considered to be substantial heterogeneity [15]. To calculate the frequency of death receptors between ovarian cancer patients, either the fixed effects model low heterogeneity or the random effects model with high heterogeneity was used to pool the data [16]. For all methods, the significance level was 5%.

Results

Study inclusion

Bibliographic searches of the databases yielded a review of 1,527 articles, including 82 from PubMed/MEDLINE, 756 from Scopus, 545 from BVS, 55 from Web of Science, and 89 from Cochrane. No additional study was identified in the gray literature search or by screening the reference list of included studies, Figure 1.

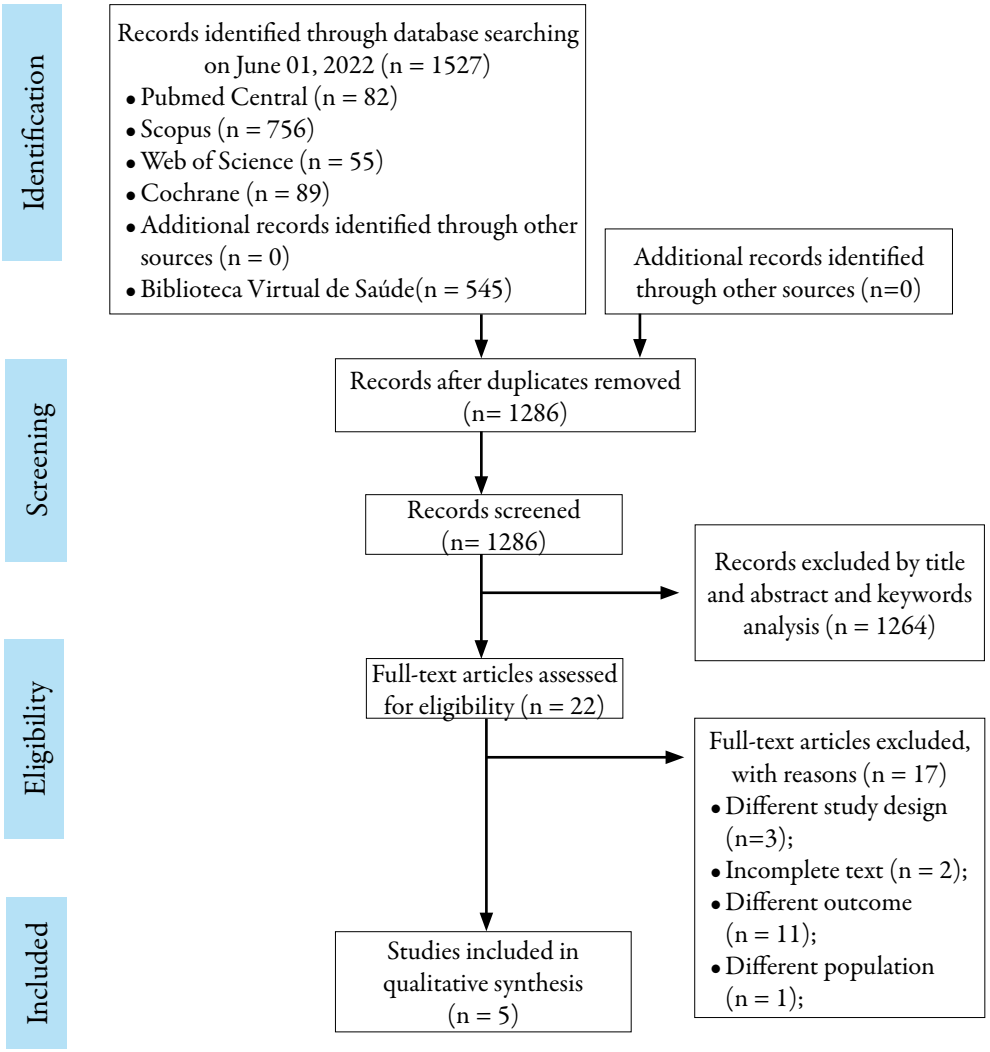

Figure 1. Flowchart of the selected articles for systematic review according to PRISMA criteria [10].

After exclusion of duplicate studies, 1,286 records were screened by title and abstract, leaving 22 studies that met the inclusion criteria. Therefore, 22 full-text articles were screened for eligibility and 17 were excluded for the following reasons: Different study design (n=2); or incomplete text (n=2); different outcomes (n=11); and different population (n=1) (Figure 1). Finally, 5 studies were selected for qualitative analysis [17-21]. Of these articles, 2 were also included in the quantitative studies and used to perform the meta-analysis [17, 19], Figure 2. The degree of agreement between the two researchers was found to be substantial, as indicated by the kappa coefficient of 0.7963.

Characteristics of the studies

According to Table 1, the studies included 809 patients with ovarian cancer.

Table 1. Main characteristics of included studies

OCP (n)	Method	Receptors/ Gene	Outcomes	Ref.
68	Immunohistochemical analysis	55 OCP with DR4 49 OCP with DR 5 54 OCP with TRAIL	• Favorable overall survival for low grade (grade 1 versus grade 2-3; *p-value* 0.047) and low stage (FIGO I/II versus III/IV; *p-value* 0.0008) in OCP with TRAIL. • DR4 and DR5 expression levels in OCP were predictors for survival benefit.	[17]
359	Immunohistochemical analysis	245 OCP with DR4 330 OCP with DR 5 49 OCP with TRAIL	• TRAIL was associated with low tumor grade and better progression-free survival (HR 0.63, *p-value* 0.018).	[19]
120	QRT-PCR	Mean TRAIL gene expression	• OCP-10-fold higher mean TRAIL expression than normal ovarian epithelial samples (*p-value* <0.001); • OCP with high TRAIL expression prolonged survival 2.2-fold higher (*p-value* 0.03); • TRAIL expression was 2.3-fold higher in cancers from women who lived >5 years than in cancers from those who died in <1 year (*p-value* 0.03);	[20]

(*Continued*)

OCP (n)	Method	Receptors/ Gene	Outcomes	Ref.
120	QRT-PCR	Mean TRAIL gene expression	• Advanced-stage (III/IV) cases, relative TRAIL expression was 2.2-fold higher (1.6 versus 0.9) in cancers of women who lived >5 years than in cancers from those who lived <1 year (*p-value* 0.18); • Association between high TRAIL expression and favorable survival (*p-valu*e 0.14).	[20]
27	qRT-PCR	19 OCP with TRAIL-R3	• No significant associations were observed between the TRAIL-3 expression level in primary ovarian cancer and the cumulative progression-free survival or the overall survival.	[18]
235	Immunohistochemical analysis	------	• DR5 and DcR1 had higher expression levels in grade 2 and 3 tumors compared with the levels in grade 0 tumors (*p-value* 0.01); • Trail and DR4 had lower expression levels in higher grade tumors (*p-valu*e 0.01) • Lower expression levels of Trail were observed for grade 3 tumors; • Grade2 tumors expressed significantly higher levels of Trail and DR4 compared with grade 3 tumors.	[21]

OCP: ovarian cancer patients.

The death receptor was identified by immunohistochemical analysis (427/809; 52.78%), 300 ovarian cancer patients (OCP) with DR4 (300/427; 70.26%), and 379 OCP with DR5 (379/427; 88.75%) by [17, 19]. The OCP with TRAIL (103/427; 24.12%) [17, 19], TRAIL-R3 (19/27; 70.37%) [18] and mean TRAIL gene expression were also quantified [20].

High expression of DR4 and DR5 in OCP were predictors of survival benefit [17]. DR5 and DcR1 had higher expression levels in grade 2 and 3 tumors compared with levels in grade 0 tumors (*p-value* 0.01). TRAIL and DR4 had lower expression levels in higher grade tumors (*p-value* 0.01). Lower expression of TRAIL was observed in grade 3 tumors, and grade2 tumors expressed significantly more TRAIL and DR4 compared with grade 3 tumors [21].

TRAIL was associated with low tumor grade and better progression-free survival (HR 0.63, p=0.018) [19], favorable overall survival in low grade (grade 1 versus grade 2-3; *p-value*) and low stage (FIGO I/II versus III/IV; *p-value* 0.0008) OCP with TRAIL [17]. Association between high TRAIL expression and favorable survival (*p-value* 0.14). Tenfold higher mean TRAIL expression than normal ovarian epithelial samples (*p-value* 0.001) with high TRAIL expression prolonged survival 2.2-fold (*p-value* 0.03). TRAIL expression was 2.3-fold higher in cancers from women who lived more than 5 years than in cancers from women who died in less than1 year (*p-value* 0.03), and in advanced stage cases (III/IV), relative TRAIL expression was 2.2-fold higher in cancers from women who lived more than 5 years than in cancers from women who lived less than 1 year (1.6 versus 0.9, *p-value* 0.18) [20]. In addition, no significant association was found between the TRAIL-3 expression level in primary ovarian cancer and cumulative progression-free survival or overall survival [18].

All five included studies examined the association between patient survival and the presence of death or TRAIL receptors using Kaplan-Meier curves and log-rank tests. They found a significant difference in patient survival (*p-value* of log-rank test<0.05) when DR5, DR4 and Flip, DcR1 and DR5, Flip and DR5, DcR2 and Cyc, TRAIL and DR5, Flip and DcR2 were detected in patients [17, 19, 21]. When TRAIL was detected, the survival rate of patients was significantly increased [19, 20].

DR4, DR5, and TRAIL incidence in patients with ovarian cancer

Two studies [17, 19] with 427 confirmed DR4 and DR5 receptors were combined in this meta-analysis. Consistent with the presence of the death receptor in OCP, the analysis revealed an incidence of DR4 in OCP of 73% (95% CI: 62% to 81%; *p-value* 0.04), DR5 in OCP of 85% (95% CI: 67% to 94%; *p-value* 0.01), and TRAIL in OCP of 44% (95% CI: 8% to 88%; *p-value* 0.01), as shown in Figure 2.

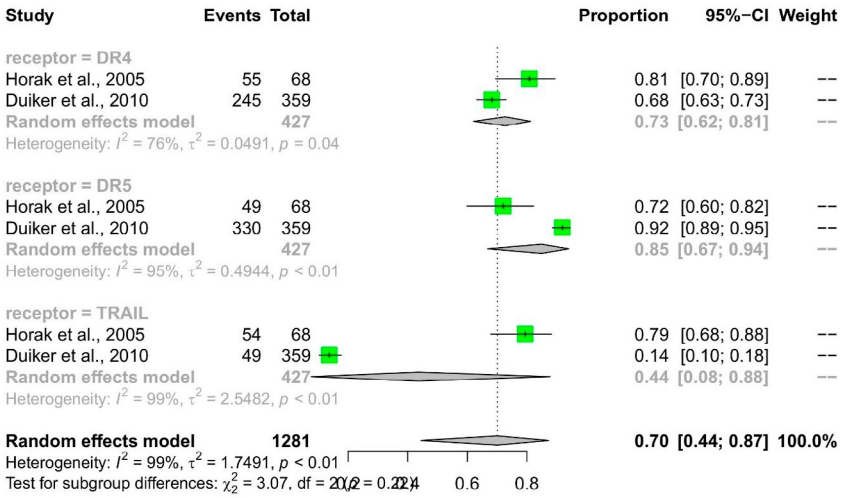

Figure 2. Forest plot of the incidence of death receptors in ovarian cancer. CI, confidence interval; heterogeneity (I^2); heterogeneity's *p-value* (*p*).

Discussion

The most effective therapeutic agents for newly diagnosed ovarian cancer are platinum analogs (either cisplatin or carboplatin) to which taxane (paclitaxel or docetaxel) is added. Recurrence of cancer after initial platinum-based chemotherapy is very common in women with advanced cancer, but the problem with treating cancer in these women is the possible development of platinum resistance [3].

Current therapeutic strategies for the treatment of cancer patients aim to overcome two essential features of cancer, namely excessive proliferation and resistance to apoptosis. Apoptosis is an essential process in several basic physiological processes and is controlled by numerous intracellular and extracellular signals [22].

Endogenous biochemical signaling pathways, which include apoptotic and non-apoptotic signaling pathways, are activated in cancer cells by TRAIL. Alterations in these signaling pathways are major hallmarks of ovarian cancer [23]. TRAIL binds to several receptors, including TRAIL-R1 (DR4), TRAIL-R2 (DR5), TRAIL-R3 (DcR1), TRAIL-R4 (DcR2), and OPG (Figure 3). When TRAIL interacts with DR4 and DR5 receptors containing a conserved death domain motif (DD), formation of the

death-inducing signaling complex (DISC) occurs with recruitment of Fas-associated protein with death domain (FADD). FADD recruits pro-caspase-8 or -10 via its death effector domain (DED), and the activated caspases-8 or -10 then cleave effector caspases-3, -6, and -7 and directly stimulate the activation of a protease cascade via the extrinsic pathway of apoptosis, ultimately leading to cell death [24, 25].

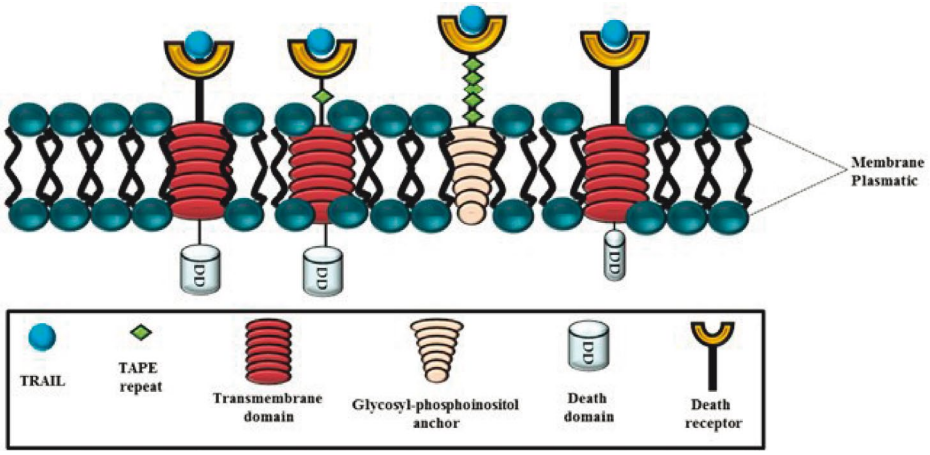

Figure 3. TRAIL-R system. TRAIL Cytokine interacts with death receptors expressed on the plasma membrane (TNFRSF10A/DR4, TNFRSF10B/DR5, TMFRSF10C/DcR1, TNFRSF10D/DcR2). Death receptors DR4 and DR5 contain the cytoplasmic death domain (DD) involved in triggering the apoptotic cascade, and decoy receptors DcR1 and DcR2 inhibit TRAIL-mediated apoptosis.

The caspase cascade can also be activated by the intrinsic pathway of apoptosis, through the formation of a complex called the apoptosome. The apoptosome is formed in the cytosol when cytochrome c is released from mitochondria in response to a cell death stimulus and binds the monomer of apoptotic protease activation factor 1 (APAF-1), promoting the formation of a heptameric APAF-1 complex accompanied by synchronized recruitment of procaspase-9. Activation of apoptosis-initiating caspase-9 also promotes activation of effector caspases [26].

Members of the Bcl-2 family such as Bid, Bax and Bak provide a link between intrinsic and extrinsic apoptosis pathways and control the life or death decision of a cell. Smac/ DIABLO, a proapoptogenic mitochondrial protein, is also released into the cytosol when the TRAIL-caspase-8-tBid-Bax cascade is required to reverse the inhibitory effect of X-linked inhibitor of apoptosis (XIAP). XIAP consists of three BIR domains, BIR1, BIR2 and BIR3, with Smac/ DIABLO interacting with the BIR2 and BIR3 domains and allowing the release of caspase-3 and caspase-9, respectively [27, 28].

In humans, the gene encoding TRAIL is located on chromosome 3q26 and is directly regulated by the p53 protein. However, the tumor suppressor gene p53 is often inactivated in ovarian cancer cells that develop resistance to TRAIL. Resistance to TRAIL can be caused by several mechanisms. For example, inactivation of Bax in mismatch repair (MMR)-deficient tumors may cause resistance to TRAIL because Bax is required for the release of Smac/ DIABLO and consequently exerts an antagonistic effect on the IAP protein family. Increased expression of caspase inhibitors such as XIAP or overexpression of Bcl-2 are mechanisms that mediate resistance to TRAIL-induced apoptosis [27, 29].

TRAIL death receptors can induce pro-inflammatory, invasion- and metastasis-promoting non-apoptotic signaling pathways under certain conditions [25], as shown in Figure 4. Indeed, anti-apoptotic signaling pathways such as NF-kB, MAPKs, p38 and other signaling pathways such as ERK1/2, PI3K/AKT and JAK-STAT repair TRAIL-induced apoptosis [27]. These survival signaling cascades have also been associated with resistance to TRAIL therapy in most primary cancer cells [30]. Akt activation upregulates the level of the c- FLIP protein, which has sequence homology to caspase-8 and -10 but lacks protease activity. Recruitment of FLIP to DISC instead of caspase-8 or -10 results in its inhibition, leading to resistance of TRAIL in ovarian cancer. Silencing of BID suggests that BID is important for TRAIL-induced cell death, and as Akt expression increases, BID transcription is downregulated. Activation of the ERK -signaling pathway leads to upregulation of the anti-apoptotic Mcl-1 protein and thus also contributes to TRAIL-resistance [31, 32].

Nowadays it has been described that TRAIL-R2 can act as a negative regulator of p53. TRAIL-R2 facilitates the degradation of p53 and regulates the stability of p53 protein by interacting with promyelocytic leukemia (PML) protein, which has elucidated an oncogenic role of TRAIL-R2 in tumorigenesis [33].

The tumor microenvironment (TME) plays an important role in modulating TRAIL signaling through cellular compounds (e.g., neutrophils, macrophages, NK cells, cytotoxic T cells, and stromal cells), hypoxia, increased acidity, mechanical stress, glucose availability, and changes in the extracellular matrix (ECM). All factors have a direct effect on tumor cell apoptosis induced by TRAIL [34, 35].

Dynamin-1, a protein involved in clathrin-mediated endocytosis (CME), regulates the endocytosis of TRAIL-DR in several cancer cells, attenuating apoptotic signals and increasing cell survival [36].

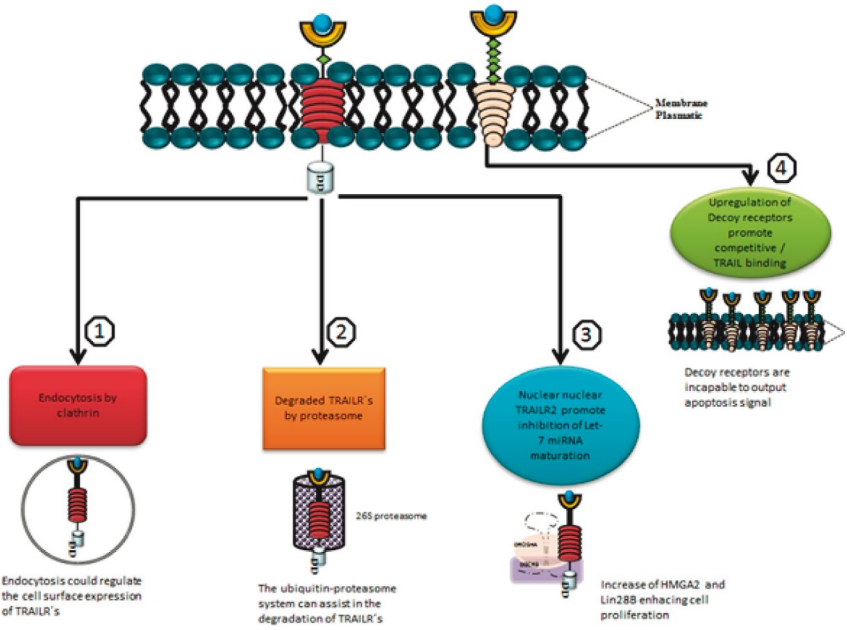

Figure 4. Mechanisms that may play a role in TRAIL-R resistance. 1) Autophagy and endocytosis might be involved in the regulation of TRAIL death receptors DR4 and DR5 [37]. 2) The TRAIL-receptors may be subject to regulation by the UPS (ubiquitin-proteasome system). The E3 ligase c-Cbl has been shown to directly regulate ubiquitination of TRAIL-R after receptor activation. Stimulation with the ligand TRAIL-induced c-Cbl-mediated mono-ubiquitination of TRAIL-R1 and TRAIL-R2, resulting in the degradation of the internalized receptors by the proteasome [38]. 3) TRAIL-R2 may be associated with the process of miRNA maturation when it interacts with the central microprocessor complex Drosha/DGCR8. Through this interaction, TRAIL-R2 inhibits the maturation of miRNA let-7 and consequently increases the levels of let-7 targets Lin28B and HMGA2. In this mechanism, inhibition of let-7 maturation by TRAIL-R2 promotes tumor cell malignancy by upregulating the Lin28B and HMGA2 genes, which increases cell proliferation [39]. 4) TRAIL-R3 effectively acts as a "decoy" receptor when expressed at much higher concentrations or has significantly higher affinity than the two "lethal" receptors (TRAIL-R4 and -R2). In this mechanism, the higher concentration in ovarian cancer could be due to the increased proliferation and apoptosis resistance inherent in this tumor type due to the competitive binding of the ligand at the cell surface [18].

Recently, it was also reported that TRAIL can induce necroptosis, a programmed form of necrosis or inflammatory cell death, by recruiting RIPK1 and RIPK3. When RIPK1 is activated, it recruits and phosphorylates RIPK3, which phosphorylates a mixed lin-

eage kinase domain like pseudokinase (MLKL), resulting in the formation of pores in the cell membrane [23, 29, 35]

As an example of treatments based on TRAIL-resistance, several reports have shown that treatment with proteasome inhibitors can upregulate the expression of TRAIL-R receptors on the cell surface, leading to increased sensitivity to TRAIL-induced apoptosis. The clinically used proteasome inhibitor bortezomib (Velcade, Millennium Pharmaceuticals, Inc., Cambridge, MA, and Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ) has been shown to increase sensitivity to TRAIL by upregulating TRAIL-R2 expression in NSLCC cells [40]. Inhibition of the proteasome triggers TRAIL-R2-dependent apoptosis in cells unable to activate the mitochondrial apoptosis pathway. In response to proteasome inhibition, TRAIL-R2 eventually accumulates in cytosolic complexes containing FADD and RIPK1, which serve to activate caspase-8 [41]. The importance of extrinsic apoptosis triggered by caspase-8 activation has been demonstrated in various scenarios, and RIPK1 is a key component of caspase-8 activating complexes (ripoptosomes) [41].

Similar to other human cancers, ovarian cancer is thought to arise from an accumulation of mutations in genes that regulate cellular proliferation and apoptosis [20]. Characteristic of all cancers is the deregulation of the apoptotic machinery, in which the extrinsic apoptotic pathway is activated by the binding of death receptors from the tumor necrosis factor (TNF) family to their corresponding cell surface receptors [19]. The authors also showed that the majority of ovarian carcinomas in their study of 382 patients expressed at least one death receptor as well as caspase 8 and its anti-apoptotic homolog c- FLIP. TRAIL expression was associated with lower tumor grade and better progression-free survival when all tumors were analyzed. These results suggest that loss of expression of TRAIL confers a survival advantage to tumor cells, possibly because they evade apoptosis induction by para- or autocrine-released TRAIL.

A study using real-time quantitative PCR in 120 epithelial ovarian cancer (11 stages I/II, 109 stages III/IV) and 8 normal ovarian surface epithelial samples found that high expression of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) gene was associated with prolonged survival in advanced ovarian cancer [20]. TRAIL has attracted particular interest because of its apparent tumor cell-specific apoptosis-inducing ability.

Bertsch and coworkers found intracellular localization of the receptors, suggesting that the intracellular TRAIL-R1/DR4 and TRAIL-R2/DR5 may provide a growth advantage or other benefits to tumor cells [39]. Correlation of expression status with clinical parameters revealed the predominant prognostic significance of high expression of

death receptors, with TRAIL-R2 and occasionally TRAIL-R1 in particular identified as negative prognostic markers. The evaluation of their value as prognostic markers for cancer mainly took into account the overall expression of TRAIL-receptors in the tissue and occasionally their presence at the cell surface [39].

Immunohistochemical analyzes of a tissue sample from 235 serous tumors of varying grade and stage to determine if there is differential protein expression for these candidates and Trail's 4 death cell receptors: Dr4, Dr5, DcR1 and DcR2 [21]. This study showed that TRAIL (Tnfsf10, Apo2L) was overexpressed in LMP tumors (low malignant potential) compared to all invasive tumors and was underexpressed in grade 3 tumors TOV (borderline and invasive) compared to grade 1 and 2 tumors TOV and overexpressed in early stages. It was observed that high expression of Dr5 was associated with poorer patient prognosis either when TOV tumors of all grades were included or when only the subset of grade 3 tumors TOV were included, compared to advanced stages when all tumors were included in the analysis [21]. Ouellet and coworkers also observed that high expression of Dr5 was associated with poorer patient prognosis either when TOV tumors of all grades or when only the subset of grade 3 tumors were included TOV [21].

The patient cohort studied by Horak and coworkers included 68 women with epithelial ovarian cancer. TRAIL was expressed by epithelial ovarian cancer cells in 40.4% at different levels. In stromal cells, TRAIL was stained in 43.9% [17]. In both cases, the staining was cytoplasmic. They found statistically significant higher expression of DR5, but not DR4, in the epithelium of ovarian cancer cells, which also had increased expression of TRAIL ($p = 0.041$).

However, there was also statistically significant expression of DR4 and DR5 in ovarian cancer cells ($p = 0.021$). They also investigated the influence of TRAIL and its receptors on the survival of ovarian cancer patients [17].

In a univariate regression analysis, neither epithelial DR4 and DR5 expression nor the levels of TRAIL or FLIPL in the epithelium and/or stroma of ovarian cancer were statistically significant predictors of survival benefit in our study population, but TRAIL showed a survival benefit at the mRNA level in advanced ovarian cancer [17]. They observed a loss of DR4 and/or DR5 expression in a corresponding number of cases, a factor that may contribute to tumor cell tolerance to TRAIL. This loss of DR4 and/or DR5 was significantly more frequent in tumors that did not overexpress FLIPL, suggesting two independent mechanisms of resistance in the TRAIL-induced apoptotic pathway in ovarian cancer. These data demonstrate that in addition to downregulation of DR4/DR5, the sensitivity of TRAIL can also be significantly altered by overexpres-

sion of FLIPL, and that increased stromal TRAIL expression confers a survival advantage for patients with advanced-stage ovarian cancer [17].

The resulting heterogeneity of ovarian cancer and the factors underlying clinical response make it difficult to define prognostic and predictive factors for individualized treatment. The absence of TRAIL-R2/R1 could be a marker for TRAIL resistance.

This meta-analysis has some limitations. The heterogeneity of our meta-analysis was high because of the small number of studies. Nevertheless, these results are consistent with the Kaplan-Meier results, in which the presence of these same death receptors (DR4 and DR5) were the only variables significantly associated with patient survival [17, 19]. Finally, it should be emphasized that the correlation found in the meta-analysis does not imply a causal relationship and that there is always the possibility of residual confounding in the included studies.

Conclusion

Our findings unveil that the presence of DR4, DR5 and TRAIL was predominantly identified in OCP using immunohistochemical analysis and qRT-PCR. Furthermore, we emphasize the crucial role played by elevated levels of DR4 and DR5 expression in OCP, predicting a survival advantage. Notably, in cases where TRAIL was detected, the survival rate of patients was significantly increased. The outcomes of meta-analytic investigations also validate the prevalence of DR4, DR5, and TRAIL in OCP, as well as the correlation between patient survival and the presence of death or TRAIL receptors. This underscores the importance of these signaling pathways as pivotal markers in the context of ovarian cancer. Finally, this study accentuates the necessity for ongoing research aimed at harnessing the potential of TRAIL in modulating cellular responses for enhanced health outcomes.

Compliance with ethical standards

Financial support: None.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Author contributions: All authors contributed to the development, analysis and drafting of this article.

References

1. J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, *et al.*, Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012, *Int. J. Cancer*, **136**, E359–E386 (2015). https://doi.org/10.1002/ijc.29210

2. R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2020, *CA Cancer J. Clin.*, **70**, 7–30 (2020). https://doi.org/10.3322/caac.21590

3. U.A. Matulonis, A.K. Sood, L. Fallowfield, B.E. Howitt, J. Sehouli, B.Y. Karlan, Ovarian cancer, *Nat. Rev. Dis. Prim.*, **2**, 16061 (2016). https://doi.org/10.1038/nrdp.2016.61

4. W.-F. Li, Z. Hu, N.-Y. Rao, C.-G. Song, B. Zhang, M.-Z. Cao, e*t al.*, The prevalence of BRCA1 and BRCA2 germline mutations in high-risk breast cancer patients of Chinese Han nationality: two recurrent mutations were identified, *Breast Cancer Res. Treat.*, **110**, 99–109 (2008). https://doi.org/10.1007/s10549-007-9708-3

5. D. de Miguel, J. Lemke, A. Anel, H. Walczak, L. Martinez-Lostao, Onto better TRAILs for cancer treatment, *Cell Death Differ.*, **23**, 733–747 (2016). https://doi.org/10.1038/cdd.2015.174

6. S.H.M. Wong, W.Y. Kong, C.-M. Fang, H.-S. Loh, L.-H. Chuah, S. Abdullah, *et al.*, The TRAIL to cancer therapy: Hindrances and potential solutions, *Crit. Rev. Oncol. Hematol.*, **143**, 81–94 (2019). https://doi.org/10.1016/j.critrevonc.2019.08.008

7. Y. Huang, X. Yang, T. Xu, Q. Kong, Y. Zhang, Y. Shen, *et al.*, Overcoming resistance to TRAIL-induced apoptosis in solid tumor cells by simultaneously targeting death receptors, c-FLIP and IAPs, *Int. J. Oncol.*, **49**, 153–163 (2016). https://doi.org/10.3892/ijo.2016.3525

8. U. Schaefer, TRAIL: a multifunctional cytokine, *Front. Biosci.*, **12**, 3813 (2007). https://doi.org/10.2741/2354

9. S. Fulda, Safety and tolerability of TRAIL receptor agonists in cancer treatment, *Eur. J. Clin. Pharmacol.*, **71**, 525–527 (2015). https://doi.org/10.1007/s00228-015-1823-1

10. J.P.T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M.J. Page, *et al.* (editors), *Cochrane Handbook for Systematic Reviews of Interventions*, Cochrane, 2021.

11. A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gøtzsche, J.P.A. Ioannidis, *et al.*, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration, *PLoS Med.*, **6**(7), e1000100 (2009). https://doi.org/10.1371/journal.pmed.1000100

12. M.B. Eriksen, T.F. Frandsen, The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review, *J. Med. Libr. Assoc.*, **106**(4), 420–431 (2018). https://doi.org/10.5195/JMLA.2018.345

13. M. Ouzzani, H. Hammady, Z. Fedorowicz, A. Elmagarmid, Rayyan—a web and mobile app for systematic reviews, *Syst. Rev.*, **5**, 210 (2016). https://doi.org/10.1186/s13643-016-0384-4

14. J.R. Landis, G.G. Koch, The measurement of observer agreement for categorical data, *Biometrics*, **33**, 159 (1977). https://doi.org/10.2307/2529310

15. W.G. Lima, J.C.M. Brito, B.G. Cardoso, V.N. Cardoso, M.C. de Paiva, M.E. de Lima, *et al.*, Rate of polymyxin resistance among *Acinetobacter baumannii* recovered from hospitalized patients: a systematic review and meta-analysis, *Eur. J. Clin. Microbiol. Infect. Dis.*, **39**(8), 1427-1438 (2020). https://doi.org/10.1007/s10096-020-03876-x

16. H. Vaez, A. Sahebkar, F. Khademi, Carbapenem-resistant *Klebsiella Pneumoniae* in Iran: a systematic review and meta-Analysis, *J. Chemother.*, **31**, 1–8 (2019). https://doi.org/10.1080/1120009X.2018.1533266

17. P. Horak, D. Pils, M. Roessler, S. Tomek, K. Elandt, R. Zeillinger, *et al.*, Common death receptor 4 (DR4) polymorphisms do not predispose to ovarian cancer, *Gynecol. Oncol.*, **97**, 514–518 (2005). https://doi.org/10.1016/j.ygyno.2005.01.021

18. L.D.C. Braga, A.P. Álvares da Silva-Ramos, P. Traiman, L.M. Silva, A. Lopes da Silva-Filho, TRAIL-R3-related apoptosis: Epigenetic and expression analyses in women with ovarian neoplasia, *Gynecol. Oncol.*, **126**, 268–273 (2012). https://doi.org/10.1016/j.ygyno.2012.04.038

19. E.W. Duiker, A.G.J. van der Zee, P. de Graeff, W. Boersma-van Ek, H. Hollema, G.H. de Bock, *et al.*, The extrinsic apoptosis pathway and its prognostic impact in ovarian câncer, *Gynecol. Oncol.*, **116**, 549–555 (2010). https://doi.org/10.1016/j.ygyno.2009.09.014

20. J.M. Lancaster, R. Sayer, C. Blanchette, B. Calingaert, R. Whitaker, J. Schildkraut, *et al.*, High expression of tumor necrosis factor-related apoptosis-inducing ligand is associated with favorable ovarian cancer survival, *Clin. Cancer Res.*, **9**(2), 762-766 (2003).

21. V. Ouellet, C. Le Page, J. Madore, M.-C. Guyot, V. Barrès, C. Lussier, *et al.*, An apoptotic molecular network identified by microarray: On the TRAIL to new insights in epithelial ovarian cancer, *Cancer*, **110**, 297–308 (2007). https://doi.org/10.1002/cncr.22812

22. T. Griffith, B. James, Tumor necrosis factor-related apoptosis-inducing ligand-induced apoptotic pathways in cancer immunosurveillance: molecular mechanisms and prospects for therapy, *Res. Reports Biochem.*, **5**, 1–10 (2015). https://doi.org/10.2147/RRBC.S59123

23. R. Liang, Y. Yao, G. Wang, E. Yue, G. Yang, X. Qi, *et al.*, Repositioning quinacrine toward treatment of ovarian cancer by rational combination with TRAIL, *Front. Oncol.*, **10**, 1118 (2020). https://doi.org/10.3389/fonc.2020.01118

24. S. Wang, W.S. El-Deiry, TRAIL and apoptosis induction by TNF-family death receptors, *Oncogene*, **22**, 8628–8633 (2003). https://doi.org/10.1038/sj.onc.1207232

25. M. Snajdauf, K. Havlova, J. Vachtenheim, A. Ozaniak, R. Lischke, J. Bartunkova, *et al.*, The TRAIL in the treatment of human cancer: An update on clinical trials, *Front. Mol. Biosci.*, **8**, 628332 (2021). https://doi.org/10.3389/fmolb.2021.628332

26. M.S. D'Arcy, Cell death: a review of the major forms of apoptosis, necrosis and autophagy, *Cell. Biol. Int.*, **43**, 582–592 (2019). https://doi.org/10.1002/cbin.11137

27. C. Falschlehner, C.H. Emmerich, B. Gerlach, H. Walczak, TRAIL signalling: Decisions between life and death, *Int. J. Biochem. Cell. Biol.*, **39**, 1462–1475 (2007). https://doi.org/10.1016/j.biocel.2007.02.007

28. N. Pathoulas, *Investigating TRAIL sensitivity in platinum-resistant ovarian cancer*, College Thesis, The College of Saint Benedict and Saint John's University, St. Joseph, Minnesota, 2019.

29. N.G. Khaider, D. Lane, I. Matte, C. Rancourt, A. Piché, Targeted ovarian cancer treatment: the TRAILs of resistance, *Am. J. Cancer Res.*, **2**, 75–92 (2012).

30. X. Dai, J. Zhang, F. Arfuso, A. Chinnathambi, M. Zayed, S.A. Alharbi, *et al.*, Targeting TNF-related apoptosis-inducing ligand (TRAIL) receptor by natural products as a potential therapeutic approach for cancer therapy, *Exp. Biol. Med.*, **240**, 760–773 (2015). https://doi.org/10.1177/1535370215579167

31. E. Razeghian, W. Suksatan, H. Sulaiman-Rahman, D.O. Bokov, W.K. Abdelbasset, A. Hassanzadeh, *et al.*, Harnessing TRAIL-induced apoptosis pathway for cancer immunotherapy and associated challenges, *Front. Immunol.*, **12**, 699746 (2021). https://doi.org/10.3389/fimmu.2021.699746

32. J. Abdulghani, W.S. El-Deiry, TRAIL receptor signaling and therapeutics, *Expert Opin. Ther. Targets*, **14**, 1091–1108 (2010). https://doi.org/10.1517/14728222.2010.519701

33. A. Willms, H. Schupp, M. Poelker, A. Adawy, J.F. Debus, T. Hartwig, et al., TRAIL-receptor 2—a novel negative regulator of p53, *Cell Death Dis.*, **12**, 757 (2021). https://doi.org/10.1038/s41419-021-04048-1

34. M. de Looff, S. de Jong, F.A.E. Kruyt, Multiple interactions between cancer cells and the tumor microenvironment modulate TRAIL signaling: Implications for TRAIL receptor targeted therapy, *Front. Immunol.*, **10**, 1530 (2019). https://doi.org/10.3389/fimmu.2019.01530

35. Z.-X. Zhang, I. Gan, A. Pavlosky, X. Huang, B. Fuhrmann, A.M. Jevnikar, Intracellular pH regulates TRAIL-induced apoptosis and necroptosis in endothelial cells, *J. Immunol. Res.*, **2017**, 1503960 (2017). https://doi.org/10.1155/2017/1503960

36. C.R. Reis, P.-H. Chen, N. Bendris, S.L. Schmid, TRAIL-death receptor endocytosis and apoptosis are selectively regulated by dynamin-1 activation, *Proc. Natl. Acad. Sci.*, **114**, 504–509 (2017). https://doi.org/10.1073/pnas.1615072114

37. J. Zhu, Q. Zhou, S. Tan, Targeting miRNAs associated with surface expression of death receptors to modulate TRAIL resistance in breast cancer, *Cancer Lett.*, **383**, 154–160 (2016). https://doi.org/10.1016/j.canlet.2016.09.021

38. D. Sarhan, P. D'Arcy, A. Lundqvist, Regulation of TRAIL-receptor expression by the ubiquitin-proteasome system, *Int. J. Mol. Sci.*, **15**, 18557–18573 (2014). https://doi.org/10.3390/ijms151018557

39. U. Bertsch, C. Röder, H. Kalthoff, A. Trauzold, Compartmentalization of TNF-related apoptosis-inducing ligand (TRAIL) death receptor functions: emerging role of nuclear TRAIL-R2, *Cell Death Dis.*, **5**, e1390 (2014). https://doi.org/10.1038/cddis.2014.351

40. D. Chen, M. Frezza, S. Schmitt, J. Kanwar, P.Q. Dou, Bortezomib as the first proteasome inhibitor anticancer drug: Current status and future perspectives, *Curr. Cancer Drug Targets*, **11**(3), 239–253 (2011). https://doi.org/10.2174/156800911794519752

41. C.T. Hellwig, M.E. Delgado, J. Skoko, L. Dyck, C. Hanna, A. Wentges, *et al.*, Proteasome inhibition triggers the formation of TRAIL receptor 2 platforms for caspase-8 activation that accumulate in the cytosol, *Cell Death Differ.*, **29**, 147–155 (2022). https://doi.org/10.1038/s41418-021-00843-7

Supplementary file: Details of the search strategy

Search in PubMed Central - PMC:

((((Receptors, TNF Related Apoptosis Inducing Ligand) OR (Tumor Necrosis Factor Receptor Superfamily, Member 10) OR (TRAIL Receptors) OR (Receptors, TRAIL) OR (Receptors, Tumor Necrosis Factor, Member 10) OR (TNF-Related Apoptosis-Inducing Ligand Receptors) OR (TNF Related Apoptosis Inducing Ligand Receptors) OR (Receptors, Tumor Necrosis Factor, Member 10d) OR (Decoy Receptor 2, Tumor Necrosis Factor) OR (Receptor, TRAIL-4) OR (Receptor, TRAIL 4) OR (TRAIL-4 Receptor) OR (DCR2 Receptor) OR (Receptor, DCR2) OR (TRAIL Receptor 4) OR (Receptor 4, TRAIL) OR (Receptors, Tumor Necrosis Factor, Member 10a) OR (Tumor Necrosis Factor Receptor Superfamily, Member 10a) OR (APO2 Receptor) OR (Receptor, APO2) OR (Receptor, TRAIL-1) OR (Receptor, TRAIL 1) OR (TRAIL-1 Receptor) OR (TRAIL Receptor 1) OR (DR4 Receptor) OR (Receptor, DR4) OR (Death Receptor-4) OR (Death Receptor 4) OR (Receptor-4, Death[Title/Abstract])) OR (Receptors, Tumor Necrosis Factor, Member 10b) OR (TRAIL Receptor 2) OR (Receptor, TRAIL-2) OR (Receptor, TRAIL 2) OR (TRAIL-2 Receptor) OR (DR5 Receptor) OR (Receptor, DR5) OR (Tumor Necrosis Factor Receptor Superfamily, Member 10b) OR (TNF-Related Apoptosis-Inducing Ligand Receptor 2) OR (TNF Related Apoptosis Inducing Ligand Receptor 2) OR (Death Receptor-5) OR (Death Receptor 5) OR (trail) OR (TNFRSF10) OR (TNFRSF10C) OR (TRAILR3)) AND ((cancer[Title/Abstract] OR cancers[Title/Abstract] OR neoplasm[Title/Abstract] OR neoplasms)[Title/Abstract])) AND (ovary[Title/Abstract] OR ovarian[Title/Abstract])) AND (survive[Title/Abstract] OR mortality[Title/Abstract] OR survivorship[Title/Abstract] OR (disease free survival) [Title/Abstract] OR (overall survival)[Title/Abstract]).

Search in SCOPUS (Elsevier):

TITLE-ABS-KEY ((receptors, AND tnf AND related AND apoptosis AND inducing AND ligand) OR (tumor AND necrosis AND factor AND receptor AND superfamily, AND member 10) OR (trail AND receptors) OR (receptors, AND trail) OR (receptors, AND tumor AND necrosis AND factor, AND member 10) OR (tnf-related AND apoptosis-inducing AND ligand AND receptors) OR (tnf AND related AND apoptosis AND inducing AND ligand AND receptors) OR (receptors, AND tumor AND necrosis AND factor, AND member AND 10d) OR (decoy AND receptor AND 2, AND tumor AND necrosis AND factor) OR (receptor, AND trail-4) OR (receptor, AND trail 4) OR (trail-4 AND receptor) OR (dcr2 AND receptor) OR (receptor, AND dcr2) OR (trail AND receptor 4)

OR (receptor AND 4, AND trail) OR (receptors, AND tumor AND necrosis AND factor, AND member AND 10a) OR (tumor AND necrosis AND factor AND receptor AND superfamily, AND member AND 10a) OR (apo2 AND receptor) OR (receptor, AND apo2) OR (receptor, AND trail-1) OR (receptor, AND trail 1) OR (trail-1 AND receptor) OR (trail AND receptor 1) OR (dr4 AND receptor) OR (receptor, AND dr4) OR (death AND receptor-4) OR (death AND receptor 4) OR (receptor-4, AND death) OR (receptors, AND tumor AND necrosis AND factor, AND member AND 10b) OR (trail AND receptor 2) OR (receptor, AND trail-2) OR (receptor, AND trail 2) OR (trail-2 AND receptor) OR (dr5 AND receptor) OR (receptor, AND dr5) OR (tumor AND necrosis AND factor AND receptor AND superfamily, AND member AND 10b) OR (tnf-related AND apoptosis-inducing AND ligand AND receptor 2) OR (tnf AND related AND apoptosis AND inducing AND ligand AND receptor 2) OR (death AND receptor-5) OR (death AND receptor 5) OR (trail) OR (tnfrsf10) OR (tnfrsf10c) OR (trailr3)) AND TITLE-ABS-KEY (cancer OR cancers OR neoplasm OR neoplasms) AND TITLE-ABS-KEY (ovary OR ovarian) AND TITLE-ABS-KEY (survive OR mortality OR survivorship OR (disease AND free AND survival) OR (overall AND survival))

Search in Web of Science:

(((TI=(trail OR TNFRSF10 OR Death Receptor)) OR AB=(trail OR TNFRSF10 OR Death Receptor)) AND (TI=(cancer OR cancers OR neoplasm OR neoplasms) OR AB=(cancer OR cancers OR neoplasm OR neoplasms)) AND (TI=(ovary OR ovarian) OR AB=(ovary OR ovarian)) AND ((TI=(survive OR mortality OR survivorship)) OR AB=(survive OR mortality OR survivorship)))

Search in Cochrane Library:

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(receptor, AND trail-1) OR (receptor, AND trail 1) OR (trail-1 AND receptor) OR (trail AND receptor 1) OR (dr4 AND receptor) OR (receptor, AND dr4) OR (death AND receptor-4) OR (death AND receptor 4) OR (receptor-4, AND death) OR (receptors, AND tumor AND necrosis AND factor, AND member AND 10b) OR (trail AND receptor 2) OR (receptor, AND trail-2) OR (receptor, AND trail 2) OR (trail-2 AND receptor) OR (dr5 AND receptor) OR (receptor, AND dr5) OR (tumor AND necrosis AND factor AND receptor AND superfamily, AND member AND 10b) OR (tnf-related AND apoptosis-inducing AND ligand AND receptor 2) OR (tnf AND related AND apoptosis AND inducing AND ligand AND receptor 2) OR (death AND receptor-5) OR (death AND receptor 5) OR (trail) OR (tnfrsf10) OR (tnfrsf10c) OR (trailr3))

#2 - (cancer OR cancers OR neoplasm OR neoplasms)

#3 - (ovary OR ovarian)

#4 - (survive OR mortality OR survivorship OR (disease AND free AND survival) OR (overall AND survival))

#5 - #1 AND 2# AND 3# AND 4#

Search in Biblioteca Virtual emSaúde - BVS (BIREME):

(((receptors, AND tnf AND related AND apoptosis AND inducing AND ligand) OR (tumor AND necrosis AND factor AND receptor AND superfamily, AND member 10) OR (trail AND receptors) OR (receptors, AND trail) OR (receptors, AND tumor AND necrosis AND factor, AND member 10) OR (tnf-related AND apoptosis-inducing AND ligand AND receptors) OR (tnf AND related AND apoptosis AND inducing AND ligand AND receptors) OR (receptors, AND tumor AND necrosis AND factor, AND member AND 10d) OR (decoy AND receptor AND 2, AND tumor AND necrosis AND factor) OR (receptor, AND trail-4) OR (receptor, AND trail 4) OR (trail-4 AND receptor) OR (dcr2 AND receptor) OR (receptor, AND dcr2) OR (trail AND receptor 4) OR (receptor AND 4, AND trail) OR (receptors, AND tumor AND necrosis AND factor, AND member AND 10a) OR (tumor AND necrosis AND factor AND receptor AND superfamily, AND member AND 10a) OR (apo2 AND receptor) OR (receptor, AND apo2) OR (receptor, AND trail-1) OR (receptor, AND trail 1) OR (trail-1 AND receptor) OR (trail AND receptor 1) OR (dr4 AND receptor) OR (receptor, AND dr4) OR (death AND receptor-4) OR (death AND receptor 4) OR (receptor-4, AND death) OR (receptors, AND tumor AND necrosis AND factor, AND member AND 10b) OR (trail AND receptor 2) OR (receptor, AND trail-2) OR (receptor, AND trail 2) OR

(trail-2 AND receptor) OR (dr5 AND receptor) OR (receptor, AND dr5) OR (tumor AND necrosis AND factor AND receptor AND superfamily, AND member AND 10b) OR (tnf-related AND apoptosis-inducing AND ligand AND receptor 2) OR (tnf AND related AND apoptosis AND inducing AND ligand AND receptor 2) OR (death AND receptor-5) OR (death AND receptor 5) OR (trail) OR (tnfrsf10) OR (tnfrsf10c) OR (trailr3)) AND (cancer OR cancers OR neoplasm OR neoplasms) AND (ovary OR ovarian) AND (survive OR mortality OR survivorship OR (disease AND free AND survival) OR (overall AND survival)))

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