User Group Clinical Guideline Services
Leitlinienprogramm Onkologie
1913 DGVS Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten
publiziert bei: AWMF online Das Portal der wissenschaftlichen Medizin

Literaturrecherchen und Evidenztabellen für die Version 3 der S3-Leitlinie Diagnostik und Therapie des Hepatozellulären Karzinoms und biliärer Karzinome

Inhaltsverzeichnis

1. Recherchen zum Bereich Hepatozelluläres Karzinom

1.1. HCC 20 Systemtherapie

Von welchen Systemtherapien profitieren Patienten mit fortgeschrittenem HCC?
Population: Patient*innen mit fortgeschrittenem HCC Interventions: Comparison: Keine Therapie oder gegen Sorafenib/ andere Therapien Outcomes: Overall survival, Progression free survival, Adverse Events, Quality of life, Time to Progression

Recherche in PubMed (06.07.2021)

Nr	Query	Hits
	Population	
#1	**Carcinoma, Hepatocellular[Mesh]** OR Hepatom*[tiab] OR ((Carcinoma*[tiab] OR Cancer[tiab] OR cancers[tiab]) AND (hepatocellular[tiab] OR liver cell[tiab] OR adult liver[tiab]))	154.123
#2	(**Neoplasms[Mesh]** OR Neoplas*[tiab] OR Tumor[tiab] OR Tumors[tiab] OR Cancer*[tiab] OR Malignanc*[tiab]) AND (hepatocellular[tiab] OR hepatic*[tiab] OR liver*[tiab] OR "**Liver"[Mesh**])	298.199
#3	#1 OR #2	344.304
	Intervention	
#4	**Sorafenib[Mesh]** OR Sorafenib[tiab] OR Nexavar[tiab] OR BAY 43-9006[tiab] OR BAY 43 9006[tiab] OR BAY 439006[tiab] OR Sorafenib N-Oxide[tiab] OR Sorafenib N Oxide[tiab] OR BAY-673472[tiab] OR BAY 673472[tiab] OR BAY 545-9085[tiab] OR BAY 545 9085[tiab] OR BAY 5459085[tiab] OR BAY-545-9085[tiab] OR BAY5459085[tiab]	9.815
#5	**"lenvatinib" [Supplementary Concept]** OR Lenvatinib[tiab] OR E 7080[tiab] OR E-7080[tiab] OR Lenvima[tiab]	1.073
#6	**regorafenib [Supplementary Concept]** OR Regorafenib[tiab] OR Stivarga[tiab] OR BAY 73-4506[tiab] OR BAY73-4506[tiab] OR BAY-73-4506[tiab]	1.403
#7	**cabozantinib [Supplementary Concept]** OR Cabozantinib[tiab] OR Cometriq[tiab] OR XL 184[tiab] OR XL184 cpd[tiab] OR XL-184[tiab] OR BMS 907351[tiab] OR BMS907351[tiab] OR BMS-907351[tiab]	1.093
#8	**ramucirumab [Supplementary Concept**] OR Ramucirumab[tiab] OR Cyramza[tiab] OR IMC 1121B[tiab] OR IMC1121B[tiab] OR IMC-1121B[tiab]	965
#9	**("Programmed Cell Death 1 Receptor"[Mesh]** OR PD-1[tiab] OR PD 1[tiab] OR programmed cell death protein 1[tiab] OR CD279 Antigen[tiab] OR Antigen, CD279[tiab]) AND (inibitor*[tiab] OR antibod*[tiab] OR antagonist[tiab]) OR PD-L1[tiab] OR PD L1[tiab]	19.160

#10	**Nivolumab[Mesh]** OR Opdivo[tiab] OR ONO-4538[tiab] OR ONO 4538[tiab] OR ONO4538[tiab] OR MDX-1106[tiab] OR MDX 1106[tiab] OR MDX1106[tiab] OR BMS-936558[tiab] OR BMS 936558[tiab] OR BMS936558[tiab]	3.389
#11	**pembrolizumab [Supplementary Concept]** OR Pembrolizumab[tiab] OR lambrolizumab[tiab] OR Keytruda[tiab] OR MK-3475[tiab]	5737
#12	(**CTLA-4 Antigen[Mesh]** OR CTLA-4[tiab] OR CD152[tiab] OR Cytotoxic T-Lymphocyte-Associated Antigen 4[tiab] OR Cytotoxic T Lymphocyte Associated Antigen 4[tiab] OR Cytotoxic T-Lymphocyte Antigen 4[tiab] OR Cytotoxic T Lymphocyte Antigen 4[tiab]) AND (inibitor*[tiab] OR antibod*[tiab] OR antagonist[tiab])	3531
#13	**Ipilimumab[Mesh]** OR Ipilimumab*[tiab] OR Yervoy[tiab] OR MDX 010[tiab] OR MDX010[tiab] OR MDX-010[tiab] OR MDX-CTLA-4[tiab] OR MDX CTLA 4[tiab]	4289
#14	**Immunotherapy, Active[Mesh]** OR Immunotherap*[tiab] OR (immun*[tiab] AND therap*[tiab])	603.925
#15	tyrosine kinase inhibitor[tiab]	16.789
#16	**Molecular Targeted Therapy[Mesh]** OR (molecular[tiab] AND therap*[tiab]) OR targeted therap*[tiab]	263.684
#17	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	837.042
#18	#3 AND #17	30.755
	Filter	
#19	(systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	672.071

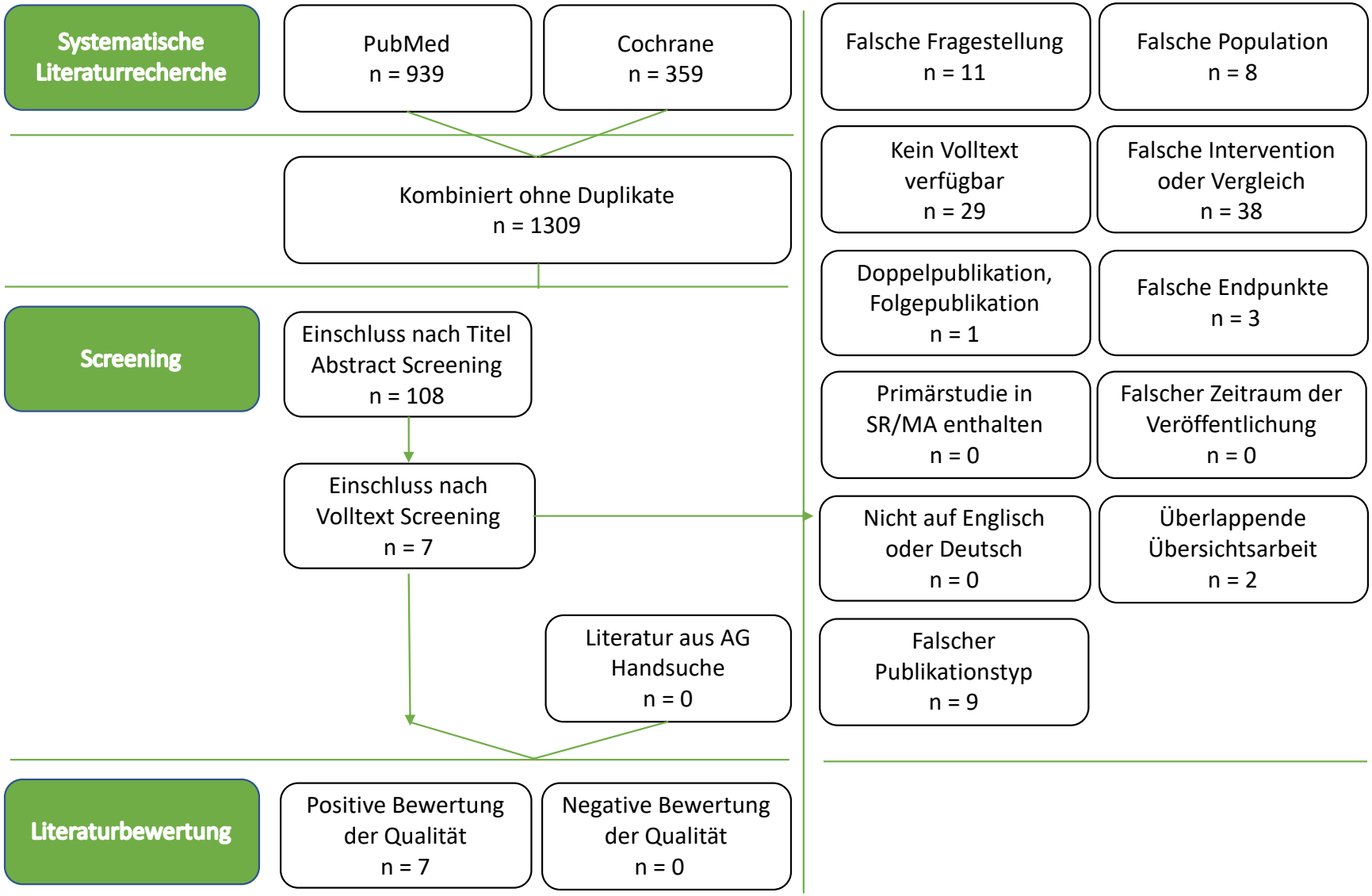
#20	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.555.270
#21	#19 OR #20	2.082.499
#22	animals[mh] NOT humans[mh]	4.856.894
#23	#21 NOT #22	2.044.760
#24	#18 AND #23	3805
#25	#24, Publication date 01/01/2019 – 30/06/2021, English and German articles	**939**

Recherche in der Cochrane Library (06.07.2021)

ID	Search	Hits
#1	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees	1817
#2	(hepatom* OR ((carcinoma OR Cancer OR cancers) AND (hepatocellular OR liver cell OR adult liver))):ti,ab,kw	10713
#3	MeSH descriptor: [Neoplasms] explode all trees	82548
#4	(Neoplasm* OR tumor OR cancer* OR malignanc*):ti,ab,kw	213909
#5	(hepatocellular OR hepatic OR liver):ti,ab,kw	60870
#6	(#3 OR #4) AND #5	17538
#7	#1 OR #2 OR #6	19134
#8	(Sorafenib OR Nexavar):ti,ab,kw	1910
#9	(lenvatinib):ti,ab,kw	351
#10	(regorafenib OR Stivarga):ti,ab,kw	536
#11	(Cabozantinib OR Cometriq):ti,ab,kw	358
#12	(ramucirumab OR Cyramza):ti,ab,kw	545
#13	MeSH descriptor: [Programmed Cell Death 1 Receptor] explode all trees	81
#14	(Programmed cell death receptor OR PD-1 OR PD 1 OR programmed cell death protein 1 OR CD279 Antigen OR Antigen, CD279):ti,ab,kw	25428
#15	(inibitor* OR antibod* OR antagonist):ti,ab,kw	68701
#16	(PD-L1 OR PD L1):ti,ab,kw	2621
#17	((#13 OR #14) AND #15) OR #16	5635

#18	(Nivolumab OR Opdivo):ti,ab,kw	1969
#19	(Pembrolizumab OR lambrolizumab OR Keytruda):ti,ab,kw	1873
#20	(TLA-4 OR CD152 OR Cytotoxic T-Lymphocyte-Associated Antigen 4 OR Cytotoxic T Lymphocyte Associated Antigen 4 OR Cytotoxic T-Lymphocyte Antigen 4 OR Cytotoxic T Lymphocyte Antigen 4):ti,ab,kw	335
#21	(inibitor* OR antibod* OR antagonist):ti,ab,kw	68701
#22	#20 AND #21	169
#23	MeSH descriptor: [Ipilimumab] explode all trees	208
#24	(Ipilimumab* OR Yervoy):ti,ab,kw	1307
#25	MeSH descriptor: [Immunotherapy, Active] explode all trees	2699
#26	(Immunotherap* OR (immun* AND therap*)):ti,ab,kw	79736
#27	(tyrosine kinase inhibitor):ti,ab,kw	2328
#28	MeSH descriptor: [Molecular Targeted Therapy] explode all trees	145
#29	((molecular AND therap*) OR targeted therap*):ti,ab,kw	21852
#30	#8 OR #9 OR #10 OR #11 OR #12 OR #17 OR #18 OR #19 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	107303
#31	#7 AND #30	4362
#32	(non-resectable OR nonresectable OR unresectable OR inoperable OR non-operable OR non operable):ti,ab,kw	8867
#33	#31 AND #32 with Cochrane Library publication date Between Jan 2019 and Jun 2021, in Cochrane Reviews, Trials	**359**

HCC 20 Systemtherapie



2. Recherchen zum Bereich Cholangiozellulärem Karzinom

2.1. CCA 11 Lokoregionäre Verfahren

Profitieren Patienten mit nicht-operablen Cholangiozellulärem Karzinom von einem transarteriellen Verfahren?
Population: Patienten mit Cholangiozellulärem Karzinom Interventions: TACE, TARE Comparison: Systemtherapie oder keine Therapie Outcomes: Overall survival, Progression free survival, Adverse Events, Quality of Life

Suche in PubMed (06.07.2021)

Nr	Query	Hits
	Population	
#1	**Cholangiocarcinoma[Mesh]** OR Cholangiocarcinoma*[tiab] OR Cholangiocellular Carcinoma[tiab] OR Carcinoma, Cholangiocellular[tiab] OR Carcinomas, Cholangiocellular[tiab] OR Cholangiocellular Carcinoma*[tiab]	17.135
#2	(**Neoplasms[Mesh]** OR Neoplas*[tiab] OR Tumor[tiab] OR Tumors[tiab] OR Cancer*[tiab] OR Malignanc*[tiab] OR carcinom*[tiab]) AND (bile duct*[tiab] OR biliary tract[tiab] OR bile canaliculi[tiab] OR cholangio*[tiab])	35.355
#3	#1 OR #2	37.640
	Intervention	
#4	**Chemoembolization, Therapeutic[Mesh]** OR Chemoembolization[tiab] OR TACE[tiab]	11.486
#5	**Radiotherapy[Mesh]** OR radiotherap*[tiab] OR ((radiation[tiab] OR radio[tiab]) AND (therap*[tiab] OR treatment*[tiab])) AND (**Embolization, Therapeutic[Mesh]** OR embolizat*[tiab] OR embolisat*[tiab] OR embolotherap*[tiab])	3.573
#6	internal radiotherapy[tiab] OR SIRT[tiab] OR radioembolization[tiab] OR TARE[tiab] OR microbrachytherapy[tiab]	3.758
#7	#4 OR #5 OR #6	16.996
#8	#3 AND #7	569
	Filter	
#9	(systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research	672.127

	review"[tiab] OR "integrative review"[tiab] OR "research synthesis"[tiab] OR "research integration"[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT "psycinfo database"[tiab]) OR pubmed[tiab] OR scopus[tiab] OR "web of science"[tiab] OR "data synthesis"[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR "meta-analysis as topic"[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	
#10	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.555.322
#11	#9 OR #10	2.082.595
#12	animals[mh] NOT humans[mh]	4.551.701
#13	#11 NOT #12	2.044.856
#14	#8 AND #13	86
#15	#14, Publication date 01/01/2019 – 30/06/2021, English and German articles	**25**

Recherche in der Cochrane Library (06.07.2021)

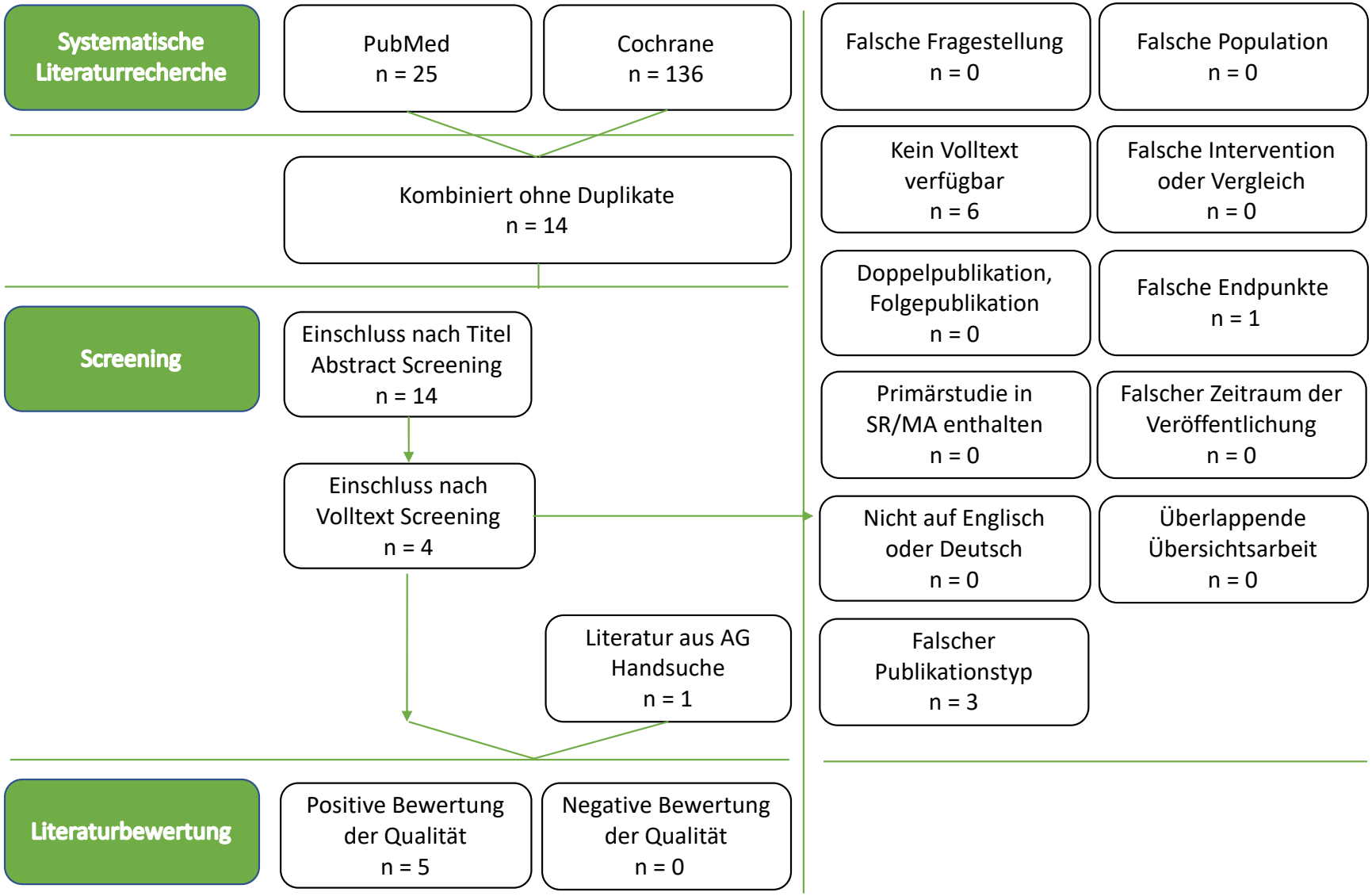
ID	Search	Hits
#1	MeSH descriptor: [Cholangiocarcinoma] explode all trees	229
#2	(Cholangiocarcinoma* OR Cholangiocellular Carcinoma OR Carcinoma, Cholangiocellular OR Carcinomas, Cholangiocellular OR Cholangiocellular Carcinoma*):ti,ab,kw	762
#3	MeSH descriptor: [Neoplasms] explode all trees	82548
#4	(Neoplas* OR Tumor OR Tumors OR Cancer* OR Malignanc* OR carcinom*):ti,ab,kw	224010
#5	(bile duct* OR biliary tract OR bile canaliculi OR cholangio*):ti,ab,kw	5853
#6	(#3 OR #4) AND #5	2180
#7	#1 OR #2 OR #6	2233
#8	MeSH descriptor: [Chemoembolization, Therapeutic] explode all trees	300

#9	(Chemoembolization OR TACE):ti,ab,kw	1611
#10	MeSH descriptor: [Radiotherapy] explode all trees	6290
#11	(radiotherap* OR ((radiation OR radio) AND (therap* OR treatment*)) AND (embolizat* OR embolisat* OR embolotherap*)):ti,ab,kw	43063
#12	(internal radiotherapy OR SIRT OR radioembolization OR TARE OR microbrachytherapy):ti,ab,kw	732
#13	#8 OR #9 OR #10 OR #11 OR #12	44997
#14	#7 AND 13	224
#15	#11 AND #21 with Cochrane Library publication date Between Jan 2019 and Jun 2021, in Cochrane Reviews, Trials	**136**

1 Dublette entfernt

Treffer aus beiden Datenbanken kombiniert: 160

CCA 11 Lokoregionäre Verfahren



2.2. CCA 15 Systemtherapie

Von welchen Systemtherapien profitieren Patient*innen mit fortgeschrittenem biliären Karzinom?
Population: Patient*innen mit Intrahepatischem CCA, Perihiläres CCA, Distales CCA, Gallenblasenkarzinom Interventions: Systemtherapie, FGFR-Inhibitore, Pemigatinib Comparison: Keine Therapie, andere Systemtherapie Outcomes: Overall survival, Progression free survival, Adverse Events, Time to Progression, Quality of Life

Suche in PubMed (06.07.2021)

Nr	Query	Hits
	Population	
#1	**Cholangiocarcinoma[Mesh]** OR Cholangiocarcinoma*[tiab] OR Cholangiocellular Carcinoma[tiab] OR Carcinoma, Cholangiocellular[tiab] OR Carcinomas, Cholangiocellular[tiab] OR Cholangiocellular Carcinoma*[tiab]	17.135
#2	(**Neoplasms[Mesh]** OR Neoplas*[tiab] OR Tumor[tiab] OR Tumors[tiab] OR Cancer*[tiab] OR Malignanc*[tiab] OR carcinom*[tiab]) AND (bile duct*[tiab] OR biliary tract[tiab] OR bile canaliculi[tiab] OR cholangio*[tiab])	35.355
#3	#1 OR #2	37.640
#4	((gallbladder[tiab] OR gall bladder[tiab] OR bilary tract[tiab]) AND (Tumor[tiab] OR Tumors[tiab] OR Cancer*[tiab] OR Malignanc*[tiab] OR carcinom*[tiab])) OR "**Gallbladder Neoplasms"[Mesh]**	15.060
#5	#3 OR #4	48.409
	Intervention	
#6	**gemcitabine [Supplementary Concept]** OR gemcitabin*[tiab] OR dFdCyd[tiab] OR LY 188011[tiab] OR LY-188011[tiab] OR Gemzar[tiab]	18.304
#7	**Cisplatin[Mesh]** OR cis-plat*[tiab] OR cis plat*[tiab] OR Platinum Diamminodichloride[tiab] OR Diamminodichloride, Platinum[tiab] OR Dichlorodiammineplatinum[tiab] OR cis-Diamminedichloroplatinum[tiab] OR cis Diamminedichloroplatinum[tiab] OR NSC-119875[tiab] OR Platino[tiab] OR Platinol[tiab] OR Biocisplatinum[tiab] OR Platidiam[tiab]	55.401
#8	**Capecitabine[Mesh]** OR capecitabin*[tiab]	7.748
#9	**Fluorouracil[Mesh]** OR 5FU[tiab] OR 5-FU[tiab] OR 5-Fluorouracil[tiab] OR 5 Fluorouracil[tiab] OR Fluoruracil[tiab] OR Adrucil[tiab] OR Carac[tiab] OR Efudix[tiab] OR Fluoro-Uracile*[tiab] OR Fluoro Uracile*[tiab] OR Efudex[tiab] OR Fluoroplex[tiab] OR Flurodex[tiab] OR Fluracedyl[tiab] OR Haemato-FU[tiab] OR Haemato FU[tiab] OR Neofluor[tiab] OR	62.014

	Onkofluor[tiab] OR Ribofluor[tiab]	
#10	**Oxaliplatin[Mesh]** OR Oxaliplatin*[tiab] OR L-OHP Cpd[tiab] OR Eloxatine[tiab] OR Eloxatin[tiab] OR ACT 078[tiab] OR ACT-078[tiab] OR ACT078[tiab]	13.029
#11	**Irinotecan[Mesh]** OR Irrinotecan[tiab] OR Camptothecin-11[tiab] OR Camptothecin 11[tiab] OR SN 38 11[tiab] OR SN-38-11[tiab] OR SN3811[tiab] OR SN 38[tiab] OR SN-38[tiab] OR NK012 Compound[tiab] OR CPT-11[tiab] OR CPT11[tiab] OR CPT 11[tiab] OR Camptosar[tiab] OR 7-Ethyl-10-hydroxycamptothecin[tiab] OR 7 Ethyl 10 hydroxycamptothecin[tiab] OR Irinotecan Hydrochloride[tiab]	8.496
#12	(**Receptors, Fibroblast Growth Factor[Mesh]** OR FGFR[tiab] OR Receptors, FGF[tiab] OR Fibroblast Growth Factor Receptor[tiab] OR Fibroblast Growth Factor Receptors[tiab] OR FGF Receptor[tiab] OR Receptor, FGF[tiab] OR FGF Receptors[tiab] OR Heparin-Binding Growth Factor Receptor[tiab] OR Heparin Binding Growth Factor Receptor[tiab]) AND (inhibitor*[tiab] OR antagonist*[tiab])	3.236
#13	**"pemigatinib" [Supplementary Concept]** OR Pemigatinib[tiab] OR Pemazyre[tiab] OR INCB054828[tiab] OR INCB-054828[tiab]	
#14	**Immunotherapy, Active[Mesh]** OR Immunotherap*[tiab] OR (immun*[tiab] AND therap*[tiab])	603.970
#15	tyrosine kinase inhibitor[tiab] OR checkpoint inhibitor[tiab]	22.129
#16	**Molecular Targeted Therapy[Mesh]** OR (molecular[tiab] AND therap*[tiab]) OR targeted therap*[tiab]	263.723
#17	**Albumin-Bound Paclitaxel[Mesh]** OR Albumin Bound Paclitaxel[tiab] OR Paclitaxel, Albumin-Bound[tiab] OR Protein-Bound Paclitaxel[tiab] OR Paclitaxel, Protein-Bound[tiab] OR Protein Bound Paclitaxel[tiab] OR Abraxane[tiab] OR ABI007[tiab] OR ABI-007[tiab] OR ABI 007[tiab]	820
#18	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	944.230
#19	#5 AND #18	4.547
Filter		
#20	(systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR	672.127

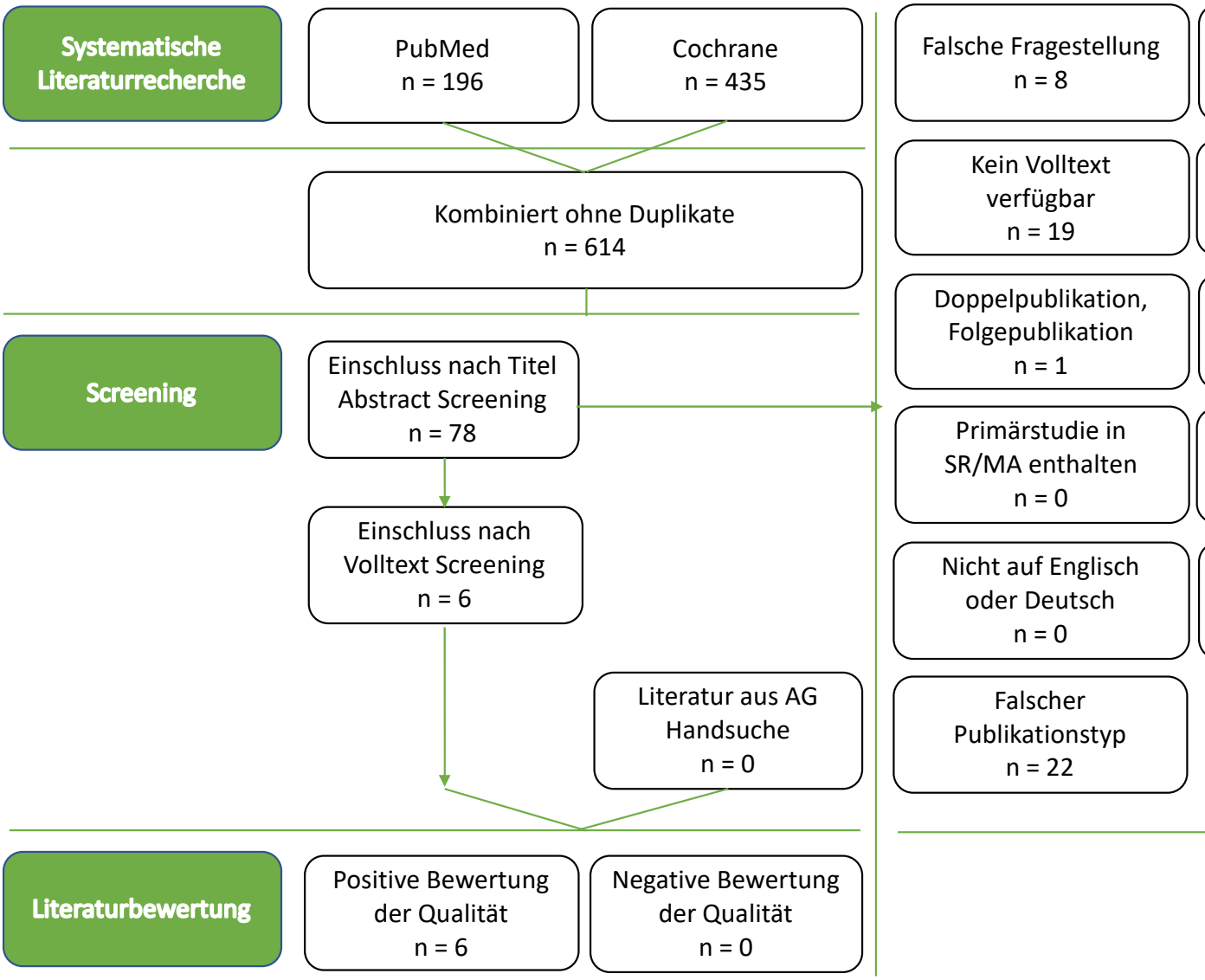
	meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	
#21	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.555.322
#22	#20 OR #21	2.082.595
#23	animals[mh] NOT humans[mh]	4.551.701
#24	#22 NOT #23	2.044.856
#25	#19 AND #24	842
#26	#25, Publication date 01/01/2019 – 30/06/2021, English and German articles	**196**

Recherche in der Cochrane Library (06.07.2021)

ID	Search	Hits
#1	MeSH descriptor: [Cholangiocarcinoma] explode all trees	229
#2	(Cholangiocarcinoma* OR Cholangiocellular Carcinoma OR Carcinoma, Cholangiocellular OR Carcinomas, Cholangiocellular OR Cholangiocellular Carcinoma*):ti,ab,kw	762
#3	MeSH descriptor: [Neoplasms] explode all trees	82548
#4	(Neoplas* OR Tumor OR Tumors OR Cancer* OR Malignanc* OR carcinom*):ti,ab,kw	224010
#5	(bile duct* OR biliary tract OR bile canaliculi OR cholangio*):ti,ab,kw	5853
#6	(#3 OR #4) AND #5	2180
#7	#1 OR #2 OR #6	2233
#8	(gallbladder carcinoma OR gall-bladder carcinoma):ti,ab,kw	281
#9	#7 OR #8	2303
#10	(gemcitabin* OR dFdCyd OR LY 188011 OR LY-188011 OR Gemzar):ti,ab,kw	6148
#11	MeSH descriptor: [Cisplatin] explode all trees	5106

#12	(Cisplatin OR cis-plat* OR cis plat* OR Platinum Diamminodichloride OR Diamminodichloride, Platinum OR Dichlorodiammineplatinum OR cis-Diamminedichloroplatinum OR cis Diamminedichloroplatinum OR NSC-119875 OR Platino OR Platinol OR Biocisplatinum OR Platidiam):ti,ab,kw	15142
#13	MeSH descriptor: [Capecitabine] explode all trees	1297
#14	(capecitabine):ti,ab,kw	4042
#15	MeSH descriptor: [Fluorouracil] explode all trees	6210
#16	(Fluorouracil OR Adrucil OR Carac OR Efudix OR Fluoro-Uracile* OR Fluoro Uracile* OR Efudex OR Fluoroplex OR Flurodex OR Fluracedyl OR Haemato-FU OR Haemato FU OR Neofluor OR Onkofluor OR Ribofluor):ti,ab,kw 10644 #20 (Oxaliplatin* OR L-OHP Cpd OR Eloxatine OR Eloxatin OR ACT 078 OR ACT-078 OR ACT078):ti,ab,kw	4934
#17	Oxaliplatin* OR L-OHP Cpd OR Eloxatine OR Eloxatin OR ACT 078 OR ACT-078 OR ACT078;ti,ab,kw	3293
#18	(Irinonectan OR Irrinotecan OR Irinononectan OR Irrinotecan OR Camptothecin OR Camptothecin OR Irinotecan Hydrochloride Hydrochloride):ti,ab,kw	965
#19	MeSH descriptor: [Receptors, Fibroblast Growth Factor] explode all trees	30
#20	(FGFR OR Receptors, FGF OR Fibroblast Growth Factor Receptor OR Fibroblast Growth Factor Receptors OR FGF Receptor OR Receptor, FGF OR FGF Receptors OR Heparin-Binding Growth Factor Receptor OR Heparin Binding Growth Factor Receptor):ti,ab,kw	582
#21	(inhibitor* OR antagonist*):ti,ab,kw	133488
#22	(#19 OR #20) AND #21	321
#23	(Pemigatinib OR Pemazyre):ti,ab,kw	8
#24	MeSH descriptor: [Immunotherapy] explode all trees	8214
#25	(Immunotherap* OR (immun* AND therap*)):ti,ab,kw	79736
#26	(tyrosine kinase inhibitor OR checkpoint inhibitor):ti,ab,kw	3030
#27	MeSH descriptor: [Molecular Targeted Therapy] explode all trees	145
#28	((molecular AND therap*) OR targeted therap*):ti,ab,kw	21852
#29	MeSH descriptor: [Albumin-Bound Paclitaxel] explode all trees	1328
#30	(Albumin Bound Paclitaxel OR Paclitaxel, Albumin-Bound OR Protein-Bound Paclitaxel OR Paclitaxel, Protein-Bound OR Protein Bound Paclitaxel OR Abraxane OR ABI007 OR ABI-007 OR ABI 007):ti,ab,kw	1653
#31	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #22 OR #23 OR #24 #25 OR #26 OR #27 OR #28 OR #29 OR #30	131668
#32	#9 AND #31 with Cochrane Library publication date Between Jan 2019 and Jun 2021, in Cochrane Reviews, Trials	**435**

CCA 15 Systemtherapie



3. Evidenztabellen

3.1. 2021 Update HCC: Systemtherapie

Inhalt: 7 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Facciorusso, A. 2021	2	Systematic review and meta-analysis (4 observational studies)
Finn, R. S. 2020	2	Randomized controlled trial, open label, phase 3.
Finn, R. S. 2020	2	Randomized controlled trial, double blind
He, S. 2021	3	Systematic review and meta-analysis (8 single arm studies, 2 RCTs, 2 retrospective cohort studies).
Parikh, N. D. 2021	2	Network meta-analysis (3 RCTs)
Rao, Q. 2020	2	Systematic review and meta-analysis (20 early phase studies and 3 RCTs)
Zhu, A. X. 2019	2	Randomized controlled trial, double blind and placebo controlled (REACH-2)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 4 Bewertung(en)

Facciorusso, A. et al. Lenvatinib versus sorafenib as first-line therapy of advanced hepatocellular carcinoma: a systematic review and meta-analysis. Am J Transl Res. 13. 2379-2387. 2021			
Evidence level/Study Types	**P - I - C**	**Outcomes/Results**	**Literature References**
Evidence level: 2 Study type: Systematic review and meta-analysis (4 observational studies) Databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Scopus, and Web of Science Search period: Inception - through	Population: Adults HCC patients not previously treated with systemic therapies (first-line setting). Intervention: Lenvatinib Comparison: Sorafenib	Primary: Overall survival Secondary: Survival rate (at 1-, and 2-year), progression-free survival (PFS), tumor response, and severe adverse event rate. Results: Five studies enrolling 1481 patients were included. No difference in terms of overall survival was detected (HR 0.81, 0.58-1.11) and median survival was 13.4 months (9.38-17.48) in lenvatinib and 11.4 months (8.46-14.47) in sorafenib patients. Lenvatinib led to a significant improvement of PFS (HR 0.67, 0.48-0.94) and median PFS was 5.88 months (3.68-8) in lenvatinib and 4.17	4 observational studies included: Kudo 2018, Kim 2020, Nakano 2020, Tomonari 2020.

November 2020. **Inclusion Criteria: (a) Patients: adults HCC patients not previously treated with systemic therapies (first-line setting); (b) Interventions: lenvatinib; (c) Comparator: sorafenib; (d) Outcome: overall survival, progression-free survival, tumor response, severe adverse event rate.** **Exclusion Criteria: (a) single cohort non-comparative studies, (b) post-hoc or sub-analyses of trials already included, (c) studies conducted in a second-line setting (i.e. after sorafenib progression).**		**months (3.08-5.25) in sorafenib patients. Lenvatinib determined a considerably higher rate of objective response (33.3%, 23.6%-43% versus 6.5%, 3.5%-9.5%; OR 7.70, 2.99-19.82), and of disease control rate (76.9%, 70.4%-83.5% versus 52.7%, 40.7%-64.6%; OR 2.41, 1.55-3.77). No difference between lenvatinib and sorafenib in terms of severe adverse event rate was observed (OR 1.31, 0.82-2.09).** **Author's Conclusion: Lenvatinib prolongs progression-free survival as compared to sorafenib in HCC patients, although this result does not translate to a significant survival benefit.**	

Methodical Notes

Funding Sources: None declared.

COI: None.

Study Quality: The risk of bias of individual studies was assessed independently by two authors in the context of the primary outcome, based on the Cochrane Collaboration's tool for assessing the risk of bias for RCTs and the Newcastle Ottawa scale [12] for non-rando- mized studies.
Quality of included studies was judged as high(2), medium(1) and low(1).

Heterogeneity: Presence of heterogeneity was measured in terms of I2 tests with I2<20% interpreted as low-level heterogeneity and I2 between 20% and 50% as moderate heterogeneity.
Heterogeneity was low to moderate in all analyses.

Publication Bias: Any po- tential publication bias was verified through visual assessment of funnel plots. No significant publication bias was found by means of visual examination of funnel plot.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of non-randomized controlled cohort / follow-up study.

He, S. et al. The Efficacy and Safety of Programmed Death-1 and Programmed Death Ligand 1 Inhibitors for the Treatment of Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. Front Oncol. 11. 626984. 2021

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References

Evidence level: 3 **Study type: Systematic review and meta-analysis (8 single arm studies, 2 RCTs, 2 retrospective cohort studies).** **Databases: Embase, PubMed, Cochrane Library and ClinicalTrials.gov.** **Search period: Inception - October 2020.** **Inclusion Criteria: (1) Study design: Randomized controlled trials (RCTs), cohort studies or single-arm studies about the treatment of HCC with PD-1 or PD-L1 inhibitors.** **(2) Population: patients with HCC.** **(3) Intervention and comparison: PD-1 or PD-L1 inhibitors were compared with placebo or other non-ICI drugs for HCC, such as sorafenib.** **(4) Outcomes: response rate, disease control rate, progression-free survival and overall survival** **Exclusion Criteria: 1) Duplicated articles. (2) Articles with too small sample size to extract data. (3) Articles that did not provide outcomes needed. (4) Articles about the combination of ICIs with other treatments for HCC. (5) Articles in other languages than English.**	**Population: Patients with HCC** **Intervention: PD-1 or PD-L1 inhibitors** **Comparison: Placebo or other non-ICI drugs for HCC, such as sorafenib**	**Primary: Response rate, disease control rate, progression-free survival and overall survival** **Secondary: -** **Results: Finally, twelve studies were included in this meta-analysis. When the corresponding outcome indicators and their 95% confidence intervals (CIs) were pooled directly, the overall RR, DCR, PFS and OS were 0.17 (0.15-0.19, I2 = 56.2%, P=0.009), 0.58 (0.55-0.61, I2 = 75.9%, P<0.001), 3.27 months (2.99-3.55, I2 = 73.0%, P=0.001), 11.73 months (10.79-12.67, I2 = 90.3%, P<0.001). Compared to the control group, treatment with ICIs significantly improved RR, PFS and OS, the OR and HRs were 3.11 (2.17-4.44, P<0.001), 0.852 (0.745-0.974, P=0.019) and 0.790 (0.685-0.911, P=0.001), respectively. However, no significant improvement in DCR was found in ICIs treatment in this meta-analysis.** **Author's Conclusion: HCC patients would benefit from ICIs treatment, however, more studies are needed in the future to provide more useful evidence for the treatment of HCC by programmed death-1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitors.**	**12 studies included: El-Khoueiry 2017, Feng 2017, Zhu 2018, Pishvaian 2018, Deva 2018, Finkelmeier 2019, Finn 2019, Yau 2019, Scheiner 2019, Qin 2020, Choi 2020, Lee 2020.**

Methodical Notes

Funding Sources: see COI section.

COI: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Study Quality: No investigation of study quality.

Heterogeneity: I2 statistic was used to evaluate the heterogeneity among studies. If I2<50% or P>0.10, then the heterogeneity was considered to be low and fixed-effects model was applied. Otherwise, the random effects model was applied.

High heterogeneity was observed in the analysis for OS (I^2 = 90%), DCR (I^2 = 76%) and PFS (I^2 = 73%). The source was not discussed or explored.

Publication Bias: Not investigated.

Notes:
Oxford level of evidence: 2 Systematic review of non-randomized controlled cohort / follow-up study.
Downgrade to evidence level 3:
Missing evaluation of study quality or publication bias. Significant heterogeneity that is not explored or explained.
Significant overlap of included studies with Rao et al 2020, but not enough to warrant exclusion (7/12 articles appear in Rao 2020).

Parikh, N. D. et al. Network meta-analysis of nivolumab plus ipilimumab in the second-line setting for advanced hepatocellular carcinoma. J Comp Eff Res. 10. 343-352. 2021

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type: Network meta-analysis (3 RCTs)** **Databases: -** **Search period: -** **Inclusion Criteria: Patients with advanced HCC who have been previously treated with sorafenib.** **Exclusion Criteria: Clinical trials for treatments indicated in specific subgroups of patients with advanced HCC (e.g., ramucirumab, indicated only for patients with AFP ≥400 ng/ml) were not included.**	**Population: Patients with advanced HCC who have been previously treated with sorafenib.** **Intervention: Not defined.** **Comparison: Not defined**	**Primary: Not defined.** **Secondary: Not defined.** **Results: Nivolumab 1 mg/kg + ipilimumab 3 mg/kg had significantly higher objective response rate (median 31.2% [95% credible interval: 19.6–44.5%]) than cabozantinib (4.2% [2.0–6.5%]) and regorafenib (4.8% [1.1–8.3%]), and significantly longer overall survival (cabozantinib: hazard ratio: 0.46 [95% credible interval: 0.27–0.79]; regorafenib: 0.56 [0.32–0.97]). Nivolumab 1 mg/kg + ipilimumab 3 mg/kg had significantly better objective response rate (difference 21.0% [4.5–37.5%]) and overall survival (hazard ratio: 0.58 [0.35–0.96]) than nivolumab monotherapy. Conclusion: Nivolumab 1 mg/kg + ipilimumab 3 mg/kg had a superior efficacy versus cabozantinib 60 mg, regorafenib 160 mg and nivolumab 3 mg/kg monotherapy as second-line therapy for advanced hepatocellular carcinoma.** **Author's Conclusion: Nivolumab 1 mg/kg + ipilimumab 3 mg/kg had a superior efficacy versus cabozantinib 60 mg, regorafenib 160 mg and nivolumab 3 mg/kg monotherapy as second-line therapy for advanced hepatocellular carcinoma.**	**Three trials included in the article: MAIC (CheckMate 040 vs CELESTIAL), CELESTIAL, RESORCE**

Methodical Notes

Funding Sources: Financial support for the study was provided by Bristol Myers Squibb.

COI: Declared, see article for sponsor list.

Study Quality: Not assesed

Heterogeneity: Not provided.

Publication Bias: Not investigated. **Notes:** **Oxford level of evidence: 1 Systematic review of randomized controlled trials.** **Downgrade to evidence level 2:** **Not a systematic review, therfor no systematic search was conducted; nor a definition of the reasearch question was provided. No assesment of study quality was performed.**

Rao, Q. et al. Clinical benefits of PD-1/PD-L1 inhibitors in advanced hepatocellular carcinoma: a systematic review and meta-analysis. Hepatol Int. 14. 765-775. 2020

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type: Systematic review and meta-analysis (20 early phase studies and 3 RCTs)** **Databases: Medline, Embase, Cochrane Library, and Web of Science** **Search period: Inception - January 31, 2020.** **Inclusion Criteria: 1) published in English; (2) study type being clinical trials, retrospective studies, and case series; (3) study including patients with advanced HCC, which can be described as "unresectable", "metastasis", "first-line treatment failure", etc.; (4) study focusing on the efficacy of checkpoint inhibitors of PD-L1 or PD-1 (but not CTLA4) such as nivolumab, pembrolizumab, atezolizumab, sintilimab, durvalumab, camrelizumab, avelumab, toripalimab, tislelizumab, or cemiplimab. PD-1/PD-L1 used in monotherapy or combination therapy was all included. Combination therapy refers to PD-1 or PD-L1 inhibitor combined with non-checkpointinhibitor agents, while monotherapy refers to only receive PD-1 or PD-L1 inhibitor therapy; (5) data for complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), objective response rate (ORR), disease control rate (DCR), overall survival (OS), progression- free survival (PFS), or median time to progression (TTP) were reported or calculable** **Exclusion Criteria: Studies with**	**Population:** **Patients with advanced HCC, which can be described as "unresectable", "metastasis", "first-line treatment failure** **Intervention:** **Checkpoint inhibitors of PD-L1 or PD-1 (but not CTLA4) such as nivolumab, pembrolizumab, atezolizumab, sintilimab, durvalumab, camrelizumab, avelumab, toripalimab, tislelizumab, or cemiplimab.** **Comparison: Not described, likely any.**	**Primary: complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), objective response rate (ORR), disease control rate (DCR), overall survival (OS), progression-free survival (PFS) and rate of adverse events (AE)** **Secondary: Subgroup analyses:** **PD-1 inhibitor or PD-L1 inhibitor and combination therapy ormonotherapy. In addition, pooled results of PD-1/PD-L1 monoclonal antibodies (mAb) combining with anti-VEGF agents were calculated separately.** **Results: A total of 20 studies with 1232 patients were included. The overall CR, PR and SD rate were 0.01 (95% CI 0.01– 0.03), 0.17 (95% CI 0.14–0.22) and 0.39 (95% CI 0.34–0.43), respectively. The overall ORR and DCR were 0.20 (95% CI 0.16–0.24) and 0.60 (95% CI 0.54–0.67), respectively. The overall PFS and OS were 3.58 months (95% CI 2.65–4.50) and 12.24 months (95% CI 10.48–14.00), respectively. For patients treated with PD-1/PD-L1 mAb combing with anti-VEGF agent, ORR was 29% (95% CI 0.15–0.43) and DCR was 77% (95% CI 0.70–0.84). For all included studies, the overall rate of AE was 0.63 (95% CI 0.45–0.78) and serious adverse events (SAE) was 0.11 (95% CI**	**23 trials included, see article for list**

sample size less than 10 patients were excluded. For the repetitive studies based on the same study patients, the latest or most comprehensive data were included.		**0.06–0.22).** **Author's Conclusion: PD-1/PD-L1 inhibitors showed favorable outcomes concerning response rates and survival periods in advanced HCC. Updated results from high-quality clinical trials are expected to validate these findings.**	

Methodical Notes

Funding Sources: None declared.

COI: Authors declare that they have no conflicts of interest.

Study Quality: "Quality of the included studies was assessed as reported in the literature, which consists of 20 items. The checklist examines the main domains including study design, population, intervention, outcome measures, statistical analysis, results/conclusions, competing interest, and sources of financial support."
No overall assesment of study quality was provided.

Heterogeneity: "Randomeffect models were adopted for all meta-analyses because of the clinical heterogeneity inherent to the data. Heterogeneity among studies was quantified by I2 test, and I2 > 50% was considered substantial heterogeneity. To reveal the high heterogeneity, subgroup analyses were performed on the basis of clinical consideration. Stratification factors included type of therapy (monotherapy vs. combination therapy), target of drug (PD-1 vs. PD-L1), evaluation criteria (RECIST vs. mRECIST), region of study (Global vs. Local), primary disease of HCC (HBV/HCV etiology ≤ 50% vs. > 50%), and CTP class (Mixture of CTP A/B/C vs. CTP A only)."
High heterogeneity was present in some analyses (DCR I^2 = 80.6%)

Publication Bias: Egger's test was performed to evaluate publication bias [17]. Stata Software, version 15.0 (StataCorp, College Station, TX) was used for meta-analysis. p value < 0.05 was considered statistically significant.
No evidence of publication bias was observed via Egger's tests in the pooled analysis of ORR, DCR, PR, SD, OS, PFS, and MTP, whereas significant publication bias was observed in the meta-analysis of CR and PD.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of non-randomized controlled cohort / follow up study.

OXFORD (2011) Appraisal Sheet: RCT: 3 Bewertung(en)

Finn, R. S. et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. New England journal of medicine. 382. 1894?1905. 2020

Population	Intervention - Comparison	Outcomes/Results

Evidence level: 2 **Study type: Randomized controlled trial, open label, phase 3.** **Number of Patient: 501 total, randomized to 336 in the atezolizumab–bevacizumab group and 165 patients in the sorafenib group.** **Recruitung Phase: March 15, 2018, and January 30, 2019.** **Inclusion Criteria: Eligible patients were 18 years of age or older and had locally advanced metastatic or unresectable hepatocellular carcinoma (or both), with the diagnosis confirmed by histologic or cytologic analysis or clinical features according to the American Association for the Study of Liver Diseases criteria for patients with cirrhosis. Eligible patients had not previously received systemic therapy for liver cancer and had measurable disease, as defined by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), that was not amenable to curative or locoregional therapies or that had progressed thereafter; a performance status score of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale (scores range from 0 to 5, with higher numbers reflecting greater disability); an A classification on the Child–Pugh liver function scale (a threecategory scale [A, B, or C], with C indicating the most severe compromise of liver function); and adequate hematologic and organ function.** **Exclusion Criteria: History of autoimmune disease, coinfection with hepatitis B or hepatitis C virus, and untreated or incompletely treated esophageal or gastric varices (assessed with esophagogastroduodenoscopy and treated according to local clinical practice) with bleeding or high risk of bleeding**	**Intervention: Atezolizumab plus Bevacizumab** **Comparison: Sorafenib**	**Primary: The coprimary end points were overall survival (the time from randomization to death from any cause) and progression-free survival (the time from randomization to disease progression according to RECIST 1.1, as assessed at an independent review facility, or death from any cause, whichever occurred first)** **Secondary: Secondary end points included the objective response rate and the duration of response according to investigator-assessed and independently- assessed RECIST 1.1 and hepatocellular carcinoma–specific modified RECIST (mRECIST) criteria; and the time to deterioration of quality of life, physical functioning, and role functioning, as reported by the patient, with deterioration defined as a decrease from baseline of 10 points or more on the EORTC QLQ–C30 maintained for two consecutive assessments or a decrease of 10 points or more in one assessment followed by death from any cause within 3 weeks. Safety and side-effect profiles were assessed on the basis of the nature, frequency, and severity of adverse events, according to NCI Common Terminology Criteria for Adverse Events, version 4.0.** **Results: The intention-to-treat population included 336 patients in the atezolizumab–bevacizumab group and 165 patients in the sorafenib group. At the time of the primary analysis (August 29, 2019), the hazard ratio for death with atezolizumab– bevacizumab as compared with sorafenib was 0.58 (95% confidence interval [CI], 0.42 to 0.79; P<0.001). Overall survival at 12 months was 67.2% (95% CI, 61.3 to 73.1) with atezolizumab–bevacizumab and 54.6% (95% CI, 45.2 to 64.0) with sorafenib. Median progression-free survival was 6.8 months (95% CI, 5.7 to 8.3) and 4.3 months (95% CI, 4.0 to 5.6) in the respective groups (hazard ratio for disease progression or death, 0.59; 95% CI, 0.47 to 0.76; P<0.001). Grade 3 or 4 adverse events occurred in 56.5% of 329 patients who received at least one dose of atezolizumab–bevacizumab and in 55.1% of 156 patients who received at least one dose of sorafenib. Grade 3 or 4**

		hypertension occurred in 15.2% of patients in the atezolizumab–bevacizumab group; however, other high-grade toxic effects were infrequent. **Author's Conclusion: In patients with unresectable hepatocellular carcinoma, atezolizumab combined with bevacizumab resulted in better overall and progression-free survival outcomes than sorafenib.**

Methodical Notes

Funding Sources: (Funded by F. Hoffmann–La Roche/Genentech.

COI: Declared, see article for list.

Randomization: 2: 1 randomization was performed through an interactive voice-response or Web-response system in permuted blocks, stratified by geographic region (Asia excluding Japan vs. the rest of the world), macrovascular invasion or extrahepatic spread of disease (presence vs. absence), baseline alphafetoprotein level (<400 vs. ≥400 ng per milliliter), and ECOG performance status (0 vs. 1).

Blinding: Open label study but blinded independent review of imaging for progressionfree survival was selected for the coprimary end point.

Dropout Rate/ITT-Analysis: Intention-to-treat analysis was performed for efficacy outcomes

Notes:
Oxford level of evidence: 2 Randomized controlled trial

Finn, R. S. et al. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. J Clin Oncol. 38. 193-202. 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: Randomized controlled trial, double blind** **Number of Patient: 413 patients randomized 2:1 (278 pembrolizumab, 135 placebo).** **Recruitung Phase: Between May 31, 2016, and November 23, 2017.** **Inclusion Criteria: Eligible patients were age 18 years or older with a radiographic or pathologic diagnosis of HCC, radiographic progression during or intolerance to sorafenib treatment, and**	**Intervention: 200 mg of pembrolizumab every 3 weeks for at least 35 cycles (approximately 2 years) plus best supportive care (BSC).** **Comparison: Saline placebo intravenously every 3 weeks for at least 35 cycles (approximately 2 years) plus best supportive care (BSC).**	**Primary: Overall survival (OS) and progression-free survival (PFS).** **Secondary: Objective response rate, partial response, disease control rate, duration of response, time to progression, and safety and tolerability.** **Results: Between May 31, 2016, and November 23, 2017, 413 patients were randomly assigned. As of January 2, 2019, median follow-up was 13.8 months for pembrolizumab and 10.6 months for placebo. Median OS was 13.9 months (95% CI, 11.6 to 16.0 months) for pembrolizumab versus 10.6 months (95% CI, 8.3 to 13.5 months) for placebo (hazard ratio [HR], 0.781; 95% CI, 0.611 to 0.998; P = .0238). Median PFS for pembrolizumab was 3.0 months (95% CI, 2.8 to 4.1 months) versus 2.8 months (95% CI, 2.5 to 4.1 months) for placebo at the first interim analysis (HR, 0.775; 95% CI, 0.609 to 0.987; P =**

Barcelona Clinic Liver Cancer stage C disease or stage B disease11 not amenable to or refractory to locoregional therapy. Patients had Child-Pugh liver class A disease,12 an Eastern Cooperative Oncology Group performance score of 0 or 1, and otherwise adequate organ function. **Exclusion Criteria: Patients who had received prior immunotherapy, including anti–PD-1, anti–PD-1 ligand (PD-L1), or anti–PD-L2 agents, or previous systemic therapy for HCC in the advanced setting other than sorafenib were excluded, as were those with clinically apparent ascites on physical examination, main portal vein invasion or inferior vena cava or cardiac involvement of HCC on the basis of imaging, or clinically diagnosed hepatic encephalopathy within the past 6 months.**	17 17	**.0186) and 3.0 months (95% CI, 2.8 to 4.1 months) versus 2.8 months (95% CI, 1.6 to 3.0 months) at final analysis (HR, 0.718; 95% CI, 0.570 to 0.904; P = .0022). Grade 3 or higher adverse events occurred in 147 (52.7%) and 62 patients (46.3%) for pembrolizumab versus placebo; those that were treatment related occurred in 52 (18.6%) and 10 patients (7.5%), respectively. No hepatitis C or B flares were identified.** **Author's Conclusion: In this study, OS and PFS did not reach statistical significance per specified criteria. The results are consistent with those of KEYNOTE-224, supporting a favorable risk-to-benefit ratio for pembrolizumab in this population.**

Methodical Notes

Funding Sources: Supported by Merck Sharp & Dohme, a subsidiary of Merck, Kenilworth, NJ.

COI: Declared, see article for list.

Randomization: Randomization was performed using an interactive voice-response/integrated Web-response system, with stratification by geographic region (Asia excluding Japan v non-Asia including Japan), macrovascular invasion (MVI; yes v no), and a-fetoprotein level (, 200 v $ 200 ng/mL).

Blinding: Double-blind study.

Dropout Rate/ITT-Analysis: Efficacy was assessed in the intention-to-treat population.

Notes:
Oxford level of evidence: 2 Randomized controlled trial.

Zhu, A. X. et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased ?-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 20. 282-296. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: Randomized controlled trial, double blind and placebo controlled (REACH-2)**	**Intervention: Ramucirumab** **Comparison: Placebo**	**Primary: Overall survival.** **Secondary: were investigator-assessed progression-free survival, which was defined as time from randomisation to radiographic progression or death,**

Number of Patient: 292 randomized 2:1 (197 intervention, 95 placebo group). **Recruitung Phase: Between July 26, 2015, and Aug 30, 2017,** **Inclusion Criteria: Eligible patients had a diagnosis of hepatocellular carcinoma based on either histopathological or cytological findings or, in the absence of histological confirmation, a diagnosis of cirrhosis and hepatocellular carcinoma with classical imaging characteristics. Eligible patients also had Barcelona Clinic Liver Cancer (BCLC) stage B or C disease that was refractory or not amenable to locoregional therapy, Child-Pugh class A liver disease, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, serum α-fetoprotein concentrations of 400 ng/mL or higher (as measured by a local laboratory), adequate haematological and biochemical parameters, and were aged 18 years or older.** **Sorafenib was the only previous systemic treatment for hepatocellular carcinoma that was allowed, and it had to have been discontinued at least 14 days before randomisation because of intolerance or disease progression. Eligible patients also had at least one measurable lesion as per the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) and adequate organ function.** **Exclusion Criteria: Patients were excluded if they had hepatic locoregional therapy after sorafenib, major surgery in the 28 days before randomisation, a history of or current hepatic encephalopathy, previous liver transplantation, oesophageal or gastric varices requiring endoscopic treatment, and uncontrolled arterial hypertension. We also excluded**		**time from randomisation to radiographic progression, the proportion of patients who achieved an objective response, patient-reported disease-related symptoms (assessed with FHSI-8), time to deterioration of FHSI-8 score, time to deterioration in ECOG performance status, and safety** **Results: Between July 26, 2015, and Aug 30, 2017, 292 patients were randomly assigned, 197 to the ramucirumab group and 95 to the placebo group. At a median follow-up of 7·6 months (IQR 4·0–12·5), median overall survival (8·5 months [95% CI 7·0–10·6] vs 7·3 months [5·4–9·1]; hazard ratio [HR] 0·710 [95% CI 0·531–0·949]; p=0·0199) and progression-free survival (2·8 months [2·8–4·1] vs 1·6 months [1·5–2·7]; 0·452 [0·339–0·603]; p<0·0001) were significantly improved in the ramucirumab group compared with the placebo group. The proportion of patients with an objective response did not differ significantly between groups (nine [5%] of 197 vs one [1%] of 95; p=0·1697). Median time to deterioration in FHSI-8 total scores (3·7 months [95% CI 2·8–4·4] vs 2·8 months [1·6–2·9]; HR 0·799 [95% CI 0·545–1·171]; p=0·238) and ECOG performance statuses (HR 1·082 [95% CI 0·639–1·832]; p=0·77) did not differ between groups. Grade 3 or worse treatment-emergent adverse events that occurred in at least 5% of patients in either group were hypertension (25 [13%] in the ramucirumab group vs five [5%] in the placebo group), hyponatraemia (11 [6%] vs 0) and increased aspartate aminotransferase (six [3%] vs five [5%]). Serious adverse events of any grade and cause occurred in 68 (35%) patients in the ramucirumab group and 28 (29%) patients in the placebo group. Three patients in the ramucirumab group died from treatment-emergent adverse events that were judged to be related to study treatment (one had acute kidney injury, one had hepatorenal syndrome, and one had renal failure).** **Author's Conclusion: REACH-2 met its primary endpoint, showing improved overall survival for ramucirumab compared with placebo in patients with hepatocellular carcinoma and α-fetoprotein concentrations of at least 400 ng/mL who had previously received sorafenib. Ramucirumab was well tolerated, with a manageable safety profile. To our knowledge, REACH-2 is the first positive phase 3 trial done in a biomarker-selected patient population with hepatocellular carcinoma.**

patients with clinically meaningful ascites resulting from cirrhosis.		

Methodical Notes

Funding Sources: This study was funded by Eli Lilly. The study funder had roles in study design of REACH and REACH-2, and was involved in data collection, analysis, and interpretation, and writing of the report

COI: Declared, see article for extensive list.

Randomization: Interactive web response system with a computergenerated random sequence. Randomisation was stratified by geographical region (region 1 [Americas, Europe, Australia, Israel] vs region 2 [Asia, excluding Japan] vs region 3 [Japan]), macrovascular invasion (yes vs no), and ECOG performance status (0 vs 1).

Blinding: Double blind study.

Dropout Rate/ITT-Analysis: Efficacy outcomes were assessed with intention-to-treat, safety analysis was performed in participants who received one dose of the study drug.

Notes:
Oxford level of evidence: 2 Randomized controlled trial.

3.2. 2021 Update CCA: Systemtherapie

Inhalt: 6 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Abou-Alfa, G. K. 2020	2	Randomized controlled trial, phase 3, placebo controlled, double blind.
Abou-Alfa, G. K. 2020	3	Phase 2 study, single arm, open label, (FIGHT-202)
Javle, M. 2021	3	Phase 2 trial, non-randomized, open label (BGJ398).
Lamarca, A. 2021	2	Randomized controlled trial, phase 3, open label.
Markussen, A. 2020	2	Randomized phase 2 trial
Subbiah, V. 2020	3	Phase 2 open label, single arm study.

OXFORD (2011) Appraisal Sheet: RCT: 6 Bewertung(en)

Abou-Alfa, G. K. et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. The lancet. Oncology. 21. 796?807. 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: Randomized controlled trial, phase 3, placebo controlled, double blind. Number of Patient: 185 randomized 2:1 to ivosidenib (124) and placebo (61). IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy) patients. Recruitung Phase: Between Feb 20, 2017, and Jan 31, 2019. Inclusion Criteria: Eligible patients were aged 18 years or older with histologically confirmed, advanced, IDH1-mutant cholangiocarcinoma. Up to two previous treatment regimens for advanced	Intervention: Ivosidenib 500 mg was given orally once daily in continuous 28-day cycles (plus or minus 2 days), starting on cycle 1 day 1. Comparison: Placebo orally once daily in continuous 28-day cycles (plus or minus 2 days), starting on cycle 1 day 1.	Primary: progression-free survival as assessed by the central IRC based on RECIST version 1.1 assessment. Progression-free survival was defined as the time from the date of randomisation to the date of first docu mentation of disease progression or death owing to any cause, whichever occurred first. Secondary: objective response rate by RECIST version 1.1; duration of response and time to response (assessed by the investigator and IRC); progression-free survival (by investigator review); pharmacokinetics and pharma codynamics; QOL assessed by EORTC QLQ-C30 and EORTC QLQ-BIL21 change from baseline and PGI-C anchor questions; and EQ-5D-5L for health economic modelling.

disease (unresectable or metastatic), with one gemcitabine-based or fluorouracil-based chemotherapy and no previous mutant IDH inhibitor therapy, were required. Progression at inclusion was determined and confirmed by the investigator on the basis of available medical history or imaging report. **Life expectancy of at least 3 months; an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1;10 a measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; and adequate haematological, hepatic, and renal function. IDH1 mutation status was confirmed centrally by next-generation sequencing on formalin-fixed, paraffin-embedded tumour tissue (from a banked tumour sample collected preferably within the last 3 years or a fresh tumour biopsy) by means of the Oncomine Focus Assay.** **Exclusion Criteria: Patients were excluded if they had received systemic anticancer therapy or an investigational agent less than 2 weeks before day 1 (washout from previous immune-based anticancer therapy being 4 weeks); had received radiotherapy to metastatic sites of disease less than 2 weeks before day 1; or had undergone hepatic irradiation, chemo embolisation, and radio frequency ablation less than 4 weeks before day 1. Patients with the following comorbidities were not permitted: active cardiac disease within 6 months before the start of study treatment; myocardial infarction; unstable angina or stroke; active hepatitis B or C viral infections; known positive HIV antibody results, or AIDS-related illness**		**Results: Between Feb 20, 2017, and Jan 31, 2019, 230 patients were assessed for eligibility, and as of the Jan 31, 2019 data cutoff date, 185 patients were randomly assigned to ivosidenib (n=124) or placebo (n=61). Median follow-up for progression-free survival was 6·9 months (IQR 2·8–10·9). Progression-free survival was significantly improved with ivosidenib compared with placebo (median 2·7 months [95% CI 1·6–4·2] vs 1·4 months [1·4–1·6]; hazard ratio 0·37; 95% CI 0·25–0·54; one-sided p<0·0001). The most common grade 3 or worse adverse event in both treatment groups was ascites (four [7%] of 59 patients receiving placebo and nine [7%] of 121 patients receiving ivosidenib). Serious adverse events were reported in 36 (30%) of 121 patients receiving ivosidenib and 13 (22%) of 59 patients receiving placebo. There were no treatment-related deaths.** **Author's Conclusion: Progression-free survival was significantly improved with ivosidenib compared with placebo, and ivosidenib was well tolerated. This study shows the clinical benefit of targeting IDH1 mutations in advanced, IDH1-mutant cholangiocarcinoma.**

Methodical Notes

Funding Sources: Agios Pharmaceuticals: The funder had a role in study design, data collection, data analysis, and data interpretation. Medical writing support was provided by the funder. The first and last authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

COI: Declared, see article for list.

Randomization: Patients were randomly assigned (2:1) to ivosidenib or matched placebo, with a block size of 6, and stratified by number of previous systemic treatment regimens for advanced disease (one vs two). Randomisation into the two treatment groups was implemented by an interactive web-based response system and generated by an independent statistical group.

Blinding: Double-blinded study.

Dropout Rate/ITT-Analysis: The intention-to-treat population was used for the primary efficacy analyses.

Safety was assessed in all patients who had received at least one dose of ivosidenib or placebo. **Notes:** **Oxford level of evidence: 2 Randomized controlled trial.**

Abou-Alfa, G. K. et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol. 21. 671-684. 2020		
Population	**Intervention - Comparison**	**Outcomes/Results**
Evidence level: 3 **Study type: Phase 2 study, single arm, open label, (FIGHT-202)** **Number of Patient: 146 patients assigned to one cohorts patients with FGFR2 fusions or rearrangements, patients with other FGF/FGFR alterations, or patients with no FGF/FGFR alterations.** **Recruitung Phase: Between Jan 17, 2017, and March 22, 2019.** **Inclusion Criteria: patients were aged 18 years or older, had a histological or cytological diagnosis of locally advanced or metastatic cholangiocarcinoma with documented disease progression following at least one previous systemic cancer therapy (previous treatment with selective FGFR inhibitors was not permitted), radiologically measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, life expectancy of at least 12 weeks, and previously treated and clinically stable brain or CNS metastases without corticosteroids for at least 4 weeks (corticosteroids were otherwise allowed without restriction). Patients were also required to have adequate hepatic and renal function (total bilirubin <1·5 × upper limit of normal [ULN], or ≥2·5 × ULN for Gilbert syndrome or a disease involving the liver; aspartate aminotransferase and alanine aminotransferase ≤2·5 × ULN; and creatinine clearance >30 mL/min calculated with the Cockcroft-Gault formula), serum phosphate less than or equal to the institutional ULN, and serum calcium within the institutional normal range**	**Intervention: Assignment to one of three cohorts: patients with FGFR2 fusions or rearrangements, patients with other FGF/FGFR alterations, or patients with no FGF/FGFR alterations. All enrolled patients received a starting dose of 13·5 mg oral pemigatinib once daily (21-day cycle; 2 weeks on, 1 week off)** **Comparison: -**	**Primary: The proportion of patients with FGFR2 fusions or rearrangements who achieved an objective response (best overall response of confirmed complete response or confirmed partial response), assessed by independent central review.** **Secondary: The proportion of patients with an objective response in patients with other FGF/FGFR alterations, in all patients with FGF/FGFR alterations, and in patients with no FGF/FGFR alterations, and duration of response, the proportion of patients with disease control, progression-free survival, overall survival, safety in all cohorts, and population pharmacokinetics** **Results: Between Jan 17, 2017, and March 22, 2019, 146 patients were enrolled: 107 with FGFR2 fusions or rearrangements, 20 with other FGF/FGFR alterations, 18 with no FGF/FGFR alterations, and one with an undetermined FGF/FGFR alteration. The median follow-up was 17·8 months (IQR 11·6–21·3). 38 (35·5% [95% CI 26·5–45·4]) patients with FGFR2 fusions or rearrangements achieved an objective response (three complete responses and 35 partial responses). Overall, hyperphosphataemia was the most common all-grade adverse event irrespective of cause (88 [60%] of 146 patients). 93 (64%) patients had a grade 3 or worse adverse event (irrespective of cause); the most frequent were hypophosphataemia (18 [12%]), arthralgia (nine [6%]), stomatitis (eight [5%]), hyponatraemia (eight [5%]), abdominal pain (seven [5%]), and fatigue (seven [5%]). 65 (45%) patients had serious adverse events; the most frequent were abdominal pain (seven [5%]), pyrexia (seven [5%]), cholangitis (five [3%]), and pleural effusion (five [3%]). Overall, 71 (49%) patients died during the study, most frequently because of disease**

Exclusion Criteria: Eligible patients had no history of HIV infection, did not have active hepatitis B or C virus infection, did not have an abnormal echocardiogram or uncontrolled cardiac disease, had no history or current evidence of ectopic mineralisation or calcification, and had no clinically significant corneal or retinal disorders confirmed by ophthalmological examination.		**progression (61 [42%]); no deaths were deemed to be treatment related.** **Author's Conclusion: These data support the therapeutic potential of pemigatinib in previously treated patients with cholangiocarcinoma who have FGFR2 fusions or rearrangements.**

Methodical Notes

Funding Sources: Incyte Corporation.

COI: Declared, see article for list.

Randomization: Non randomized study.

Blinding: Open-label study.

Dropout Rate/ITT-Analysis: All enrolled patients were analyzed,

Notes:
Oxford level of evidence: 3 Non-randomized controlled cohort.

Javle, M. et al. Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. Lancet Gastroenterol Hepatol. . . 2021

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type: Phase 2 trial, non-randomized, open label (BGJ398).** **Number of Patient: 122 previously treated patients with advanced or metastatic cholangiocarcinomapatients, of whom 108 with FGFR2 fusions or rearrangements.** **Recruitung Phase: Between June 23, 2014, and March 31, 2020.** **Inclusion Criteria: Eligible patients in cohort 1 were aged 18 years or older and had histologically or cytologically confirmed cholangiocarcinoma. Patients with cancer of the gallbladder or ampulla of Vater were not eligible. Patients were required to have local or central laboratory determination of FGFR2 fusions or rearrangements by a validated test done by an accredited laboratory, previous treatment with at least one regimen containing gemcitabine for advanced or metastatic disease, documented**	**Intervention: Infigratinib** **Comparison: -**	**Primary: objective response rate, defined as the proportion of patients with a best overall response of a confirmed complete or partial response, as assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors, version 1.1** **Secondary: Secondary endpoints were investigatorassessed objective response rate, BICR-assessed and investigator-assessed best overall response, BICRassessed and investigator-assessed disease control rate , time to response, BICR-assessed and investigator-assessed progression-free survival per RECIST (version 1.1), overall survival (defined as the time from the start of treatment to death due to any cause), safety, and tolerability.** **Results: Between June 23, 2014, and March 31, 2020, 122 patients were**

progression following that previous regimen or discontinuation from the previous regimen because of toxicity, an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less (with an ECOG performance status of 2 considered on a case-bycase basis), and evidence of measurable disease according to RECIST, version 1.1. **Exclusion Criteria: Patients were not eligible if they had been previously treated, or were currently being treated, with a mitogen-activated protein kinase kinase inhibitor, infigratinib, or another selective FGFR inhibitor. Patients were also excluded if they had neurological symptoms related to an underlying disease that required increasing doses of corticosteroids, current evidence of corneal or retinal disorders (confirmed by ophthalmic examination), or a history or current evidence of extensive tissue calcification. Patients with an absolute neutrophil count of less than 1000 cells per #L, a platelet count of less than 75 000 platelets per #L, a haemoglobin concentration of less than 9·0 g/dL, a total bilirubin concentration of more than 1·5-times the upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase concentrations of more than 2·5 × the ULN (>5 × the ULN in the presence of liver metastases), a serum creatinine concentration of more than 1·5-times the ULN, and a calculated or measured creatinine clearance of less than 45 mL/min, were excluded.**		**enrolled into our study, of whom 108 with FGFR2 fusions or rearrangements received at least one dose of infigratinib and comprised the full analysis set. After a median follow-up of 10·6 months (IQR 6·2–15·6), the BICR-assessed objective response rate was 23·1% (95% CI 15·6–32·2; 25 of 108 patients), with one confirmed complete response in a patient who only had non-target lesions identified at baseline and 24 partial responses. The most common treatment-emergent adverse events of any grade were hyperphosphataemia (n=83), stomatitis (n=59), fatigue (n=43), and alopecia (n=41). The most common ocular toxicity was dry eyes (n=37). Central serous retinopathy-like and retinal pigment epithelial detachment-like events occurred in 18 (17%) patients, of which ten (9%) were grade 1, seven (6%) were grade 2, and one (1%) was grade 3. There were no treatment-related deaths.** **Author's Conclusion: Infigratinib has promising clinical activity and a manageable adverse event profile in previously treated patients with locally advanced or metastatic cholangiocarcinoma harbouring FGFR2 gene fusions or rearrangements, and so represents a potential new therapeutic option in this setting.**

Methodical Notes

Funding Sources: QED Therapeutics and Novartis.

COI: Declared, see article for list.

Randomization: Non-randomized study.

Blinding: Open-label study.

Dropout Rate/ITT-Analysis: Intention to treat principle not applicable, 14 patients were excluded due to missing FGFR2 fusions or rearrangement

Notes:
Oxford level of evidence: 3 Non-randomized controlled cohort.

Lamarca, A. et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 22. 690-701. 2021

Population	**Intervention - Comparison**	**Outcomes/Results**

Evidence level: 2 **Study type: Randomized controlled trial, phase 3, open label.** **Number of Patient: 162 randomized 1:1 to FOLFOX (n=81) or ASC alone (n=81).** **Recruitung Phase: Between March 27, 2014, and Jan 4, 2018** **Inclusion Criteria: Patients were eligible if they were aged 18 years or older and had histologically or cytologically verified locally advanced or metastatic biliary tract cancer (including cholangiocarcinoma, gallbladder carcinoma, and ampullary carcinoma) with documented radiological disease progression to previous first-line cisplatin and gemcitabine chemotherapy. Any other form of first-line systemic chemotherapy or additional line of first-line chemotherapy (including rechallenge with cisplatin and gemcitabine) was not allowed. Patients who had been started on firstline cisplatin and gemcitabine for whom the cisplatin was stopped due to toxicity (with continuation of gemcitabine) were eligible.** **Exclusion Criteria: Patients with clinical evidence of metastatic disease to the brain and those with clinically significant cardiovascular disease were excluded**	**Intervention: Active symptom control (ASC) and FOLFOX. FOLFOX chemotherapy was administered intravenously every 2 weeks for a maximum of 12 cycles (oxaliplatin 85 mg/m², L-folinic acid 175 mg [or folinic acid 350 mg], fluorouracil 400 mg/m² [bolus], and fluorouracil 2400 mg/m² as a 46-h continuous intravenous infusion).** **Comparison: ASC alone. FOLFOX chemotherapy was administered intravenously every 2 weeks for a maximum of 12 cycles (oxaliplatin 85 mg/m², L-folinic acid 175 mg [or folinic acid 350 mg], fluorouracil 400 mg/m² [bolus], and fluorouracil 2400 mg/m² as a 46-h continuous intravenous infusion).**	**Primary: Overall survival, defined as the time from randomisation to death from any cause.** **Secondary: progression-free survival (time between randomisation and radiological disease progression or death of any cause, whichever occurred first) and radiological response as per RECIST version 1.1 for the ASC plus FOLFOX group only; and assessment of adverse events, quality of life, and health economics in both groups.** **Results: Between March 27, 2014, and Jan 4, 2018, 162 patients were enrolled and randomly assigned to ASC plus FOLFOX (n=81) or ASC alone (n=81). Median follow-up was 21·7 months (IQR 17·2–30·8). Overall survival was significantly longer in the ASC plus FOLFOX group than in the ASC alone group, with a median overall survival of 6·2 months (95% CI 5·4–7·6) in the ASC plus FOLFOX group versus 5·3 months (4·1–5·8) in the ASC alone group (adjusted hazard ratio 0·69 [95% CI 0·50–0·97]; p=0·031). The overall survival rate in the ASC alone group was 35·5% (95% CI 25·2–46·0) at 6 months and 11·4% (5·6–19·5) at 12 months, compared with 50·6% (39·3–60·9) at 6 months and 25·9% (17·0–35·8) at 12 months in the ASC plus FOLFOX group. Grade 3–5 adverse events were reported in 42 (52%) of 81 patients in the ASC alone group and 56 (69%) of 81 patients in the ASC plus FOLFOX group, including three chemotherapy-related deaths (one each due to infection, acute kidney injury, and febrile neutropenia). The most frequently reported grade 3–5 FOLFOX-related adverse events were neutropenia (ten [12%] patients), fatigue or lethargy (nine [11%] patients), and infection (eight [10%] patients).** **Author's Conclusion: The addition of FOLFOX to ASC improved median overall survival in patients with advanced biliary tract cancer after progression on cisplatin and gemcitabine, with a clinically meaningful increase in 6-month and 12-month overall survival rates. To our knowledge, this trial is the first prospective, randomised study providing reliable, high-quality evidence to allow an informed discussion with patients of the potential benefits and risks from second-line FOLFOX chemotherapy in advanced biliary tract cancer. Based on these findings, FOLFOX should become standard-of-care chemotherapy in second-line treatment for advanced biliary tract cancer and the reference regimen for further clinical trials.**

Methodical Notes
Funding Sources: Cancer Research UK, StandUpToCancer, AMMF (The UK Cholangiocarcinoma Charity), and The Christie Charity, with additional funding from The Cholangiocarcinoma Foundation and the Conquer Cancer Foundation Young Investigator Award for translational research **COI: Declared, see article for list.** **Randomization: Randomisation was done following a minimisation algorithm using platinum sensitivity, serum albumin concentration, and stage as stratification factors.** **Blinding: open-label study.** **Dropout Rate/ITT-Analysis: All analyses were carried out as intention to treat. Similar number of losses to follow-up in each group.** **Notes:** **Oxford level of evidence: 2 Randomized controlled trial.**

Markussen, A. et al. Treatment of Patients with Advanced Biliary Tract Cancer with Either Oxaliplatin, Gemcitabine, and Capecitabine or Cisplatin and Gemcitabine-A Randomized Phase II Trial. Cancers (Basel). 12. . 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: Randomized phase 2 trial** **Number of Patient: 100 patients were included. 50 patients received oxaliplatin, gemcitabine, and capecitabine. 50 received cisplatin and gemcitabine.** **Recruitung Phase: July 2014 - November 2017.** **Inclusion Criteria: Patients were eligible for the study if they were ≥18 years and had a histopathological diagnosis of nonresectable, recurrent, or metastatic BTC or a cytologic diagnosis of carcinoma, in combination with radiological findings confirming the diagnosis. Intrahepatic, perihilar, extrahepatic, and gallbladder cancers could be included—but not ampullary cancer.** **Exclusion Criteria: The exclusion criteria were**	**Intervention: Oxaliplatin 50 mg/m2 every second week, with an infusion time of 30 min, gemcitabine 1000 mg/m2 every second week, with an infusion time of 30 min, and capecitabine 650 mg/m2 twice-daily and continually in a 2-week cycle. The combined treatment time in the outpatient clinic was 2 h.** **Comparison: Cisplatin and gemcitabine, each cycle lasted 3 weeks and comprised cisplatin 25 mg/m2, with an infusion time of 60 min, and gemcitabine 1000 mg/m2, with an infusion time of 30 min, on day 1 and day 8.**	**Primary: PFS** **Secondary: OS, response rate, and toxicity.** **Results: One-hundred patients were included. Forty-seven patients received oxaliplatin, gemcitabine, and capecitabine with a median progression-free survival (mPFS) of 5.7 months (95% CI 3.0–7.8) and a median overall survival (mOS) of 8.7 months (95% CI 6.5–11.2). Forty-nine patients received cisplatin and gemcitabine with a mPFS of 7.3 months (95% CI 6.0–8.7) and a mOS of 12.0 months (95% CI 8.3–16.7). This trial confirms a mOS of 12 months with cisplatin and gemcitabine, as found in earlier trials. With a superior tumor control rate of 79% vs. 60% (p = 0.045), a difference in the mPFS of 1.6 months (HR = 0.721, p = 0.1), and a difference in the mOS of 3.3 months (HR = 0.731, p = 0.1), cisplatin and gemcitabine should still be considered the standard first-line treatment for advanced biliary tract cancer.** **Author's Conclusion: Our conclusion is that, even though the triple combination was more convenient in terms of the infusion time and number of visits, cisplatin and gemcitabine should still be considered the standard first-line treatment for BTC.**

clinically significant comorbidity, concurrent cancer, pregnancy, breastfeeding, or known intolerance to one or more of the study drugs.		

Methodical Notes

Funding Sources: This investigation has received no external funding.

COI: The authors have declared no conflict of interest.

Randomization: The randomization was done by permutated block randomization, stratified by performance status.

Blinding: Not blinded.

Dropout Rate/ITT-Analysis: Similar dropout rates when comparing groups. No intention to treat analysis was performed.

Notes:
Oxford level of evidence: 2 Randomized controlled trial
No intention to treat analysis was performed. Partial blinding could have been achieved.

Subbiah, V. et al. Dabrafenib plus trametinib in patients with BRAF(V600E)-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. Lancet Oncol. 21. 1234-1243. 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type: Phase 2 open label, single arm study.** **Number of Patient: 43 patients with BRAFV600E-mutated biliary tract cancer.** **Recruitung Phase: March 12, 2014, and July 18, 2018.** **Inclusion Criteria: Patients were eligible for inclusion in the biliary tract cancer cohort if they were aged 18 years or older; had BRAFV600E-mutated histologically or cytologically confirmed unresectable, metastatic, locally advanced, or recurrent adenocarcinoma of the biliary tract or gallbladder with no other standard treatment options available; measurable disease, based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1;19 an Eastern**	**Intervention: +Patients were treated with dabrafenib 150 mg twice daily and trametinib 2 mg once daily (both oral administration) until unacceptable toxicity, disease progression, death, or discontinuation for any other reason. Treatment beyond progression was allowed if the patient was expected to receive clinical benefit.** **Comparison: -**	**Primary: overall response rate, defined as either a complete or partial response using RECIST version 1.1, assessed both by the investigator and by independent central review.** **Secondary: Progression-free survival, duration of response, overall survival, and safety** **Results: Between March 12, 2014, and July 18, 2018, 43 patients with BRAFV600E-mutated biliary tract cancer were enrolled to the study and were evaluable. Median follow-up was 10 months (IQR 6–15). An investigator-assessed overall response was achieved by 22 (51%, 95% CI 36–67) of 43 patients. An independent reviewer-assessed overall response was achieved by 20 (47%, 95% CI 31–62) of 43 patients. The most common grade 3 or worse adverse event was increased γ-glutamyltransferase in five (12%) patients. 17 (40%) patients had serious adverse events and nine (21%) had treatment-related serious adverse events, the most frequent of which was**

Cooperative Oncology Group performance status of 0–2; and adequate baseline organ function. Patients must have progressed on or shown intolerance to treatment with a gemcitabine-based chemotherapy regimen **Exclusion Criteria: Since the safety of dabrafenib and trametinib combination treatment has not been studied in biliary obstruction, we excluded patients with biliary tract cancer who had more than three times the upper limit of normal bilirubin levels or untreatable biliary obstruction. Therefore, patients with jaundice were not treated.**		**pyrexia (eight [19%]). No treatment-related deaths were reported.** **Author's Conclusion: Dabrafenib plus trametinib combination treatment showed promising activity in patients with BRAFV600E-mutated biliary tract cancer, with a manageable safety profile. Routine testing for BRAFV600E mutations should be considered in patients with biliary tract cancer.**

Methodical Notes

Funding Sources: sponsored by GlaxoSmithKline, with input from a steering committee; the current sponsor of the trial is Novartis Pharmaceuticals. Data collection and data analysis were initially done by GlaxoSmithKline before responsibility was assumed by Novartis. Data interpretation was done by all authors, including employees of Novartis. Medical writing support was funded by Novartis. All authors had full access to study data and share final responsibility for the content of the report and the decision to submit for publication.

COI: Declared, see article for list.

Randomization: Single arm, not randomized.

Blinding: Open-label

Dropout Rate/ITT-Analysis: Not applicable.

Notes:
Oxford level of evidence: 3 non-randomized controlled cohort.

3.3. 2021 Update CCA: Lokoregionäre Verfahren

Inhalt: 5 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Edeline, J. 2020	3	Phase 2 clinical trial
Ke, Q. 2020	2	Systematic review and meta-analysis (22 cohort studies)
Liu, J. B. 2020	2	Systematic review and meta-analysis (9 observational studies)
Mosconi, C. 2021	3	Systemic Review and Meta-Analysis (31 observational studies included).
Zhen, Y. 2019	3	Systematic review and meta-analysis (16 cohort studies)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 4 Bewertung(en)

Ke, Q. et al. The effect of adjuvant therapy for patients with intrahepatic cholangiocarcinoma after surgical resection: A systematic review and meta-analysis. PLoS One. 15. e0229292. 2020

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: Systematic review and meta-analysis (22 cohort studies) Databases: MedLine, Embase, the Cochrane Library, Web of Science Search period: Jan.1st 1990 to Aug. 31st 2019. Inclusion Criteria: criteria. i) patients with ICC confirmed by pathology; ii) patients receiving surgical resection; iii) groups must include AT group and non-AT group; iv) outcomes must include the long-term outcomes. Exclusion Criteria: i)	Population: Patients with Intrahepatic cholangiocarcinoma (ICC) confirmed by pathology receiving surgical resection. Intervention: adjuvant therapy Comparison: non-adjuvant therapy	Primary: Overall survival (OS) Secondary: recurrence-free survival (RFS) Results: 22 studies with 10181 patients were enrolled in this meta-analysis, including 832 patients in the chemotherapy group, 309 patients in the transarterial chemoembolization (TACE) group, 1192 patients in the radiotherapy group, 235 patients in the chemoradiotherapy group, and 6424 patients in the non-AT group. The pooled HR for the OS rate and RFS rate in the AT group were 0.63 (95%CI 0.52~0.74), 0.74 (95%CI 0.58~0.90), compared with the non-AT group. Subgroup analysis showed that the pooled HR for the OS rate in the AT group compared with non-AT group were as follows: chemotherapy group was 0.57 (95%CI = 0.44~0.70),	22 cohort studies included, see article for list.

patients including gallbladder carcinoma or extrahepatic cholangiocarcinoma; ii) patients receiving neoadjuvant therapy; iii) patients receiving palliative resection; iv) data on the long-term outcomes was not available; v) studies based on overlapping cohorts deriving from the same center; vi) reviews, comments, letters, case report, and conference abstract.		TACE group was 0.56 (95%CI = 0.31~0.82), radiotherapy group was 0.71 (95%CI = 0.39~1.03), chemoradiotherapy group was 0.73 (95%CI = 0.57~0.89), positive resection margin group was 0.60 (95%CI = 0.51~0.69), and lymph node metastasis (LNM) group was 0.67 (95%CI = 0.57~0.76). Author's Conclusion: With the current data, we concluded that AT such as chemotherapy, TACE and chemoradiotherapy could benefit patients with ICC after resection, especially those with positive resection margin and LNM, but the conclusion needed to be furtherly confirmed.	

Methodical Notes

Funding Sources: This work was supported by Startup Fund for scientific research, Fujian Medical University (Grant number: 2018QH1195), but no authors in this study received a salary from this fund.

COI: NO authors have competing interests.

Study Quality: The quality of non-randomized studies was assessed by the modified Newcastle-Ottawa Scale (NOS), and more than 7 stars were defined as high quality, 4~6 star as medium quality, and <4 stars as low quality.
Study quality ranged from 5-9, but most studies were of high quality.

Heterogeneity: Heterogeneity was substantial in several analyses: overall survival between adjuvant therapy and operation only I^2 = 79.4%; p =0.000 and overall survival s between adjuvant TACE and operation only I^2 = 68.1%; p =0.014.
This is investigated in a subgroup analyis for radio and chemoradiotherapy.

Publication Bias: was determined using Begg's and Egger's tests, and "trim and fill" method was introduced to check the effect of potentially unpublished studies on the present result. Publication bias analysis was conducted in the primary endpoint comparing between AT group and non-AT group. Asymmetry was observed in the funnel plot (Fig 8) with significant publication bias in the egger's test (p = 0.004) but not in the Begg's test (p = 0.09). "Trim and fill" analysis was then conducted, and 5 more studies were found to be potentially unpublished. The adjusted HR for the OS in the AT group was 0.73 (95%CI 0.63–0.85), compared with the non-AT group, indicating that the present result could not be affected by the unpublished studies

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies.

Liu, J. B. et al. Prognosis for intrahepatic cholangiocarcinoma patients treated with postoperative adjuvant transcatheter hepatic artery chemoembolization. Curr Probl Cancer. 44. 100612. 2020

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: Systematic review and meta-analysis	Population: ICC patients Intervention:	Primary: 1-, 3-, and 5-year OS Secondary: Hazard ratio	9 observational studies included: Alibert 2008, Li

(9 observational studies) Databases: Embase, the Cochrane Library, and PubMed. Search period: Inception - June 18, 2018. Inclusion Criteria: (1) were reported on ICC (case group: ICC patients treated with TACE; control group: ICC patients treated without using TACE), (2) were published in the English literature, and (3) could provide or aid in computation of prognostic data in both the postoperative case and control groups, including 1-, 3-, and 5-year OS and hazard ratio (HR). Exclusion Criteria: (1) they lacked complete data and could not be used for statistical analysis, (2) they were nonoriginal articles, such as reviews, letters, and overviews, and (3) they were repeated publications on the same data. In those cases, only the latest reports or the articles with the complete information were included.	TACE Comparison: No TACE	Results: Nine controlled clinical trials involving 1724 participants were included in this study; patients came mainly from China, Italy, South Ko- rea, and Germany. In the OS meta-analysis, the 1-year and 3-year OS showed significant heterogeneity, but not the 5-year OS. TACE increased the 1-year OS (odds ratio = 2.66, 95% CI: 1.10-6.46) of the patients with ICC, but the 3- and 5-year OS rates were not significantly increased. The results had no publication bias, but the stability was weak. The HR had significant heterogeneity (I 2 = 0%, P = 0.54). TACE significantly de- creased the HR of ICC patients (HR = 0.59, 95% CI: 0.48-0.73). The results had no publication bias, and the stability was good. Author's Conclusion: Treatment with TACE is effective for patients with ICC. Regular updating and further research and analysis still need to be carried out.	A 2016, Li J 2015, Li T 2013, Lu 2016, Scheuermann 2013, Shen 2011, Wu 2012.

Methodical Notes

Funding Sources: Funding: This study was supported partly by grants from the National Natural Science Foundation of China.

COI: No potential conflicts of interest were disclosed.

Study Quality: All the selected publications were assessed by quality evaluation criteria for cohort study provided by the Newcastle-Ottawa Scale, including Exposed selection, Comparability, and Outcome, with a full score of 9.
). The results showed that the quality scores of the nine articles included were above 5-7 points.

Heterogeneity: The heterogeneity test was performed using the Q-test based on chi-square and I 2 statistics. In the OS meta-analysis, the 1-year and 3-year OS showed significant heterogeneity, but not the 5-year OS. The HR had significant heterogeneity (I 2 = 0%, P = 0.54). In the HR analysis no publication bias was found by Egger's test (t = 1.59, P = 0.25), suggesting that the result was stable.
In a sensitivity analysis the combined HR values were reversed, indicating that the results were unstable. No subgroup analysis was performed.

Publication Bias: Egger's test was used to test the publication bias. The publication bias was evaluated by Egger's method, and no publication bias was identified (1-year OS, t = 0.23, P = 0.83; 3-year OS, t = 0.29, P = 0.80; and 5-year OS, t = 0.57, P = 0.63), indicating that the results were stable and reliable.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis (9 cohort studies)
High heterogeneity was observed. In a sensitivity analysis the combined HR values were reversed, indicating that the results were unstable.

Mosconi, C. et al. Transarterial Chemoembolization and Radioembolization for Unresectable Intrahepatic Cholangiocarcinoma-a Systemic Review and Meta-Analysis. Cardiovasc Intervent Radiol. 44. 728-738. 2021

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type: Systemic Review and Meta-Analysis (31 observational studies included).** **Databases: PubMed and Web of Science databases** **Search period: Inception - 1 March 2020** **Inclusion Criteria: "studied of IAT for unresectable ICC, to understand in a timely fashion causes and consequences of different indications and results between TACE and TARE, with the final aim to clarify whether one single IAT can be superior to the alternative, evaluating objective response, clinical adverse events and survival of the pooled study populations for each IAT group identified."** **Exclusion Criteria: not described.**	**Population: Patients with unresectable ICC.** **Intervention: TACE** **Comparison: TARE**	**Primary: Overall survival after IAT was considered as the primary end point.** **Secondary: Occurrence of clinical adverse events (not including biochemical toxicities) and tumour overall response rate (complete response ? partial response) defined according to the response evaluation criteria in solid tumours.** **Results: A total of 31 articles (of 793, n.1695 patients) were selected for data extraction, 13 were on TACE (906 patients) and 18 were on TARE (789 patients). Clinical and tumour characteristics showed moderate heterogeneity between the two groups. The median survival after TACE was 14.2 months while after TARE was 13.5 months (95%C.I.: 11.4–16.1). The survival difference was small (d = 0.112) at 1 year and negligible at 2 years (d = 0.028) and at 3 years (d = 0.049). The radiological objective response after TACE was 20.6% and after TARE was 19.3% (d = 0.032). Clinical adverse events occurred in 58.5% after TACE, more frequently than after TARE (43.0%, d = 0.314).** **Author's Conclusion: In conclusion, IATs are promising treatments for improving outcomes for patients with unresectable ICC. To date, TACE and TARE provide similar good outcomes, except for adverse events. Therefore, the decision about techniques is determined by ability to utilize these resources and patient specific factors (liver function or lesion dimension).**	**31 observational studies included, see article for list.**

Methodical Notes

Funding Sources: This study was not supported by any funding.

COI: The authors declare that they have no conflict of interest.

Study Quality: The quality of each selected study was assessed using the Newcastle–Ottawa Scale (NOS) checklist.

Quality of the included studies ranged from 6-8 out 9.

Heterogeneity: "significant heterogeneity would exist both within patients treated either with TACE or TARE when comparing single studies, as well as when comparing the two techniques across all pertinent studies."

Publication Bias: Not investigated.

Notes:
Systematic review and meta-analysis of cohort studies
Downgrade to evidence level 3
Lacking description of criteria for inclusion or exclusion. No investigation of publication bias. Substantial heterogeneity in all results limits causal inference and is not investigated by subgroups or sensitivity analysis.

Zhen, Y. et al. A pooled analysis of transarterial radioembolization with yttrium-90 microspheres for the treatment of unresectable intrahepatic cholangiocarcinoma. Onco Targets Ther. 12. 4489-4498. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type: Systematic review and meta-analysis (16 cohort studies)** **Databases: the Cochrane Library, Embase, PubMed, SCI** **Search period: Inception to October 2018.** **Inclusion Criteria: 1. Clinical trials or studies 2. Studies that described TARE with 90Y microspheres in the treatment of unresectable ICC** **Exclusion Criteria: 1. Review articles, animal studies, abstracts, case reports 2. Duplicated clinical studies 3. Studies with fewer than 10**	**Population: Patients with unresectable ICC.** **Intervention: TARE with 90Y microspheres** **Comparison: nondescript (non-TARE)**	**Primary: Median OS** **Secondary: Disease control rate (DCR).** **Results: There were 16 eligible studies included in this pooled analysis. The pooled median overall survival (OS) from 12 studies was 14.3 (95% CI: 11.9–17.1) months. Based on Response Evaluation Criteria in Solid Tumors (RECIST), no complete response was reported, and the median of partial response, stable disease and progressive disease were 11.5% (range: 4.8–35.3%), 61.5% (range: 42.9–81.3%) and 22.7% (range: 12.5–52.4%) respectively. The pooled disease control rate (DCR) from nine studies was 77.2% (95% CI: 70.2–84.2%). According to the type of microspheres, subgroup analysis was performed, the median OS in the glass microspheres group was 14.0 (95% CI: 9.1–21.4) months, and 14.3 (95% CI: 11.5–17.8) months in the resin microspheres group. The DCR was 77.3% (95% CI: 63.5–91.1%) and 77.4% (95% CI: 66.8–87.9%) in the glass and resin microspheres groups respectively. Most of the side effects reported in the included studies were mild and did not require intervention.** **Author's Conclusion: TARE with 90Y microspheres is safe and effective for patients with unresectable ICC with acceptable side effects. And it seems that the type of microsphere has no influence on therapeutic efficacy.**	**16 cohort studies: Saxena 2010, Mosconi 2016, Rafi 2013, Mouli 2013, Hoffmann 2012, Jia 2017, Soydal 2016, Swinburne 2017, Reimer 2018, Orwat 2017, Paprottka 2017, Gangi 2018, Filippi 2015, Beuzit 2016, Camacho 2014.**

cases			

Methodical Notes

Funding Sources: not described.

COI: The authors report no conflicts of interest in this work.

Study Quality: The quality of the studies was independently evaluated by two reviewers based on the Downs and Black quality assessment checklist.
Study quality was evaluated but not reported or discussed.

Heterogeneity: Mild and moderate heterogeneity was shown in pooled median OS and DCR. These estimates were robust in the sensitivity analysis.

Publication Bias: An Egger test was used to assess publication bias, and Metaninf was used for sensitivity analysis, a two-sided P<0.05 was regarded as significant. No significant publication bias was identified in pooled analysis.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies
Downgrade to evidence level 3:
Lacking definition of criteria for inclusion or exclustion.Study quality was evaluated but not reported or discussed.

OXFORD (2011) Appraisal Sheet: RCT: 1 Bewertung(en)

Edeline, J. et al. Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma: A Phase 2 Clinical Trial. JAMA Oncol. 6. 51-59. 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type: Phase 2 clinical trial** **Number of Patient: 41** **Recruitung Phase: patients were aged 18 years or older, had unresectable ICC.** **Inclusion Criteria: e patients were aged 18 years or older, had unre- sectable ICC, a measurable lesion (≥2 cm), either noncirrhotic liver or cirrhosis with Child-Pugh score less than B8 (a score ofliver function in which lower scores indicate better liver function), Eastern Cooperative Oncology Group performance status of 0 or 1, no or limited extrahepatic disease (limited**	**Intervention: Concomitant first-line chemotherapy with cisplatin, 25 mg/m2, and gemcitabine, 1000 mg/m2 (gemcitabine reduced to 300 mg/m2 for the cycles just before and after SIRT), on days 1 and 8 of a 21-day cycle for 8 cycles. Selective internal radiotherapy was administered during cycle 1 (1 hemiliver disease) or cycles 1 and 3 (disease involving both hemilivers) using glass Y90 microspheres.** **Comparison: -**	**Primary: Response rate at 3 months according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.** **Secondary: Toxic effects, progression-free survival, overall survival, disease control rate, and response rate according to Choi criteria.** **Results: Of 41 patients included in the study, 26 (63%) were male, with a mean (SD) age of 64.0 (10.7) years. Response rate according to RECIST was 39% (90% CI, 26%-53%) at 3 months according to local review and was confirmed at 41% as best response by central review; disease control rate was 98%. According to Choi criteria, the response rate was 93%. After a median follow-up of 36 months (95% CI, 26-52 months), median progression-free survival was 14 months (95% CI, 8-17 months), with progression-free survival rates of 55% at 12 months and 30% at 24 months. Median overall survival was 22 months (95% CI, 14-52 months), with overall survival rates of 75% at 12 months and 45% at 24 months. Of 41**

extra- hepatic disease was defined as hilar lymph node ≤3 cm or <5 lung nodules, each ≤10 mm), adequate hematologic or kid- ney function, albumin level of at least 28 g/L (to convert to mil- ligrams per deciliter, divide by 10), and bilirubin level less than or equal to 3 times the upper limit of norma **Exclusion Criteria: Patients who had undergone resection and experienced intrahepatic unresect- able recurrence could be included in the study.**		**patients, 29 (71%) had grades 3 to 4 toxic effects; 9 patients (22%) could be downstaged to surgical intervention, with 8 (20%) achieving R0 (microscopic-free margins) surgical resection. After a median of 46 months (95% CI, 31 months to not reached) after surgery, median relapse-free survival was not reached among patients who underwent resection** **Author's Conclusion: Combination chemotherapy and SIRT had antitumor activity as first-line treatment of unresectable ICC, and a significant proportion of patients were downstaged to surgical intervention. A phase 3 trial is ongoing.**

Methodical Notes

Funding Sources: -

COI: Declared, see article.

Randomization: not randomized.

Blinding: not blinded

Dropout Rate/ITT-Analysis: -

Notes:
Artikel stammt aus der Handsuche
Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment Benefits): 3 Non-randomized controlled cohort

Versionsnummer: **3.0**

Erstveröffentlichung: **05/2013**

Überarbeitung von: **07/2022**

Nächste Überprüfung geplant: **05/2027**