Cancer Treatment Reviews 77 (2019) 11–19

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Systematic or Meta-analysis Studies

Prognostic value of receptor tyrosine kinase-like orphan receptor (ROR) family in cancer: A meta-analysis

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ARTICLE INFO

Keywords:
Receptor tyrosine kinase-like orphan receptor
ROR
ROR1
ROR2
Cancer
Meta-analysis

ABSTRACT

Introduction: Identification of membrane proteins expressed exclusively on tumor cells is a goal for cancer drug development. The receptor tyrosine kinase-like orphan receptor type 1 and 2 (ROR1/2), are type-I transmembrane proteins expressed in cancer but not in adult normal tissue. Here, we explore the prognostic role ROR1/2 expression on patient outcome.

Methods: A systematic search of electronic databases identified publications exploring the effect of ROR1/2 on overall survival (OS). Hazard ratios (HR) from collected data were pooled in a meta-analysis using generic inverse-variance and random effects modeling. Subgroup analyses were conducted based on disease site or tumor type.

Results: Twenty five studies met the inclusion criteria. ROR1 was associated with worse overall survival (HR 2.13, 95% confidence interval (CI) 1.62–2.80; $P < 0.001$) with subgroup analysis showing the strongest association between ROR1 and OS was in lung cancer. There was no significant difference between solid tumors and hematological malignancies (HR 2.15, 95% CI 1.52–3.06 vs. HR 2.02, 95% CI 1.46–2.84; subgroup difference $P = 0.80$). ROR2 was also associated with worse OS (HR 1.84, 95% CI 1.43–2.38; $P < 0.001$). There was no significant difference between disease sites although the highest association seen was in head and neck cancers (HR 3.19, 95% CI 1.13–8.97) and the lowest in gynecological cancers (HR 1.19, 95% CI 0.71–2.00; subgroup difference $P = 0.10$).

Conclusions: ROR1 and ROR2 expression is associated with adverse outcome in several tumors. ROR1/2 warrants study as a target for developmental therapeutics.

Introduction

Identification of membrane proteins expressed preferentially on tumor cells is a goal of drug development [1]. This approach permits the design of vectorized compounds such as antibody drug conjugates (ADCs), or the development of cellular therapies targeting tumoral cells and reduces undesirable side effects of therapeutic targeting of normal tissue [2]. Such strategies have shown clinical activity, including trastuzumab emtansine (TDM1), an ADC against HER2, or tisagenlecleucel, a chimeric antigen receptor T-cell (CAR-T) therapy against B-cells expressing CD19 [3,4].

Receptor tyrosine kinases are transmembrane proteins involved in the transmission of external signals through ligand binding. Phosphorylation of the kinase domain results in the activation of intracellular signaling cascades that result in modifications of cellular functions [5]. The receptor tyrosine kinase-like orphan receptor (ROR) type 1 and 2 (ROR1 and ROR2), are type-I transmembrane proteins that lack kinase activity but interact with the non-canonical Wnt pathway to mediate intracellular communication [6]. They play a key role in the embryonic development, and mutations of this family of receptors are linked with developmental syndromes [7–9].

ROR1 and ROR2 are highly expressed in human tumors including breast, lung or ovarian cancer, among others [10]. In addition, expression of these receptors has been associated with an increase in proliferation and survival through the activation of several signaling pathways such as phosphatidylinositol 3-kinase/Protein Kinase B

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https://doi.org/10.1016/j.ctrv.2019.05.006
Received 9 April 2019; Received in revised form 25 May 2019; Accepted 26 May 2019

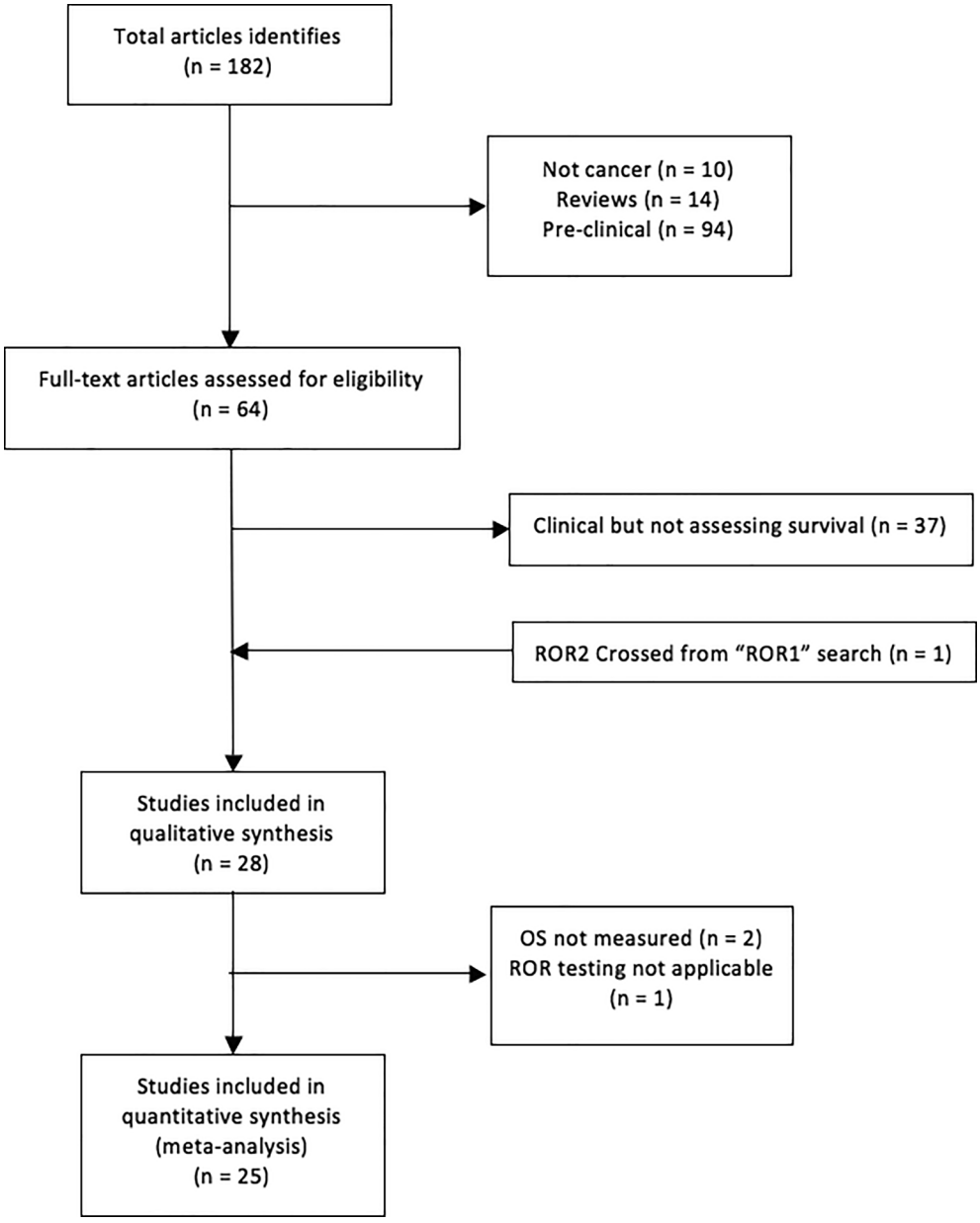


Fig. 1. Flow chart of study selection process for ROR1 and ROR2.

(PI3K/AKT) or mitogen-activated protein kinase (MAPK/p38) [11,12].

In recent years, several strategies have been developed aiming to use these receptors as drug development targets for ADCs or antibody binding nanoparticles, or to develop CAR-T cells, taking advantage of their limited expression in non-malignant tissue in adults [13–15]. In this review, we summarize existing published data on the prognostic association of ROR protein expression in cancer.

Methods

Data sources and searches

This analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [16]. An electronic search of MEDLINE (host: Pubmed) from 1946 to February 4th, 2019 was performed using the search terms: "Receptor-tyrosine-kinase-like orphan receptor 1" or "ROR1" and "Cancer"; with filters: humans. The search was then repeated using the search terms "Receptor-tyrosine-kinase-like orphan receptor 2" or "ROR2" and "Cancer". Citation lists of retrieved articles were screened manually to ensure sensitivity of the search strategy.

Study selection

Eligibility criteria for studies included: (i) studies of humans (adult and children); (ii) patients with hematological or solid tumors; (iii) reporting a hazard ratio (HR) for overall survival (OS) or survival curves allowing estimation of the hazard ratio for OS; (iv) available as

Table 1
Characteristics of included studies for ROR1.

Ref	Year	# of patients	Tumors	Population	Detection method	Agent used	Cutoff used	Outcomes included
19	2012	295	Breast	Adult	IHC	Alexa-647–conjugated monoclonal Ab (mAb; 4A5)	> 50% staining	OS
20	2014	100	Ovarian	Adult	IHC	Rabbit polyclonal Ab (1:200, Abcam)	Product of intensity and percentage scores (both 1 to 3). Final score > 2 was considered positive	OS, RFS
21	2014	285	Ovarian	Adult	Western Blot	N/A	Relative ROR1 mRNA expression (High = upper third)	OS, RFS
22	2015	424	Gastric	Adult	IHC	Rabbit polyclonal Ab (1:25; Abcam)	> 50% staining	OS
23	2016	210	Triple negative breast	Adult	IHC	Rabbit polyclonal Ab (1:100 dilution; proteintech)	Product of intensity and percentage scores (both 1 to 3). Final score > 2 was considered positive	OS, RFS
24	2016	1568	CLL	Adult	IHC	Alexa-647–conjugated monoclonal Ab (mAb; 4A5)	> 50% staining	OS, RFS
26	2016	161	Lung	Adult	IHC	Anti-ROR1 (Abcam, ab135669, 1:20)	Product of intensity and percentage scores	OS
27	2017	166	Colorectal	Adult	IHC	Polyclonal rabbit Ab(1:20, Abcam)	> 50% staining	OS
28	2017	150	Triple negative breast	Adult	IHC	N/A	N/A	OS
29	2018	87	Endometrial	Adult	IHC	Anti-ROR1 (Abcam ab135669)	Intensity strong = 3	OS

Legend: IHC = Immunohistochemistry, CLL = Chronic lymphocytic lymphoma, Ab = antibody, OS = Overall survival, RFS = Residual free survival.

full-text publication; (v) clinical trials, cohort or case-control studies; and (vi) English language publication. Case reports, conference abstracts and letters to editors were excluded. Titles identified by the initial search were evaluated and potentially relevant publications were retrieved in full. Two authors (JFA and PP) reviewed full articles independently for eligibility and one author did the data collection (RS). Disagreements were resolved by consensus.

Data extraction

The following data were collected from included studies using a predesigned abstraction form: name of first author, year of publication, journal, number of patients included in analysis, primary malignancy, protein expression, methods used for the evaluation of ROR1 and ROR2, and cut-off used for defining ROR intensity. The outcome of interest was OS comparing ROR1 or ROR2 expression to no expression as defined by individual studies. In cases where the HR was not reported, it was estimated from survival curves for OS independently using methods described by Parmar et al. [17]. Otherwise, it was extracted directly from published reports. We applied a hierarchal approach to the collection of HRs, preferring those reported from multivariable analyses to univariable HR and finally to HRs estimated from survival plots.

Statistical analysis

Extracted data were pooled using RevMan 5.3 analysis software (Cochrane Collaboration, Copenhagen, Denmark). Estimates for HRs were pooled and weighted by generic inverse variance and computed by random effects modeling. Statistical heterogeneity was assessed using the Cochran's Q and I^2 statistics. Subgroup analyses were performed for different disease sites. Differences between the subgroups were assessed using methods described by Deeks et al [18]. Sensitivity analyses were performed excluding studies in pediatric tumors and when ROR1/2 expression was evaluated in the peri-tumoral stroma rather than in the membrane or cytoplasm. All statistical tests were two sided, and statistical significance was defined as $p < 0.05$. No correction was applied for multiple statistical testing.

Results

Eleven retrospective studies comprising 3529 patients were identified for ROR1 [19–29] and 15 retrospective studies comprising 3034 patients were identified for ROR2 [25,29–44] (Fig. 1). The characteristics of included studies are described in Table 1 for ROR1 and Table 2 for ROR2. All studies with ROR1 where in adults and 1 study did not include usable OS data. One study did not report OS outcomes and 1 study explored ROR2 gene expression rather than protein expression. Therefore, both were excluded. Study populations included patients with breast, ovarian, gastric, pancreatic, leukemia, lymphoma, melanoma, lung, colorectal, endometrial, sarcoma, hepatocellular, medulloblastoma, glioblastoma, and squamous cell carcinoma.

Overall survival

ROR1

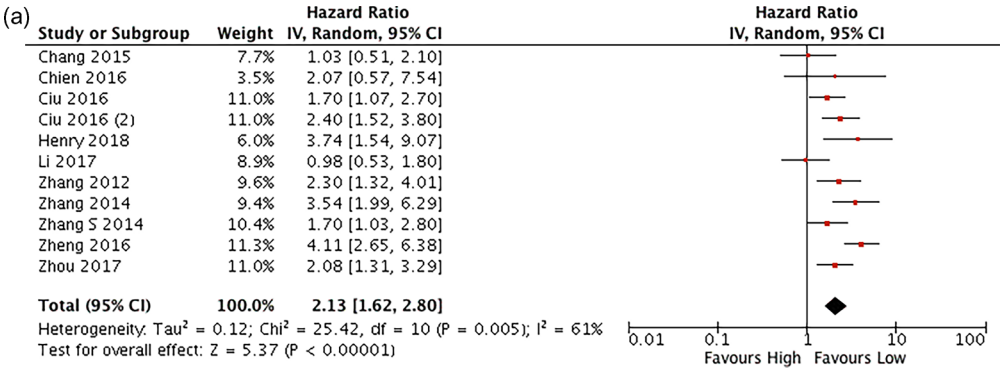
Data for the association between ROR1 and OS were reported in 10 studies. ROR1 was associated with worse overall survival (HR 2.13, 95% confidence interval (CI) 1.62–2.80; $P < 0.001$, Fig. 2A). Heterogeneity was statistically significant (Cochran Q $P = 0.005$, $I^2 = 61\%$). The magnitude of worse OS with ROR1 expression was greatest in lung cancer (HR 4.11, 95% CI 2.65–6.38) followed by gynecological cancers (HR 2.67, 95% CI 1.55–4.61) and chronic lymphocytic leukemia (CLL) (HR 2.02, 95% CI 1.46–2.84). Subgroup analysis showed that the association between ROR1 and OS was significantly greater in lung cancer compared to the other disease sites (Subgroup difference $P = 0.04$,

Table 2
Characteristics of included studies for ROR2.

Ref	Year	# of patients	Tumors	Population	Detection Method	Agent used	Cutoff used	Outcomes included
30	2012	647	GIST + Sarcoma	Adult	IHC	Mouse monoclonal Ab (1:25)	Strong staining (score = 2)	OS
31	2012	82	Hepatocellular carcinoma	Adult	IHC	PAB3386 (Abnova, 1:200)	Product of intensity and percentage scores	OS
32	2012	76	Medulloblastoma	Children	IHC	Mouse monoclonal Ab (1:25	≥ 50%	OS, RFS
33	2015	59	Chondrosarcoma	Adult	IHC	Rabbit polyclonal Ab (Abgent Company)	≥ 25%	OS
34	2015	295	Breast Cancer	Adult	IHC	Anti-human Ab HPA021868(1:50)	Any staining considered +	OS
35	2014	184	Colorectal	Adult	IHC	Polyclonal rabbit Ab (LifeSpan BioSciences)	Product of intensity and percentage scores (both 1 to 3). Final score > 2 was considered positive	OS
37	2015	214	Ovarian	Adult	IHC	Anti-ROR2 Ab (Sigma HPA021868)	Not reported	OS, RFS
38	2015	162	Pancreatic	Adult	IHC	Polyclonal rabbit Ab (LifeSpan BioSciences)	≥ 50%	OS
39	2015	163	Glioblastoma	Adult	IHC	Monoclobal Ab (1:1000, LifeSpan Biosciences)	> Weak staining	OS
40	2015	219	Lung	Adult	IHC	Primary antibody (1:100; LS-C99125, LifeSpan BioSciences)	≥ 60%	OS
41	2015	94	Cervical	Adult	IHC	Primary mouse Ab (Abcam; 1:200)	Product of intensity and percentage scores (positive > 6)	OS, RFS
42	2016	22	Lymphoma	Adult	IHC	Rabbit Ab (1:200, HPA021868, Sigma)	> 10%	OS
43	2017	126	Gallbladder	Adult	IHC	Rabbit polyclonal Ab (Abgent)	≥ 25%	OS
44	2017	97	Squamous	Adult	IHC	Polyclonal rabbit Ab (Novus Biologicals)	Not reported	OS
29	2018	87	Endometrial	Adult	IHC	Anti-ROR2 Ab (QED Bioscience 34045; 1:100)	Intensity strong = 3	OS

Legend: GIST = Gastrointestinal stromal tumor, IHC = Immunohistochemistry, CLL = Chronic lymphocytic lymphoma, Ab = antibody, OS = Overall survival, RFS = Residual free survival.

(a)



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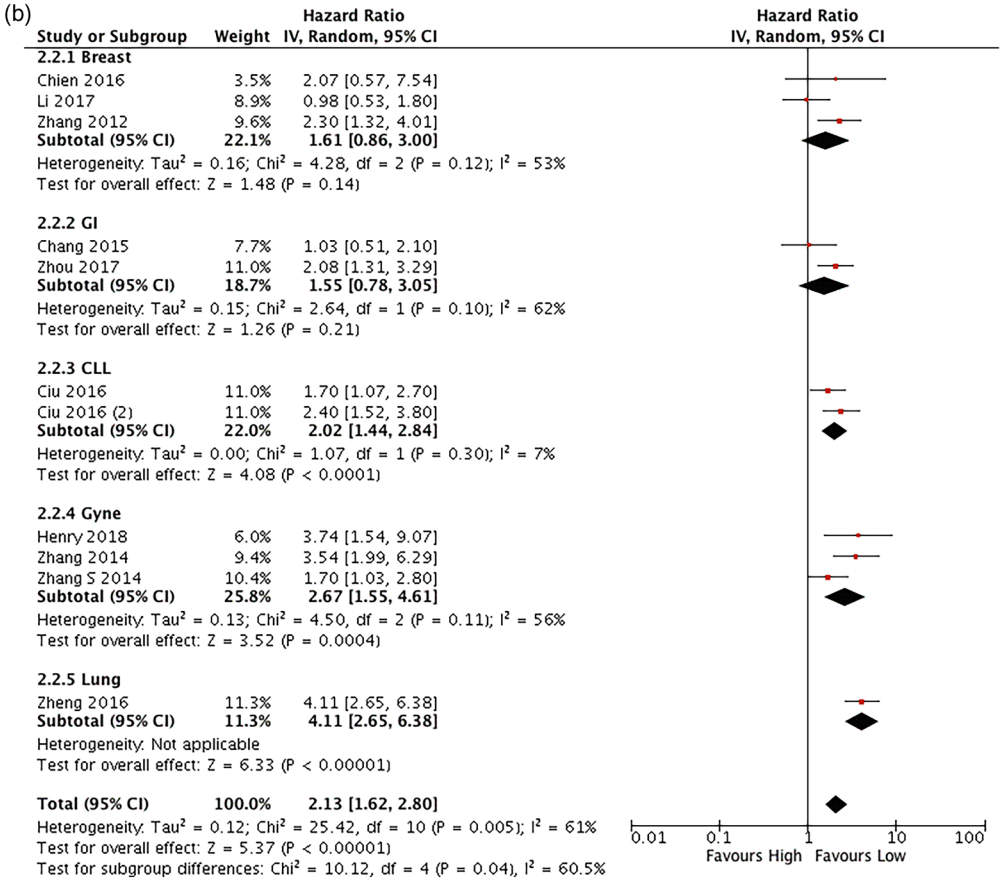

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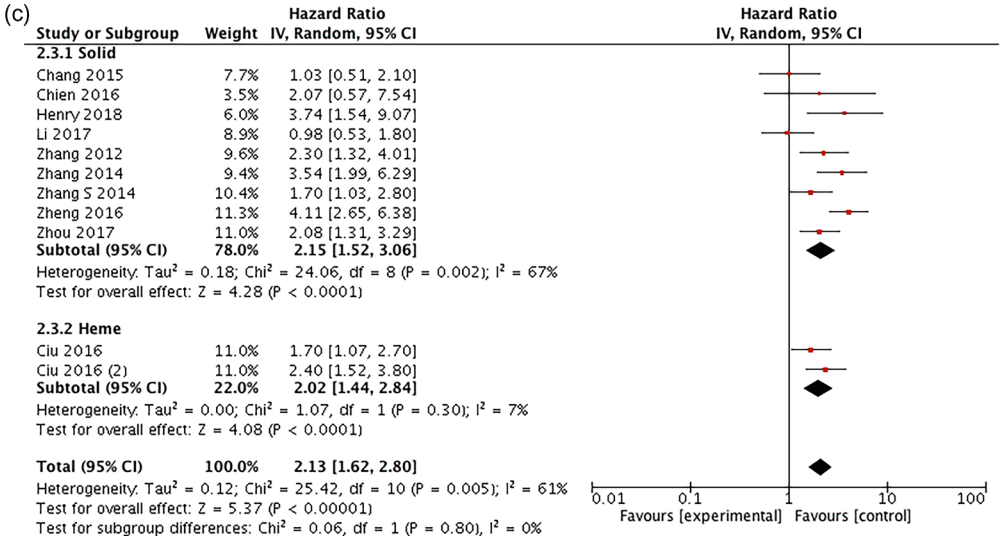

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Fig. 2. Forest plot showing hazard ratios for overall survival, ROR1 overall (A); and by subgroups based on disease site (B); or solid tumors vs. hematological malignancies (C). Hazard ratios for each study are represented by squares: the size of the square represents the weight of the study in the meta-analysis; the horizontal line crossing the square represents the 95% confidence interval. All statistical tests were two-sided. The diamonds represent the estimated pooled effect. Test for overall effect based on z-test. All *P* values are two-sided. CI = confidence interval; OR = odds ratio.

Fig. 2B). Exclusion of the lung cancer studies resulted in borderline significant heterogeneity (Cochran Q P = 0.07, I^2 = 44%) and non-significant differences between disease-site subgroups (Subgroup difference P = 0.32). There was no significant difference between solid tumors and hematological malignancies (Solid tumors: HR 2.15, 95% CI 1.52–3.06; Hematological malignancies: HR 2.02, 95% CI 1.46–2.84; subgroup difference P = 0.80, Fig. 2C).

ROR2

Data for the association between ROR2 and OS were reported in 15 studies. ROR2 was associated with worse overall survival (HR 1.84, 95% CI 1.43–2.38; P < 0.001, Fig. 3A). Heterogeneity was statistically significant (Cochran Q P < 0.001, I^2 = 59%). The association with worse OS was of significantly different magnitude among different disease sites with the highest association seen for head and neck cancers (HR 3.19, 95% CI 1.13–8.97), lung cancer (HR 2.72, 95% CI 1.7–4.34) and sarcoma (HR 2.54, 95% CI 1.29–5.01) and the lowest association seen for gynecological cancers (HR 1.19, 95% CI 0.71–2.00; subgroup difference P = 0.1; Fig. 3B). Improved overall survival was noted in the pediatric group (HR 0.18, 95% CI 0.04–0.89; subgroup difference P = 0.006). Excluding the above mentioned malignancies (head and neck and central nervous system, and gynecological); there was no significant difference between the remaining tumors (Subgroup difference P = 0.40) and heterogeneity was borderline non-significant (Cochran Q P = 0.04, I^2 = 47%).

Discussion

The orphan receptor tyrosine kinases ROR1 and ROR2 are transmembrane glycoproteins highly expressed during the embryonic and fetal development, but with little expression in adult normal tissues [45]. In contrast, a number of tumors express these proteins in a constitutive manner. In the present article we describe the prognostic value of expression of ROR1 and ROR2 in a several tumor types. This highlights the possible utility of this family of proteins as therapeutic targets.

The mechanism underlying the expression of ROR proteins in tumors is that oncogenic transformed cells re-acquire genomic programs present during embryonic development, but that are repressed typically in healthy adult cells. Of interest, in the one pediatric study there appears to be a protective effect with ROR2 expression, however, it is difficult to draw conclusions as to whether this observation is meaningful or simply a chance finding. The differential expression of these receptors in tumors makes them interesting targets for the design of ADCs or CAR-T cells.

In recent years, there has been an upsurge of interest in ROR1/2 due to its therapeutic potential for the treatment of cancers. Monoclonal antibodies targeting ROR1 have been developed [46,47]. In a preclinical study, Cirmtuzumab (UC-961), a first-in-class humanized mAb against ROR1, exerted anti-tumor effect in CLL [14,15]. Several other high affinity ROR1 monoclonal antibodies had been tested in CLL and mantle cell lymphoma (MCL) [48]. The observation of this clinical activity has been the basis for the development of ADCs targeting ROR proteins with such agents currently in early stages of clinical development. As can be seen in Table 3, most trials have focused on B-cell CLL, small lymphocytic lymphoma and MCL. In our analysis, we identified only one study that assessed the prognostic impact of ROR1 in patients with CLL patients. The current emphasis of therapeutic efforts in hematologic malignancies may be based on the desire to explore a more homogeneous population of predominantly monoclonal malignancies. However, the efficacy in solid tumors is also under evaluation mainly in non-small cell lung cancer, triple negative breast cancer and soft tissue sarcoma. In our analysis, it was noted that tumors with high expression of ROR1/2 such as non-small cell lung cancer, sarcoma, and oral squamous cell carcinoma also had worse prognosis. In this context it may be possible that future clinical trials could include malignancies that are more susceptible to the effect of high ROR1/2 expression.

Another therapeutic approach against ROR1 is the development of CAR-T cell therapy. Engineered T cells expressing a ROR1-specific chimeric antigen receptor can recognize the tumor cells and has been shown to exhibit significant anti-tumor effects in B-cell CLL [49,50]. An ongoing phase I clinical trial is assessing an ADC targeted treatment against ROR2. Finally, other strategies to target ROR1 have been evaluated in the preclinical setting, as is the case for the use of small tyrosine kinase inhibitors against ROR1 [51]. However, to our knowledge, this has not resulted in any clinical development.

This study has limitations. This is a retrospective analysis of published articles. Therefore, it is susceptible to publication bias and also relies on summary data not individual patient data. Furthermore, for some included studies (11 of 26), we estimated HR from survival plots as these were not reported in the individual articles. Subgroup analysis showed that there was significant difference in the prognostic value of ROR1/2 expression based on whether HRs were extracted or estimated. This can add some uncertainty about the precision of the results. Finally, only 2 cohorts reported data on hematologic malignancies (both CLL), therefore additional data on the prognostic value of ROR1 expression in hematological malignancies is warranted.

In conclusion, we describe the adverse association of ROR1 and ROR2 expression and outcome in several cancers. Ongoing studies highlight the importance of this family of receptors as novel therapeutic targets.

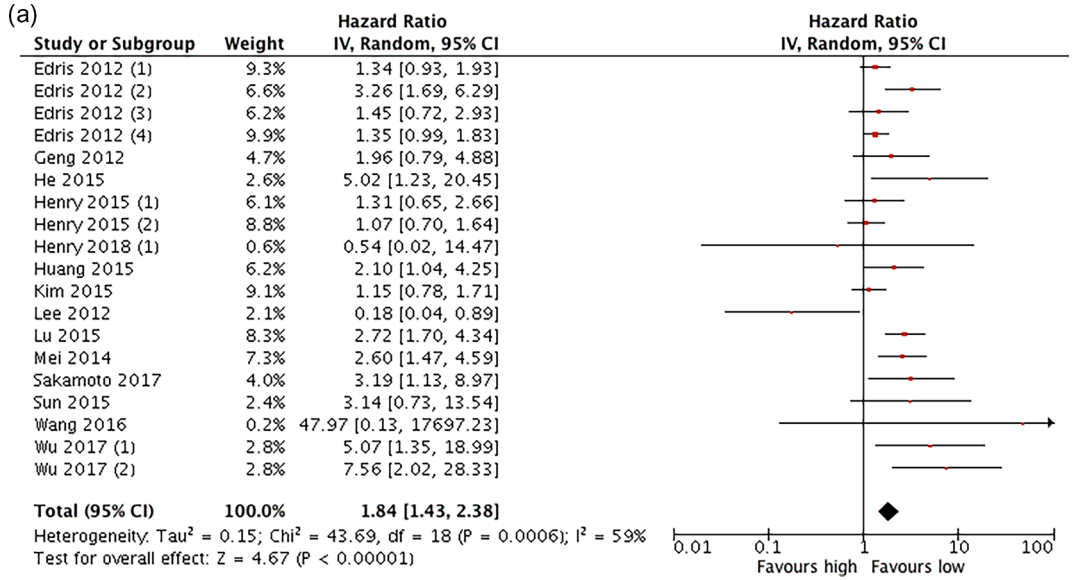
Authors' disclosure of potential conflict of interest

- Dr. Eitan Amir reports personal fees from Genentech/Roche, personal fees from Apobiologix, personal fees from Myriad Genetics, personal fees from Agendia, outside the submitted work.
- Dr. Alberto Ocaña reports personal fees from Entrechem, Servier and Daiichi-Sankyo outside the submitted work.
- Dr Atanasio Pandiella reports personal fees from Daiichi-Sankyo outside the submitted work.
- Pedro Pérez-Segura: personal fees from Merck and MSD outside the submitted work.

Author contribution

- Concept and Design: Alberto Ocaña
- Financial Support: N/A
- Collection and assembly of data: Jesús Fuentes Antrás, Paloma Peinado and Ramy Saleh

(a)



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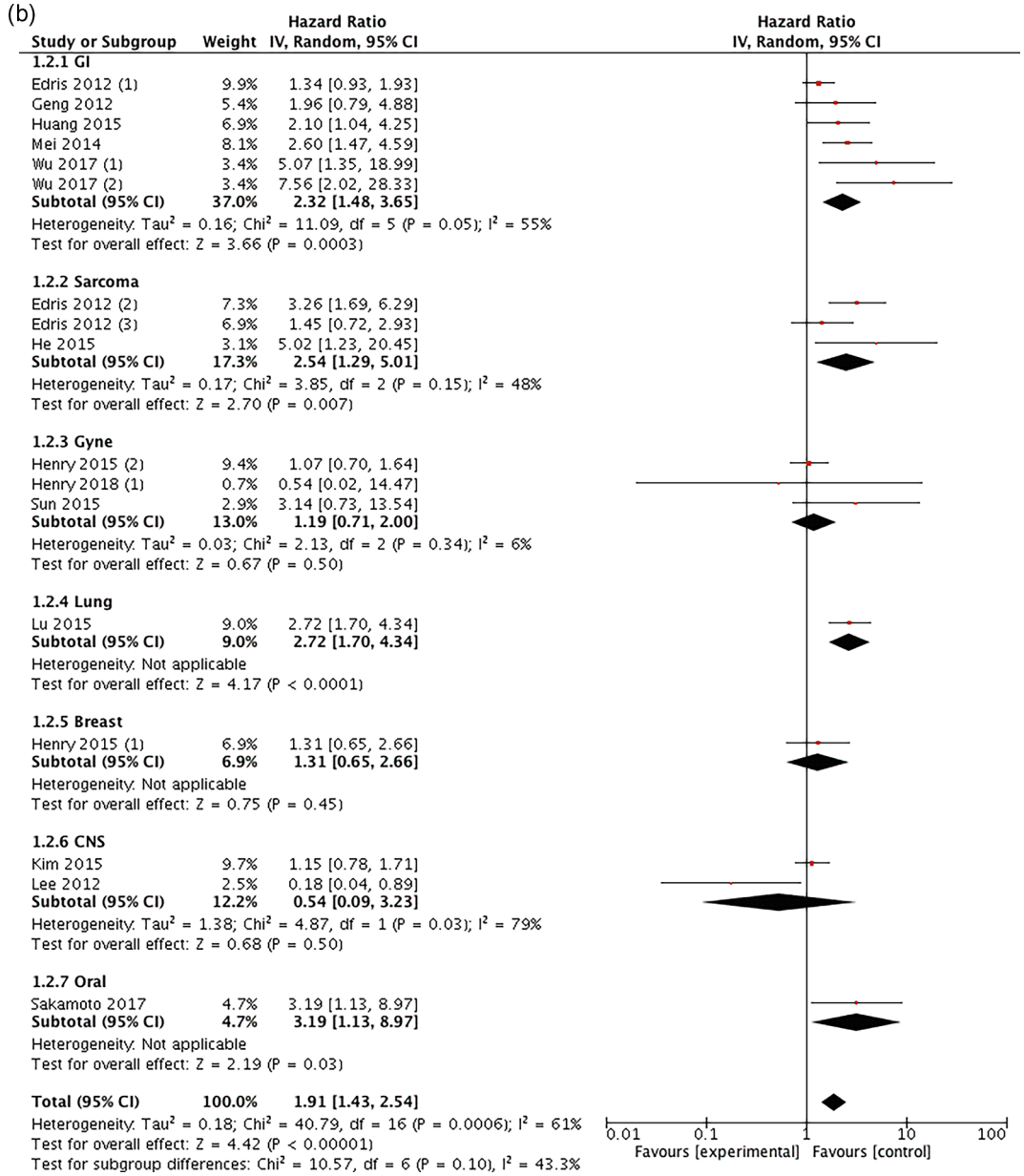

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Fig. 3. Forest plot showing hazard ratios for overall survival, ROR2 overall (A); and by subgroups based on disease site (B). Hazard ratios for each study are represented by squares: the size of the square represents the weight of the study in the meta-analysis; the horizontal line crossing the square represents the 95% confidence interval. All statistical tests were two-sided. The diamonds represent the estimated pooled effect. Test for overall effect based on z-test. All *P* values are two-sided. CI = confidence interval; OR = odds ratio.

Table 3
Clinical trials targeting ROR1/2.

Study	Sponsor	Conditions	Phase	Experimental arm(s)	Status
NCT02706392. Genetically Modified T-Cell Therapy in Treating Patients With Advanced ROR1 + Malignancies	Fred Hutchinson Cancer Research Center National Cancer Institute (NCI)	Recurrent Adult Acute Lymphoblastic Leukemia Recurrent Mantle Cell Lymphoma Refractory Chronic Lymphocytic Leukemia Breast Cancer Non-Small Cell Lung Cancer Triple-Negative Breast Carcinoma	Phase 1	Chimeric Anti-ROR1 T-cell Receptor-expressing Autologous T-lymphocytes	Recruiting
NCT02194374. Autologous ROR1R-CAR-T Cells for Chronic Lymphocytic Leukemia (CLL)	M.D. Anderson Cancer Center CLL Global Research Foundation Alliance	•B-cell Chronic Lymphocytic Leukemia •Small Lymphocytic Lymphoma	Phase 1	•Dose Escalation and expansion Cohorts with ROR1R-CAR-T cells/kg	Withdrawn
NCT03088878. A Study of the Cirmtuzumab and Ibrutinib in Patients With B-Cell Lymphoid Malignancies	University of California, San Diego California Institute for Regenerative Medicine (CIRM) Oncternal Therapeutics	•B-cell Chronic Lymphocytic Leukemia •Small Lymphocytic Lymphoma •Mantle Cell Lymphoma	Phase 1b/2	•Phase 1b - Dose Finding Cirmutuzumab followed by Cirmtuzumab plus ibrutinib •Phase 1b - Dose Expansion Cirmtuzumab plus ibrutinib •Phase 2 safety and efficacy evaluation Cirmtuzumab plus ibrutinib	Recruiting
NCT03420183. A Study of Cirmtuzumab and Ibrutinib in Patients With B-Cell Lymphoid Malignancies	Oncternal Therapeutics, Inc University of California, San Diego (CIRM)	•B-cell Chronic Lymphocytic Leukemia •Small Lymphocytic Lymphoma •Mantle Cell Lymphoma	Phase 1b/2	•Phase 1b - Dose Finding Cirmutuzumab followed by Cirmtuzumab plus ibrutinib •Phase 1b - Dose Expansion Cirmtuzumab plus ibrutinib •Phase 2 safety and efficacy evaluation Cirmtuzumab plus ibrutinib	Recruiting
NCT02776917. Study of Cirmtuzumab and Paclitaxel for Metastatic or Locally Advanced, Unresectable Breast Cancer	Barbara Parker, MD Collaborator: Oncternal Therapeutics, Inc	HER2 negative metastatic, or locally advanced, unresectable breast cancer	Phase 1b	Cirmtuzumab + Paclitaxel	Recruiting
NCT02222688. UC-961 (Cirmtuzumab) in Relapsed or Refractory Chronic Lymphocytic Leukemia	Thomas Kipps Thomas Kipps, University of California, San Diego	Chronic Lymphocytic Leukemia	Phase 1	Cirmtuzumab	Active, not recruiting
NCT02860676. Extension Study of UC-961 (Cirmtuzumab) for Patients With Chronic Lymphocytic Leukemia Treated Previously With UC-961	University of California, San Diego	Chronic Lymphocytic Leukemia	Phase 1	Cirmtuzumab	Active, not recruiting
NCT03504488. CAB-ROR2-ADC Safety and Efficacy Study in Patients With Solid Tumors	BioAtla, LLC	•Solid Tumor •Non Small Cell Lung Cancer •Triple Negative Breast Cancer •Soft Tissue Sarcoma	Phase 1/2	Dose escalation and expansion. BA3021, a conditionally active biologic (CAB) ROR2-targeted antibody drug conjugate (CAB-ROR2- ADC)	Recruiting
NCT03393936. Safety and Efficacy of CCT301 CAR-T in Adult Subjects With Recurrent or Refractory Stage IV Renal Cell Carcinoma	Shanghai Sinobioway Sunterra Biotech Shanghai Public Health Clinical Center	Refractory Stage IV Renal Cell Carcinoma	Phase 1/2	Dose escalation and expansion. Autologous T Cell Modified Chimeric Antigen Receptor (CAR) CCT 301–38 or CCT 301–59	Recruiting

- Data analysis and interpretation: Eitan Amir and Ramy Saleh
- Manuscript writing: All authors
- Final approval of manuscript: All authors

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