SUPPLEMENTARY MATERIAL *for* "Potential ototoxicity of insulin-like growth factor 1 receptor-targeted therapy: An *in silico* drug repurposing study of the regenerating cochlear neuron transcriptome"

Table S1. List of genes reported to be significantly up- or down-regulated during SGN regeneration in Wu et al. [1]

	Reason for exclusion from CLUE query		
Gene symbol	**Invalid HUGO symbol or Entrez ID**	**Valid HUGO symbol or Entrez ID, but not part of BING space**	**logFC**
Up-regulated			
Isyna1			0.457
Mrto4			0.469
Uck2			0.469
Armc8			0.490
Abhd2			0.496
Nup93			0.505
Lmnb1			0.519
Mrps18b			0.548
Ick			0.551
Mpp6			0.554
Prkg2			0.576
Syn2		X	0.659
Asns			0.660
Abhd2			0.667
Fam171b		X	0.670
Shox2			0.708
Abhd2			0.730
Syt4		X	0.736
Gng3			0.753
Srm			0.851
Nefm			0.866
Chac1			0.984
B3gnt5		X	0.992

Spock3			1.012
Abcg5			1.171
Hba-a1	X		1.320
Down-regulated			
Saa3	X		-2.150
Ifi27l2a	X		-1.814
Dynlrb2		X	-1.560
Ccl5			-1.412
Chrna10			-1.325
Cep41			-1.306
Plac8			-1.256
AA467197	X		-1.231
Aoc3			-1.224
Tmem204			-1.159
Cox7a1			-1.102
Gng8		X	-1.103
Apod			-1.021
Bcl6			-0.944
Acpp			-0.938
Cd40			-0.893
Scrg1			-0.862
Scin			-0.819
Gstm2			-0.794
Chrna1			-0.776
Nme5			-0.752
Chst5			-0.734
Slc26a4			-0.718
Gstt3	X		-0.702
Flt1			-0.676
Wdr45			-0.666
Gstm2			-0.662
Pon2			-0.644
Lrrc8a		X	-0.628
Lrrc48	X		-0.616
Gstm2			-0.564
Manba			-0.563
Naprt		X	-0.545
Mb			-0.487
Rnf182		X	-0.454
Csad			-0.453

Ccdc190		X	-0.441

Abbreviations: BING, Best INFerred Genes; HUGO, Human Genome Organization; ID, identification; logFC, log fold change (in expression); SGN, spiral ganglion neuron.

Table S2. Search terms for the literature review in PubMed and ClinicalTrials.gov

Drug Name	Pharmacological Action/ Targets	Drug search terms	Otological search terms
Teprotumumab	Fully human monoclonal antibody that inhibits signaling at the insulin-like growth factor I (IGF-1) receptor and thyrotropin receptor [2]	"teprotumumab" OR "Tepezza"	"hearing" OR "hearing loss" OR "deaf" OR "deafness" OR "tinnitus" OR "vertigo" OR "ear pain" OR "ear discomfort" OR "hypoacusis" OR "ototoxic" OR "ototoxicity" OR "dizziness" OR "labyrinth" OR "audiometry" OR "audiogram"
R1507[a]	Fully human monoclonal antibody that inhibits signaling at the IGF-1 receptor and thyrotropin receptor [3]	"R1507"	
Cixutumumab	Fully human monoclonal antibody that inhibits signaling at the IGF-1 receptor [4]	"cixutumumab" OR "IMC-A12"	
Ganitumab	Fully human monoclonal antibody that inhibits signaling at the IGF-1 receptor [5]	"ganitumab" OR "AMG-479"	
Figitumumab	Fully human monoclonal antibody that inhibits signaling at the IGF-1 receptor [6]	"figitumumab" OR "CP-751871"	
Dalotuzumab	Recombinant humanized monoclonal antibody that inhibits signaling at the IGF-1 receptor [7]	"dalotuzumab" OR "MK-0646"	
Ceritinib	Tyrosine kinase inhibitor which blocks production of anaplastic lymphoma kinase (ALK) [8]	"ceritinib" OR "LDK378" OR "Zykadia"	
Ganetespib	Resorcinolic triazolone inhibitor of the molecular chaperone Hsp90, which is an upstream modifier of ALK [9]	"ganetespib" OR "STA-9090"	
Linsitinib	Small molecule inhibitor of the IGF-1 receptor and the insulin receptor [10]	"linsitinib"	

Note: [a] R1507 is also listed as the experimental name of teprotumumab but was included separately as it was not possible to determine whether alterations had occurred to the molecule prior to its market entry as teprotumumab/Tepezza.

Table S3. Characteristics of the studies and trials included in the literature review

Author/ClinicalTrial.gov ID	Study design	Treatment groups, N	Otologic AEs
Ceritinib			
Kim et al. [11] (NCT01283516)	Non-randomized, open-label, dose-escalation, phase I trial; 50 to 750 mg 1x daily	N=304 with tumors with genetic abnormalities in anaplastic lymphoma kinase (ALK)	500 mg: vertigo 1/10; 700 mg: tinnitus 1/5; 750 mg: vertigo 7/255, tinnitus 7/255, hearing impaired 1/255, dizziness 1/255; Total: vertigo 8/304, hearing impaired 1/304, tinnitus 8/304, dizziness 42/304, serious dizziness 1/304.
NCT02040870	Non-randomized, open-label, phase I/II trial; 750 mg every 28 days	N=103 with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring a confirmed ALK rearrangement	Deafness 1/103, ear pain 1/103, dizziness 12/103
NCT02276027	Non-randomized, open-label, phase II trial; 750 mg 1x daily	N=26 with advanced NSCLC	Unilateral deafness 1/26, tinnitus 7/26, vertigo 1/26, dizziness 9/26
Soria et al. [12] (NCT01828099)	Randomized, open-label, phase III trial comparing ceritinib (750 mg/daily) vs. platinum chemotherapy	N=189 (ceritinib) and N=175 (chemotherapy) with stage IIIB/IV ALK-rearranged non-squamous NSCLC	Ceritinib: tinnitus 4/189, dizziness 22/189, serious dizziness 2/189 Chemotherapy: tinnitus 16/175, dizziness 17/175
Nishio et al. [13] (NCT01685138)	Open-label phase II study; 750 mg/daily	N=124 treatment-naive adults with ALK-activated NSCLC	Vertigo 1/124, dizziness 21/124, serious dizziness 3/124
Chow et al. [14] (NCT02336451)	Non-randomized, open-label phase II study, dosing not reported	N=156 with ALK-positive NSCLC metastatic to the brain and/or leptomeninges	Vertigo 7/156, dizziness 22/156, serious dizziness 1/156
Fischer et al. [15] (NCT01742286)	Open-label phase I study, various dosing	N=83 pediatric with malignancies with a ALK mutation	300 mg/fasting: dizziness 2/12, ear pain 1/12, external ear inflammation 1/12, hypoacusis 1/12, ear infection 1/12 510 mg/fasting: dizziness 1/13; 500 mg/food: dizziness 2/42, ear pain 3/42, ear infection 2/42, serious ear infection 1/42

Hida et al. [16] (NCT01685060)	Open-label phase II study, 750 mg/daily	N=140 with ALK-activated NSCLC	Dizziness 15/140
NCT02513667	Non-randomized, open-label phase II study, 10 weeks 750 mg/daily	N=13 with ALK-rearranged metastatic lung adenocarcinoma	Dizziness 2/13, vertigo 1/13
Kiura et al. [17] (NCT01828112)	Randomized, open-label phase III comparing ceritinib (750 mg/daily) vs. chemotherapy	N=115 (ceritinib) and N=113 (chemotherapy)	Ceritinib: dizziness 10/115 Chemotherapy: dizziness 6/113, severe dizziness 1/113
Cixutumumab			
Ferrarotto et al. [18]	Randomized open-label, phase II trial *(*10mg/kg alone or with 500mg/m^2 cetuximab every 2 weeks)	N=91 with recurrent/metastatic head and neck squamous cell carcinoma	Monotherapy: dizziness 3/47; Combination therapy: dizziness 7/44, ear pain 5/44
Chugh et al. [19] (NCT00720174)	Non-randomized, open-label, phase I trial (cixutumumab 1, 3, or 6 mg/kg with doxorubicin 75 mg/m^2)	N=29 with unresectable, locally advanced, or metastatic soft tissue sarcoma	Ear and labyrinth disorders 2/29
Dasari et al. [20] (NCT01204476)	Non-randomized, open-label, phase I trial; everolimus (10 mg daily), octreotide (20 mg every 21 days) constant, cixutumumab escalating doses of 10 mg/kg and 15 mg/kg every 21 days of a 21 day cycle	N=19 with advanced low- or intermediate-grade neuroendocrine cancer	15 mg/kg: 15 patients had baseline and end of study audiometry assessments: grade 1 change in hearing sensitivity unilaterally 4/15, bilateral changes (grade 1 and grade 2) 1/15. Changes in hearing sensitivity were not clinically significant and were identified on audiograms.
Schwartz et al. [21] (NCT01016015)	Non-randomized, open-label, phase II trial (weekly cixutumumab 6 mg/kg, IV and temsirolimus 25 mg in 6-week cycles)	N=174 with locally advanced, metastatic, or recurrent soft tissue sarcoma or bone sarcoma	Dizziness 13/174
Wilky et al. [22] (NCT01061749)	Non-randomized, open-label, dose-escalation with expansion trial cohort, phase I trial; Maximally tolerated combination dose: selumetinib 50 mg twice daily, cixutumumab 12 mg/kg every 2 weeks	N=30 with advanced solid malignancies	Dizziness 3/30, tinnitus 1/30

Lerario et al. [23] (NCT00778817)	Randomized, open-label, phase II trial; cixutumumab 10 mg/kg every 2 weeks and mitotane 2 g daily (subsequently adjusted according to serum levels/symptoms)	N=20 with inoperable recurrent, metastatic, or primary adrenocortical cancer	Tinnitus (grade I) 8/20, dizziness 5/20
NCT00520481	Non-randomized, open-label, phase II trial; 10 or 20 mg/kg every 3 weeks until disease progression or intolerable toxicity	N=41 with asymptomatic, chemotherapy-naive, metastatic, androgen-independent prostate cancer	10 mg/kg: ear disorder 2/31, vertigo 2/31, dizziness 2/31; 20 mg/kg: dizziness 1/10
NCT01413191	Non-randomized, open-label, interventional, phase II trial; 10 mg/kg on days 1 and 15 for 4 week courses	N=18 with metastatic melanoma of the eye	Ear and labyrinth disorders 4/18, tinnitus 1/18, dizziness 5/18
NCT01142388	Randomized, open-label phase II; cixutumumab 10 mg/kg on days 1 and 15 of every 28 day cycle, and paclitaxel 80 mg/m^2 on days 1, 8, and 15 of every 28 day cycle	N=44 with metastatic esophageal or gastroesophageal junction (GEJ) cancer	Control: dizziness 2/40; Treatment: dizziness 5/44
Argiris et al. [24] (NCT00955305)	Randomized, open-label phase II trial; carboplatin, paclitaxel, bevacizumab, and cixutumumab	N=82 with advanced non-squamous NSCLC	Control: dizziness 7/83; Treatment: dizziness 8/82
NCT01026623	Open-label phase I/II trial; cixutumumab and temsirolimus in varying dosages	N=16 with metastatic castration-resistant prostate cancer	Dizziness 1/16 (IMC-A12 6 mg/kg, temsirolimus 20 mg)
NCT00781911	Non-randomized, open-label phase II trial; cixutumumab 10 mg/kg every 2 weeks	N=43 with metastatic, well or moderately differentiated carcinoid or islet cell carcinoma	Control: deafness 2/31, ear discomfort 1/31, ear pain 2/31, vertigo 2/31, dizziness 12/31; ICC: Deafness 2/12, dizziness 2/12, ear discomfort 1/12, ear pain 1/12
NCT01232452	Randomized, open-label, phase II trial; Treatment: pemetrexed + cisplatin + cixutumumab for up to 4 cycles; Control: pemetrexed + cisplatin	N=85 with advanced non-squamous NSCLC	Treatment: dizziness 11/85, serious vertigo 2/85, vestibular disorder 1/85, non-serious vertigo 9/85; Control: dizziness 5/81, non-serious vertigo 4/81
NCT00778167	Open-label phase I/randomized phase II study; three dosage regimens of erlotinib hydrochloride + cixutumumab	N=18 with advanced NSCLC	Erlotinib hydrochloride 150 mg once daily with cixutumumab 15 mg/kg IV in 21-day cycles. dizziness 2/18
Yu et al. [25] (NCT01120236)	Randomized, open-label phase II study; androgen deprivation +	N=101 with hormone sensitive metastatic prostate cancer	Androgen deprivation + cixutumumab: dizziness 23/101,

	cixutumumab vs. androgen deprivation		tinnitus 6/101; Androgen deprivation: dizziness 9/104, tinnitus 1/104.
NCT00870870	Randomized, open-label Phase II trial; C1: gemcitabine + carboplatin + cetuximab (GCC); C2: gemcitabine + cisplatin + cetuximab (GCiC); TX1: GCC + cixutumumab; TX2: GCiC + cixutumumab	N=31 with advanced/metastatic NSCLC	(C1) Dizziness 1/4; (C2) ear discomfort 2/29, hypoacusis 1/29, tinnitus 5/29, dizziness 8/29; (TX2): ear discomfort 1/25, hypoacusis 2/25, tinnitus 2/25, balance disorder 3/25, dizziness 4/25.
Higano et al. [26] (NCT00785538)	Open-label phase I study	N=24 with advanced solid tumors	Dizziness 3/24
Hussain et al. [27] (NCT00683475)	Randomized, open-label phase II study; C: cixutumumab + mitoxantrone + prednisone; R: ramucirumab + mitoxantrone + prednisone	N=66 with metastatic prostate cancer	C: dizziness 9/66; R: dizziness 12/66
NCT01160458	Open-label phase II study; 20 mg/kg	N=20 with mesothelioma	Dizziness 5/20
NCT00887159	Randomized, open-label phase II study; Arm A: cisplatin + etopside; Arm B: cisplatin + etopside + vismodegib; Arm C: cisplatin + etopside + cixutumumab	N=106 with extensive small cell lung cancer	Arm C: Serious dizziness 1/52, hearing impaired 2/52, tinnitus 6/52, dizziness 13/52; Arm A: Tinnitus 4/53, dizziness 8/53; Arm B: Hearing impaired 4/53, tinnitus 5/53, serious tinnitus 1/53, dizziness 9/53
NCT00668148	Open-label phase II study; 10 mg/kg	N=111 with advanced or metastatic soft tissue and Ewing's sarcoma	Dizziness 6/111
NCT00617708	Randomized, open-label phase I and II study; TX: erlotinib + gemcitabine + cixutumumab; Control: erlotinib + gemcitabine	N=123 with metastatic pancreatic cancer	Treatment: auditory/ear-other AE 2/66, serious dizziness 1/66, dizziness 10/66; Control: dizziness 7/57
NCT00728949	Randomized, open-label phase II study; Dual Tx: cixutumumab and schedule of last antiestrogen therapy to which their disease became refractory; Mono Tx: cixutumumab	N=93 with advanced/metastatic breast cancer	Dual Tx: dizziness 8/56; Mono Tx: dizziness 3/37

NCT00503685	Randomized, open-label phase II study; TX1: 10 mg/kg IMC-A12; TX2: cetuximab 500 mg/m^2 followed by 10 mg/kg IMC-A12; TX3: cetuximab 500 mg/m^2 followed by 10 mg/kg IMC-A12	N=64 with metastatic colorectal cancer	TX1: dizziness 3/23; TX2: dizziness 2/21; TX3: dizziness 1/20
NCT00906373	Non-randomized, open-label phase II study; (1*)* 10 mg/kg cixutumumab; (2) 20 mg/kg cixutumumab	N=47 with advanced hepatocellular carcinoma	(1) Hearing impaired 1/6; (2) Ear discomfort 5/41
NCT00986674	Randomized, open-label phase II study; Arm 1: carboplatin + paclitaxel + cetuximab; Arm 2: carboplatin + paclitaxel + cixutumumab; Arm 3: carboplatin + paclitaxel + cetuximab + cixutumumab	N=90 with advanced NSCLC	Arm 1: dizziness 3/44; Arm 2: dizziness 6/42; Arm 3: dizziness 5/48
NCT00617734	Randomized, open-label phase II study; Mono: cixutumumab 10 mg/kg; Dual: cixutumumab 10 mg/kg + cetuximab 500 mg/m^2	N=97 with metastatic squamous cell carcinoma head and neck cancer	Monotherapy: dizziness 3/47; Dual therapy: dizziness 6/44, ear pain 5/44
Dalotuzumab			
Rugo et al. [28] (NCT01605396)	Randomized, open-label, phase II trial comparing ridoforolimus 10 mg QD 5 ×/week + dalotuzumab 10 mg/kg/week + exemestane 25 mg/day (R/D/E), vs. ridaforolimus 30 mg QD 5 ×/week + exemestane 25 mg/day (R/E)	N=40 (R/D/E) and N=40 (R/E) with postmenopausal, high-proliferation (Ki67 index staining ≥15%), ER+ breast cancer (BC) that progressed after nonsteroidal aromatase inhibitor	R/D/E: Grade 1 hearing loss 1/39, dizziness 1/39 R/E: Grade 1 hearing loss 1/40, dizziness 6/40
Ellis et al. [29] (NCT00869752)	Non-randomized, open-label, phase I-II trial of two doses of dalotuzumab (5 or 10 mg/kg IV weekly) + cisplatin (25 mg/m^2) and etoposide (100 mg/m^2) every 21 days	N=12 with chemotherapy-naïve advanced NSCLC	Hearing loss 2/12, one of grade 3 that was attributed to cisplatin
Huang et al. [30] (NCT00799240)	Randomized, open-label, parallel assignment, phase II trial of cisplatin + pemetrexed with or without dalotuzumab	N=12 (dalotuzumab) and N=14 (no dalotuzumab) with stage IV non-squamous lung cancer	Pemetrexed + cisplatin: grade 2 tinnitus 4/14

			Dalotuzumab with pemetrexed + cisplatin: grade 2 tinnitus 3/12, grade 3 hearing toxicity 1/12
Brana et al. [31] (NCT01243762)	Non-randomized, open label phase I study of 7 dose combinations of dalotuzumab, MK-0752, or ridaforolus	N=47 with advanced cancer	Dalotuzumab 7.5 mg/kg + MK-0752 1800 mg: dizziness 1/4; Dalotuzumab 10 mg/kg + MK-0752 1800 mg: ear discomfort: 2/13, hearing impaired 1/13, tinnitus 1/13; Dalotuzumab 10 mg/kg + MK-2206 135 mg: dizziness 3/8; Dalotuzumab 10 mg/kg + MK-2206 150 mg: dizziness 1/10, ear discomfort 1/10, middle ear effusion 1/10, vertigo 1/10; Dalotuzumab 10 mg/kg + MK-2206 200 mg: dizziness 1/3
Sclafani et al. [32] (NCT00614393)	Randomized, quadruple blinded phase II/III study of (1) dalotuzumab 10mg/kg Q1W; (2) dalotuzumab 15 mg/kg/7.5 mg/kg Q2W; (3) dalotuzumab 10 mg/kg Q1W; (4) dalotuzumab 15 mg/kg/7.5 mg/kg Q2W versus placebo + cetuximab + irinotecan	N=556 with metastatic colorectal cancer (CRC)	(1) dizziness 16/180, serious deafness bilateral 2/180; (3) deafness 1/10; (4) dizziness 21/180, ear infection 1/180; Control: dizziness 21/178
NCT01609231	Randomized, open-label phase IIA study comparing dalotuzumab + irinotecan vs. cetuximab + irinotecan	N=11 with metastatic CRC	Dalotuzumab + irinotecan: dizziness 1/6, ear discomfort 1/6, vertigo 1/6
NCT00694356	Non-randomized, open-label phase I study of 3 doses of dalotuzumab	N=15 with relapsed or refractory locally advanced or metastatic solid tumors	5 mg/kg: dizziness 1/6; 15 mg/kg/7.5 mg/kg: ear congestion 1/6
NCT00635778	Non-randomized, open-label phase I study of 7 doses of dalotuzumab	N=50 with relapsed or refractory locally advanced or metastatic cancers	2.5 mg/kg: vertigo 1/3; 10 mg/kg: deafness 1/3, ear infection 1/3; 15 mg/kg: dizziness 2/21
Moran et al. [33] (NCT00654420)	Randomized, open-label phase I/IIA study of (1) dalotuzumab 5 mg/kg + erlotinib; (2) dalotuzumab 10 mg/kg + erlotinib;	N=95 with recurrent NSCLC	(2) dizziness 1/16; (3) dizziness 5/37; (4) vertigo 2/38, dizziness 3/38

	(3):dalotuzumab 10 mg/kg + erlotinib; or (4) erlotinib only		
Figitumumab			
Becerra et al. [34] (NCT00560560)	Non-randomized, open-label, phase II trial; A: 20 mg/kg in 3 week cycles; B: 30 mg/kg	N=83 with metastatic CRC that was refractory to ≥2 systemic therapies	A: cerumen impaction 1/85, deafness 2/85, hypoacusis 2/85, tinnitus 1/85, vertigo 1/85, serious dizziness 1/85, dizziness 3/85; B: serious bilateral deafness 1/83, deafness 2/83, hypoacusis 2/83, deafness bilateral 1/83, deafness unilateral 1/83, motion sickness 1/83, ear pain 1/83, dizziness 3/83
Langer et al. [35] (NCT00596830)	Randomized, open-label, phase III trial; figitumumab (F) + paclitaxel and carboplatin; Control: paclitaxel and carboplatin alone	N=671 with stage IIIB/IV or recurrent NSCLC disease with non-adenocarcinoma histology	Tx: dizziness 37/338, serious dizziness 1/338, vertigo 1/338; Control: dizziness 32/333
Yin et al. [36]	Non-randomized, open-label, phase I trial; single dose of 10 or 20 mg/kg	N=28 healthy males	3 cases of tinnitus were reported at 10 mg/kg but none at 20 mg/kg. Tinnitus resolved in 2 participants within 21 and 171 days, respectively, from the start of symptoms; in the third participant, Tinnitus resolved within 25 days in one ear but was ongoing in the other ear 227 days after dosing. Two of the 3 participants with tinnitus also had an abnormal audiogram of mild severity.
NCT00729833	Non-randomized, open-label, sequential cohort, dose escalation, phase I trial; A: figitumumab (F) 10 mg/kg on day 1 of each cycle 3-week + sunitinib (S) 25 mg; B: F 10 mg/kg + S 37.5 mg; C: F 20 mg/kg + S 25 mg; D: F 20mg/kg + S 25 mg schedule 2/1	N=45 with advanced solid tumors	A: deafness bilateral 1/20, tinnitus 2/20, dizziness 3/20; B: dizziness 1/7; C: ear infection 1/12; D: tinnitus 1/6.
NCT00560573	Non-randomized, open-label, phase I trial; figitumumab 6 mg/kg (A), 10 mg/kg (B), 20 mg/kg (C,	N=45 with advanced NSCLC	A: deafness 1/6, hypoacusis 1/6, ototoxicity 1/6, tinnitus 2/6; C: ototoxicity 3/6, tinnitus 2/6; D: deafness 1/10, motion sickness

	D, E, F) + cisplatin + gemcitabine/pemetrexed		1/10, ototoxicity 3/10, tinnitus 1/10; E: hypoacusis 1/7, ototoxicity 2/7, tinnitus 1/7, dizziness 4/7; F: deafness 1/13, hypoacusis 2/13, ototoxicity 3/13, tinnitus 2/13
Scagliotti et al. [37](NCT00673049)	Randomized, open-label, phase III trial; A: IV 20 mg/kg figitumumab on days 1 and 2 in cycle 1 and on day 1 every 3 weeks, in combination with erlotinib 150 mg daily; B: erlotinib 150 mg daily; C erlotinib, then figitumumab 20 mg/kg as a single-agent therapy in 3-week cycles on study Days 1 and 2 in Cycle 1, and on Day 1 every 3 weeks.	N=662 with advanced NSCLC with non-adenocarcinoma histology	A: serious bilateral deafness 1/289, deafness 1/289, neurosensory deafness 1/289, unilateral deafness 2/289, ear disorder 1/289, ear pain 1/289, hearing impaired 1/289, tinnitus 3/289, tympanic membrane perforation 1/289, vertigo 3/289, positional vertigo 1/289, vestibular disorder 1/289, dizziness 16/289; B: ear pain 1/290, tinnitus 2/290, dizziness 4/290; C: ear pain 1/83, hearing impaired 1/83, dizziness 3/83
NCT00976508	Non-randomized, open-label, safety and tolerability, phase I trial; A: IV figitumumab 20 mg/kg every 3 weeks up to 1 year + pegvisomat 10 mg B: IV figitumumab 20 mg/kg every 3 weeks up to 1 year + pegvisomat 20 mg.	N=23 with advanced solid tumors	A: ear discomfort 1/17, sudden hearing loss 1/17, dizziness 2/17; B: ear discomfort 2/6, hearing impaired 1/6
Olmos et al. [38] (NCT00474760)	Non-randomized, open-label phase I study; T1: figitumumab (F) 3 mg/kg; T2: F 6 mg/kg; T3: F 10 mg/kg; T4: F 20 mg/kg; T5: F 20 mg/kg RP2D; T6: F 20 mg/kg recommended phase II dose (RP2D) ACC+ sarcoma; T7: F 20 mg/kg recommended phase II dose (Ewings sarcoma).	N=65 with advanced solid tumors	T2: dizziness 1/3; T5: dizziness 2/13; T6: dizziness 4/29; T7: ear congestion 1/11, ear pain 2/11, tinnitus 1/11, dizziness 1/11
NCT00147537	Randomized, open-label phase Ib/II; T1: CP-751,871 0.05 mg/kg + paclitaxel + carboplatin (P+C); T2: CP-751,871 0.1 mg/kg + P+C;	N=300 with advanced NSCLC	T1: dizziness 2/3; T5: dizziness 1/3; T6: tinnitus 1/3; T7: ear disorder 1/17, tinnitus 1/17, vertigo 1/17, dizziness 1/17; T8: tinnitus

	T3: CP-751,871 0.8 mg/kg + P+C; T4: CP-751,871 1.5 mg/kg + P+C; T5: CP-751,871 3 mg/kg + P+C; T6: CP-751,871 6 mg/kg + P+C; T6: CP-751,871 10 mg/kg + P+C; T7: CP-751,871 20 mg/kg + P+C; T8: CP-751,871 + P+C + erlotinib; T9: CP-751,871 + P+C; T10: P+C; T11: P+C + additional CP-751,871		1/7, dizziness 3/7; T9: ear congestion 1/17, hearing impaired 1/17, hypoacusis 1/17, ear infection 1/17, dizziness: 4/17; T10: ear disorder 1/163, hypoacusis 7/163, tinnitus 8/163, vertigo 3/163, deafness 6/163, ear discomfort 1/163, ear pain 3/163, ear infection 1/163, dizziness 27/163, serious dizziness 1/163; T11: tinnitus 1/56, dizziness 4/56; T12: ear disorder 1/22, tinnitus 1/22, vertigo 1/22, cerumen impaction 1/22, deafness 2/22, vestibular disorder 1/22, dizziness 4/22. G: dizziness 46/300, serious dizziness 1/300, ear infection 2/300, vestibular disorder 1/300, ear pain 3/300, ear discomfort 1/300, deafness 8/300, cerumen impaction 1/300, vertigo 5/300, tinnitus 13/300, hypoacusis 8/300, hearing impaired 1/300, ear disorder 3/300, ear congestion 1/300
NCT00977561	Randomized, open-label phase II study; figitumumab + cisplatin or carboplatin + etoposide; Ctr: cisplatin or carboplatin + etoposide	N=9 with extensive stage small cell lung cancer	Tx: deafness: 1/5; Ctr: tinnitus 1/4, dizziness 1/4
Ganetespib			
NCT01111838	Non-randomized, open-label, single-arm, phase II trial (200 mg infusion, 1x week for 3 weeks)	N=15 with refractory metastatic CRC	Tinnitus 1/15, dizziness 1/15
NCT01039519	Non-randomized, open-label phase II study (200 mg infusion, 1x week for 3 weeks)	N=27 with metastatic/unresectable gastrointestinal stromal tumor (GIST)	Ear discomfort 1/27, dizziness 4/27, labyrinthitis 1/27
NCT01798485	Randomized, open-label phase III study comparing ganetespib (150 mg/m^2) + docetaxel (75 mg/m^2) vs. docetaxel (75 mg/m^2)	N=338 (ganetespib + docetaxel) and N=342 (docetaxel) with advanced NSCLC	ganetespib + docetaxel: vertigo 1/338, dizziness 24/338 docetaxel: dizziness 21/342

NCT01200238	Non-randomized, open-label phase II study comparing 2 dosages (150 vs. 200 mg/m^2 infusions)	N=17 with metastatic ocular melanoma	150 mg/m^2: dizziness 2/10, ear and labyrinth disorder 1/10
Meehan et al. [39] (NCT02192541)	Open-label phase I study of ganetespib 100 mg/m^2 + ziv-aflibercept 4 mg/kg or ganetespib 100 mg/m^2 + ziv-aflibercept 3 mg/kg	N=5 with advanced gastrointestinal carcinomas, NSCLC, urothelial carcinomas, or sarcomas	Ganetespib 100 mg/m^2 + ziv-aflibercept 3 mg/kg: dizziness 1/3
NCT01962948	Non-randomized, open-label phase I/II study of three combinations: (1) 100 mg/m^2 ganetespib + 80 mg/m^2 paclitaxel; (2) 125 mg/m^2 ganetespib + 80 mg/m^2 paclitaxel; (3) 150 mg/m^2 ganetespib + 80 mg/m^2 paclitaxel	N=12 with recurrent, platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer	(1) hearing loss 1/3; (3) hearing loss 1/6, tinnitus 1/6, vertigo 1/6
NCT01227018	Open-label phase II study (175 mg infusion, 1x week for 3 weeks)	N=14 with metastatic pancreas cancer	Dizziness 1/14
Ganitumab			
Strosberg et al. [40] (NCT01024387)	Non-randomized, open-label, phase II trial (18 mg/kg over 60 min every 3 weeks)	N=60 with metastatic low- and intermediate-grade carcinoid or pancreatic neuroendocrine tumors	Hearing impairment 1/60, ear or labyrinth disorders 1/60, dizziness 3/60
NCT01708161	Non-randomized, open-label, single arm, phase Ib/II trial (various doses of alpelisib + 12 mg/kg ganitumab)	N=46 with *PIK3CA* mutated or amplified solid tumors, *PIK3CA* mutated or amplified HR+ BC	Alpelisib 350 mg + ganitumab 12 mg/kg: ear congestion 1/10, hearing impairment 1/10; Alpelisib 300 mg + ganitumab 12 mg/kg (in HR+ BC): ear congestion 1/10, ear pain 1/10, tinnitus 1/10; All: dizziness 11/46.
NCT00719212	Non-randomized, open-label, phase II trial (18 mg/kg on day 1 of each 21-day cycle)	N=61 with recurrent platinum-sensitive ovarian epithelial (including fallopian tube and primary peritoneal) carcinoma failing frontline chemotherapy	Deafness 1/61, dizziness 6/61
NCT00718523	Randomized, double-blinded, placebo controlled, phase II trial of (1) paclitaxel/carboplatin chemotherapy vs. (2) ganitumab +	N= 77 (1) and N=88 (2) with debulked stage III and IV ovarian epithelial (including fallopian tube and primary peritoneal) carcinoma	(1) deafness neurosensory 1/77, tinnitus 4/77, vertigo 4/77, dizziness 15/77;

	paclitaxel/carboplatin chemotherapy		(2) tinnitus 3/88, vertigo 8/88, serious dizziness 1/88, dizziness 9/88
Teprotumumab			
Douglas et al. [2] (NCT03298867)	Randomized, double-masked, placebo-controlled, phase III trial; 8 infusions, one every 3 weeks; initial dose 10 mg/kg, followed by 20 mg/kg for the remaining seven infusions	N=83 with Graves disease, active, moderate to severe thyroid eye disease (TED) and ocular symptoms (n=41 in treatment group)	Hearing impairment 5/41 (2x hypoacusis, resolved; 1x deafness, resolved; 1x autophony, resolved; 1x mild patulous eustachian tube, resolved); 32F had hypoacusis (mild) - onset d75, resolved d76; 66M had hypoacusis (moderate) - onset d108, resolved d 283, d167 peaked tympanometry and hearing threshold between 35-55 pantonal R and 35-70 dB pantonal L, moderate hearing impairment R, mild hearing impairment L; 79F had deafness (moderate) - onset d134, resolved d337, d166 peaked tympanograms in normal pressure range and bilat symmetrical pantonal hearing loss, d253 improvement; 60F had autophony (mild) - onset d84, resolution around 4 months after 8th infusion, d29 ear discomfort + dizziness (d29-51), oropharyngeal pain d81-87; 39F had Eustachian tube patulous (mild), onset d153, resolved d304, rhinorrhea d151-152, periodontitis d154-ongoing at last follow up; dizziness 3/41
Smith et al. [41] (NCT01868997)	Randomized, double-masked, placebo-controlled, phase II trial; 8 infusions, one every 3 weeks; initial dose 10 mg/kg, followed by 20 mg/kg for the remaining 7 infusions	N=87 with active TED (n=42 in treatment group)	Hearing impairment 3/42 (1x unilateral hearing impairment onset 16 weeks after end of Tx, 1x mild bilateral hearing impairment (resolved), 1x tinnitus in a patient with history of tinnitus); 59F had hyperacusis: reported d112 that her voice echoed when she spoke and

			has occasional bilateral tinnitus with brief dizziness, audiology: d112 R ear w mild hearing loss at 6kHz, L w mild conductive to mixed hearing loss at 4-8kHz, excellent word recognition bilateral, normal tympanograms, d203 stable from prior evaluation; 43F had Eustachian tube dysfunction (moderate), deafness unilateral (moderate), medical history of chronic sinusitis, d274 moderate mixed hearing loss with possible recruitment L, R normal, d497 overall improvement; 60M had deafness (mild) - medical history of intermittent tinnitus after exposure to loud noise, d222 96% word recognition R, 92% L; patient suffering from tinnitus with handicapping moderate high frequency sensorineural bilateral hearing loss, hearing aid eval recommended
Xin et al. [42] (NCT03461211)	Non-randomized, open-label, phase III extension trial; 8 infusions, one every 3 weeks; initial dose 10 mg/kg, followed by 20 mg/kg for the remaining seven infusions	N=51 with active TED	Five patients experienced 6 events of hearing impairment; ear discomfort 4/51, autophony 1/51, hypoacusis 3/51, tinnitus 2/51, vertigo 2/51, deafness 1/40 (occurred in follow up period), dizziness 1/37
Sears et al. [43]	Prospective observational case series; 8 infusions, one every 3 weeks; initial dose 10 mg/kg, followed by 20 mg/kg for the remaining seven infusions	N=27 with TED	22/27 patients developed new or worsening otologic symptoms after an average of 3.8 teprotumumab doses; Ear plugging, fullness, and pressure 13/27 (10/11 resolved), muffled hearing, hearing loss, and diminished word recognition 11/27 (5/11 resolved), tinnitus and ear popping 10/27 (10/10 resolved),

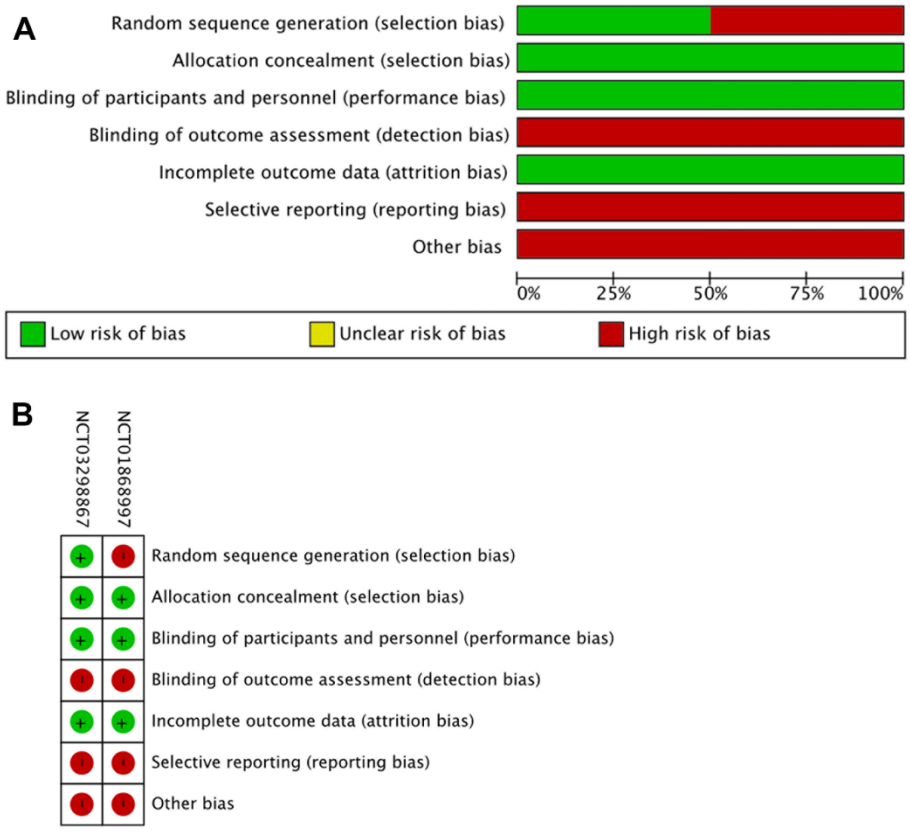
			autophony 7/27 (5/6 resolved). Three symptomatic patients lost to follow-up. 13/19 complete resolution of otologic symptoms, 6/19 persistence of at least one otologic symptom. Patients with persistent hearing loss received audiometric testing, showing decreased hearing thresholds. 4/6 required hearing aids
NCT00773383	Randomized, open-label study; teprotumumab 9 mg/kg once/week + erlotinib 150 mg once daily	N=34 with stage IIIB/IV NSCLC	Vertigo 2/34
Ramalingam et al. [44] (NCT00760929)	Randomized, double blinded, placebo controlled study; T1: teprotumumab 9 mg/kg; T2: teprotumumab 16 mg/kg; Control 1: placebo 9 mg/kg; Control 2: placebo 16 mg/kg	N=116 with advanced NSCLC	T1: dizziness 5/59; T2: dizziness 2/57; Ctr1: dizziness 4/26; Ctr2: dizziness 3/29
Pappo et al. [3] (NCT00642941)	Non-randomized, open label phase II study; teprotumumab 9 mg/kg once weekly until disease progression, intercurrent illness, unacceptable toxicity, prolonged (2-week) time off treatment, withdrawal, loss to follow-up, investigator decision, or death	N=317 with various cancers	Ear pain 6/317, tinnitus 5/317, ear discomfort 5/317, dizziness 14/317
NCT00796107	Open-label study; 2.5 mg letrozole + 16 mg/kg teprotumumab	N=6 with advanced BC	Vertigo 1/6, dizziness 1/6.

Table S4. Clinical trial and observational real-world data on otologic AEs in patients treated with teprotumumab

Clinical Trial/ Publication	Patients treated with teprotumumab, n	Reported Otologic AEs, n (%)				Patients with otologic AEs, n (%)
		Hearing	Tinnitus	Other	Total AEs	
Clinical trial, pre-approval						
NCT01868997, Smith et al. (2017) [41]	43	3 (7%)	2 (4.7%)	0 (0%)	5 (11.6%)	3 (7%)
NCT03298867, Douglas et al. (2020) [2]	41	3 (7.3%)	0 (0%)	2 (4.9%)	5 (12.2%)	5 (12.2%)
Clinical trial, post-approval						
NCT03461211	51	4 (7.8%)	2 (3.9%)	5 (9.8%)	11 (21.6%)	5 (9.8%)
Observational real-world						
Sears et al. (2022) [43]	27	11 (40.7%)	10 (37%)	20 (74.1%)	41 (151.9%)	22 (81.5%)

Caption: NCT01868997 and NCT03298867 were used in teprotumumab's United States FDA approval application (application number 761143Orig1s000 [45]). Combined, the two trials have reported 10 events of new or worsening hearing impairment, tinnitus, or other otologic AEs (including deafness, eustachian tube dysfunction, hyperacusis, hypoacusis, tinnitus, ear discomfort, and autophony) in 84 teprotumumab-treated patients, representing an incidence of 11.9%. The combined prevalence of otologic AEs in these trials was 9.5% (8/84 patients). NCT03461211 reported 11 otologic AEs in 51 teprotumumab-treated patients, representing an incidence of 21.6%, and a prevalence of 9.8% (5 of 51 patients). In an observational study of patients receiving teprotumumab in real-world clinical practice (Sears et al.), 22 of 27 patients were reported as having a total of 41 new or worsening otologic AEs (81.5% prevalence), an incidence of 151.9%. Abbreviations: AE, adverse event; FDA, Food and Drug Administration.

Fig S1. Results of the risk of bias analysis for the clinical trials included in the meta-analysis



Caption: The risk of bias analysis of the two placebo-controlled clinical trials of teprotumumab for thyroid eye disease included in the meta-analysis (ClinicalTrials.gov Identifiers: NCT01868997 and NCT03298867), overall (A) and for each trial (B). There was a high risk of bias related to blinding of outcome assessment data, selective reporting bias, and other bias in both trials.

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