

Supplementary Material

Clinical Drug Investigation

Cancer drugs reimbursed with limited evidence on overall survival and quality of life: do follow-up studies confirm patient benefits?

Gabriella Chauca Strand,^a Naimi Johansson,^{a, b} Niklas Jakobsson,^c Carl Bonander,^{a, d} Mikael Svensson,^{a, e}

^a School of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Västra
Götalands Län, Sweden

^b University Health Care Research Center, Faculty of Medicine and Health, Örebro University, Örebro, Örebro Län, Sweden

^c Karlstad Business School, Karlstad University, Faculty of Arts and Social Sciences, Karlstads Business School, Karlstad,
Värmlands Län, Sweden

^d Centre for Societal Risk Management, Karlstad University. Faculty of Arts and Social Sciences, Karlstad, Värmlands Län,
Sweden

^e Department of Pharmaceutical Outcomes & Policy, University of Florida, Gainesville, Florida, USA

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Figure S1. Flow-diagram for the updated PubMed search, 24th – 26th October 2022.

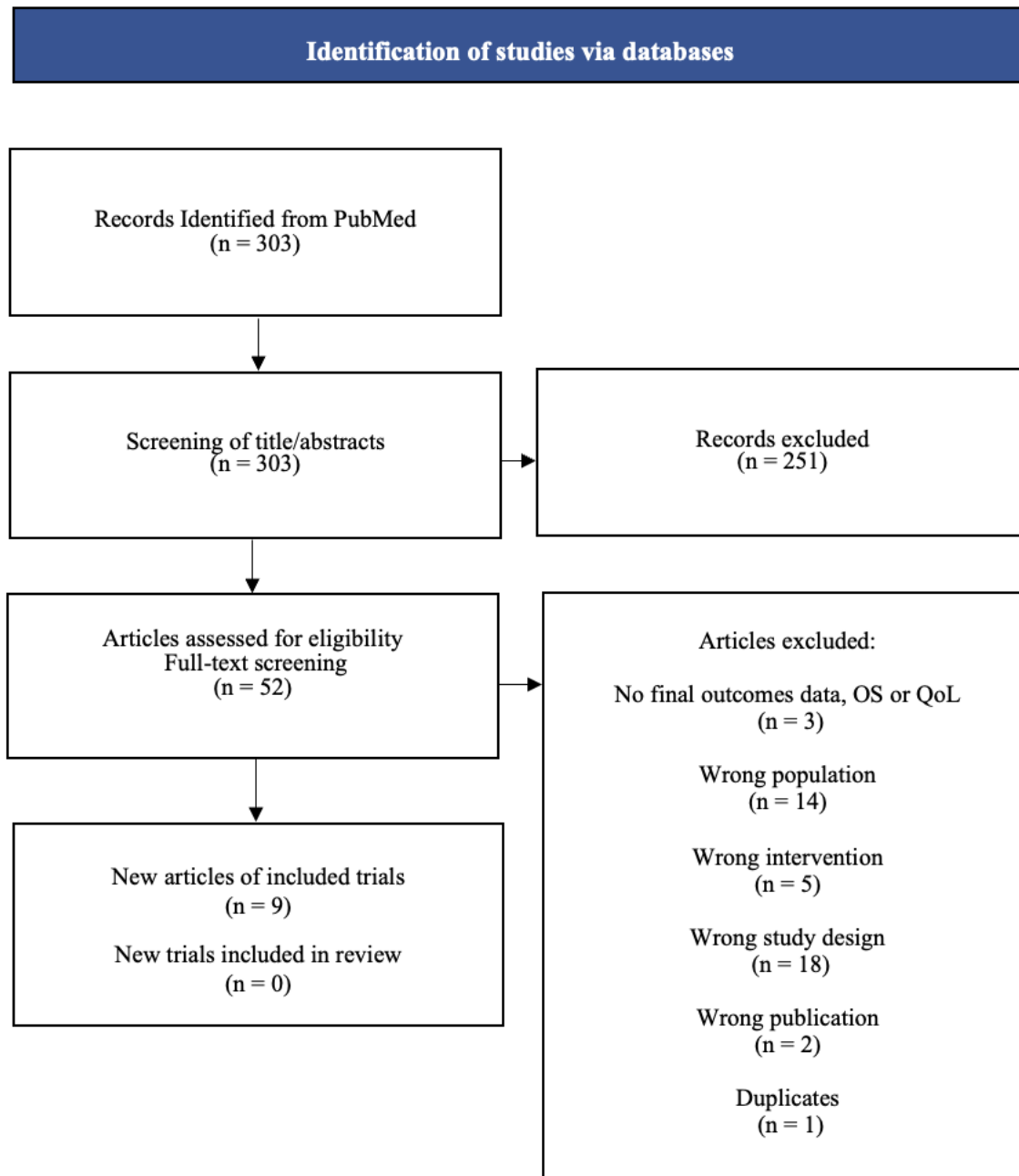


Figure S2. Trial Characteristics

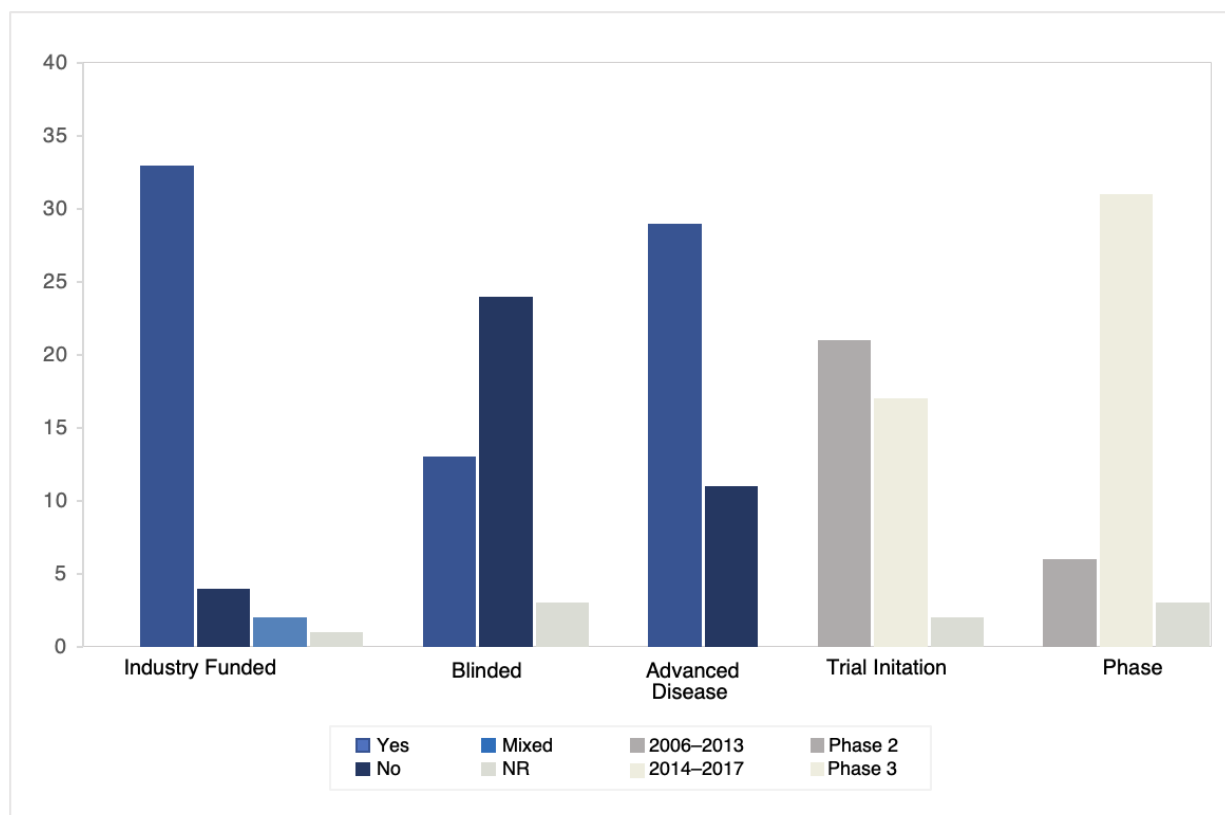


Table S1. Overview of drug-indications identified for follow-up and available evidence on OS and QoL at the year of decision, 2010-2020

Drug	Indication	HR OS	QoL	HR PFS	Status	Decision Date
Everolimus	Patients with advanced RCC, following VEGFR-targeted therapy treatment.	0.87 (0.65–1.17)	Not stated	Not stated		2010-09-07
Nilotinib®	Newly diagnosed patients with Ph+ CML.	Not stated	Not stated	Not applicable	Orphan	2011-10-07
Axitnib	Patients with advanced RCC after failure of prior treatments with sunitinib or cytokines.	0.97 (Not stated)	Not stated	0.67 (Not stated)		2013-01-31
Brentuximab Vedotin	Patients with recurrent or refractory CD30+ Hodgkin's Lymphoma; following ASCT or following at least two prior therapies when ASCT or chemotherapy is not a treatment option or will be doing a ASCT (used as neo-adjuvant treatment).	Single arm study	Single arm study	Single arm study		2013-06-20
Bosutinib	Patients with Ph+ CML in chronic, accelerated or blast phase previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.	Single arm study	Single arm study	Single arm study	Orphan	2013-10-03
Dabrafenib	Patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	0.76 (0.48–1.21)	Not stated	0.37 (Not stated)		2014-02-20

Cabozantinib	Patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.	0.83 (0.6–1.14)	Not stated	0.28 (0.19-0.4)	Orphan	2014-11-20
Olaparib	Maintenance treatment of patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer with BRCA-mutations who are in response to platinum-based chemotherapy.	0.73 (0.45–1.17)	Not stated	0.35 (0.25–0.49)	Orphan	2015-02-24
Idelalisib	Patient with follicular lymphoma that is refractory to two previous treatments.	Single arm study	Single arm study	Single arm study		2015-02-24
Ponatinib 1	Patients with CML in chronic, accelerated or blast phase, who are resistant to dasatinib or nilotinib; or who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not appropriate; or who have a T315I mutation.	Single arm study	Single arm study	Single arm study	Orphan	2015-03-27
Ponatinib 2	Patients with Ph+ Acute lymphocytic leukemia who are resistant to dasatinib and for whom subsequent treatment with imatinib is not appropriate; or who have T315I mutation.	Single arm study	Single arm study	Single arm study	Orphan	2015-03-27
Ceritinib	Patients with advanced ALK+ non-small cell lung cancer who previously have been treated with crizotinib.	Single-arm study	Single-arm study	Single arm study		2015-12-11
Palbociclib	Patients with locally advanced or metastatic HR+, HER2- breast cancer (in combination with an aromatase inhibitor).	0.81 (0.5–1.3)	Not stated	0.65 (0.51–0.84)		2017-06-15

Osimertinib	Patients with locally advanced or metastatic non-small cell lung cancer with EGFR T790M-mutation.	0.72 (0.48–1.09)	Not stated	0.3 (0.23–0.41)		2017-09-28
Alectinib 1	Patients with ALK+ advanced non-small cell lung cancer who have been previously treated with crizotinib.	Not stated	Not stated	0.32 (Not stated)		2017-11-24
Fulvestrant	Patients with ER+ locally advanced or metastatic breast cancer in postmenopausal women not previously treated with endocrine therapy.	0.86 (0.63–1.22)	Not stated	0.80 (0.64–1)		2018-01-25
Ribociclib	In combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with locally advanced or metastatic HR+, HER- breast cancer.	0.75 (0.52–1.8)	Not stated	0.57 (0.46–0.70)		2018-01-25
Alectinib 2	As first-line treatment for patients with ALK+ advanced, non-small cell lung cancer.	0.76 (0.46–1.2)	Not stated	0.5 (0.36–0.70)		2018-04-20
Lorlatinib	Patients with ALK+ advanced non-small cell lung cancer whose disease has progressed after treatment with alectinib or certinib as first ALK tyrosine kinase inhibitor therapy; or crizotinib and at least another ALK TKI.	Single arm study	Single arm study	Single arm study		2019-09-26
Niraparib	As maintenance treatment for patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response after platinum-based chemotherapy.	Not stated	Not stated	0.27 (0.17-0.41)	Orphan	2019-11-22

Venetoclax	In combination with obinutuzumab for the treatment of adults with previously untreated CLL.	Not stated	Not stated	0.31 (0.22-0.44)	2020-08-27
Larotrectinib	Treatment of patients with solid tumors with NTRK-gene fusion with locally advanced or metastatic disease or where surgical resection is likely to result in severe morbidity or who have no satisfactory treatment options.	Single arm study	Single arm study	Single arm study	2020-10-22

Note: Characteristics of all drug indications with limited evidence of improvements at the year of reimbursement decision. Results on OS, QoL and PFS are based on the clinical evidence presented in the decision dossiers and assessment by TLV.¹ Four additional drug-indications were excluded due to restrictions of reimbursement to a specific indication with shown improvement (n=1). Having studies with statistically non-significant study results according to the predefined study protocols were likewise excluded if the p-value was less than our defined threshold of 0.05 (n=2). One drug-indication was additionally excluded due to evidence of improvement in a subgroup of the pivotal study prior to the decision made by TLV (n=1). No evidence of improvement for the total population, for which the reimbursement was granted, was however found in our review.

Abbreviations: ALK+, anaplastic lymphoma kinase-positive; ASCT, autologous stem cell transplantation; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; HR+, hormone-receptor positive; HER2, human epidermal growth factor receptor 2; NTRK, Neurotrophic tyrosine receptor kinase; OS, overall survival; PFS, progression-free survival; Ph+, Philadelphia chromosome-positive; QoL, quality of life; RCC, renal cell carcinoma; TKI, tyrosine-kinase inhibitor.

^aAlectinib and Ponatinub were followed for two different indications for lung cancer, chronic myelogenous leukemia, and acute lymphocytic leukemia respectively. Based on the separate assessment made for the indications these were regarded as individual observations.

¹ All data used to assess clinical and cost-effectiveness evidence used to support the initial reimbursement decision was extracted from official decision dossiers for each drug indication. The information can be retrieved from the Swedish Dental and Pharmaceutical Benefits Agency's (TLV) official database [<https://www.tlv.se/beslut/sok-priser-och-beslut-i-databasen.html>] or upon request at the agency using information of the drug substance, cancer form and date of decision.

Tables S2-S21. Search strategies for each drug-indication

Alectinib 1

Pubmed		
#1	Alecensa OR alectinib	751
#2	Non-small Cell Lung Cancer OR Non-small Cell Lung Cancer* OR Non-Small-Cell Lung Carcinoma OR Non-Small-Cell Lung Carcinoma* OR Non Small Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma* OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung Carcinoma* OR Nonsmall Cell Lung Cancer OR Nonsmall Cell Lung Cancer* OR Adenocarcinoma OR Adenocarcinoma* OR Squamous cell carcinoma OR Squamous cell carcinoma* OR Large cell carcinoma OR Large cell carcinoma* OR lung neoplasms[MeSH Terms] OR lung neoplasm[MeSH Terms] OR carcinoma, bronchogenic[MeSH Terms] OR NSCLC	874,462
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,377,750
#4	#1 AND #2 AND #3	83
Time filter	#1 AND #2 AND #3 Filter: 2016-2022	72

ClinicalTrials.gov		
Search	Non Small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Adenocarcinoma OR Squamous cell carcinoma OR Large cell carcinoma	Alecensa OR alectenib
Filters	Phase 2, 3, 4 + Not applicable	
Results		32

Alectinib 2

PubMed		
#1	Alecensa OR alectinib	751
#2	Non-small Cell Lung Cancer OR Non-small Cell Lung Cancer* OR Non-Small-Cell Lung Carcinoma OR Non-Small-Cell Lung Carcinoma* OR Non Small Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma* OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung Carcinoma* OR Nonsmall Cell Lung Cancer OR Nonsmall Cell Lung Cancer* OR Adenocarcinoma OR Adenocarcinoma* OR Squamous cell carcinoma OR Squamous cell carcinoma* OR Large cell carcinoma OR Large cell carcinoma* OR lung neoplasms[MeSH Terms] OR lung neoplasm[MeSH Terms] OR carcinoma, bronchogenic[MeSH Terms] OR NSCLC	874,462
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,377,750
#4	#1 AND #2 AND #3	83
Time filter	#1 AND #2 AND #3 Filter: 2017–2022	67
ClinicalTrial.gov		
Search	Non Small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Adenocarcinoma OR Squamous cell carcinoma OR Large cell carcinoma	Alecensa OR alectenib
Filter	Phase 2, 3, 4 + Not applicable	
Result		32

Axitinib

	PubMed	
#1	Inlyta OR Axitinib	1,244
#2	Renal cell carcinoma OR Renal cell carcinoma* OR renal cell cancer* OR nephroid carcinoma OR nephroid carcinoma* OR adenocarcinoma kidney OR adenocarcinoma kidney* OR Renal Cell Cancer OR Renal Cell Cancer* OR Renal Adenocarcinoma OR Renal Adenocarcinoma* OR Renal Carcinoma OR Renal Carcinoma* OR Renal Cell Adenocarcinoma OR Renal Cell Adenocarcinoma* OR Chromophobe Renal Cell Carcinoma OR Chromophobe Renal Cell Carcinoma* OR Sarcomatoid Renal Cell Carcinoma OR Sarcomatoid Renal Cell Carcinoma* OR Papillary Renal Cell Carcinoma OR Papillary Renal Cell Carcinoma* OR Chromophil Renal Cell Carcinoma OR Chromophil Renal Cell Carcinoma* OR Clear Cell Renal Carcinoma OR Clear Cell Renal Carcinoma* OR Grawitz Tumor OR Clear Cell Renal Cell Carcinoma OR Clear Cell Renal Cell Carcinoma* OR Hypernephroid Carcinoma OR Hypernephroid Carcinoma* OR Hypernephroma OR Hypernephroma* OR Collecting Duct Carcinoma Kidney OR Collecting Duct Carcinoma* Kidney OR Collecting Duct Carcinoma of the Kidney OR Renal Collecting Duct Carcinoma OR Renal Collecting Duct Carcinoma* OR Collecting Duct Carcinoma OR Collecting Duct Carcinoma* OR RCC OR kidney neoplasm OR kidney neoplasm*	155,136
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,378,208
#4	#1 AND #2 AND #3	219
Time filter:	#1 AND #2 AND #3 Filter: 2012–2022	185

	ClinicalTrial.gov	
Search	Renal cell carcinoma OR nephroid carcinoma OR adenocarcinoma kidney OR Renal Cell Cancer OR Renal Adenocarcinoma OR Renal Carcinoma OR Renal Cell Adenocarcinoma OR Chromophobe Renal Cell Carcinoma OR Sarcomatoid Renal Cell Carcinoma OR Papillary Renal Cell Carcinoma OR Chromophil Renal Cell OR Clear Cell Renal Carcinoma OR Grawitz Tumor OR Clear Cell Renal Cell Carcinoma OR Hypernephroid Carcinoma OR Hypernephroma OR Collecting Duct Carcinoma Kidney OR Collecting Duct Carcinoma of the Kidney OR Renal Collecting Duct Carcinoma OR RCC OR kidney neoplasm	Inlyta OR Axitinib
Filters	Phase 2, 3, 4 + Not applicable	
Results		56

Bosutinib

PubMed		
#1	Bosulif OR Bosutinib	635
#2	Chronic Myelogenous Leukemia OR Chronic myeloid leukemia OR Chronic granulocytic leukemia OR CML OR CGL OR Granulocytic Leukemia OR Myeloid Leukemia OR Myelogenous Leukemia OR Myelocytic Leukemia OR Chronic Monocytic Leukemia OR Chronic Myelogenous Leukemia* OR Chronic myeloid leukemia* OR Chronic granulocytic leukemia* OR Granulocytic Leukemia* OR Myeloid Leukemia* OR Myelogenous Leukemia* OR Myelocytic Leukemia* OR Chronic Monocytic Leukemia* OR Monocytic Leukemia* OR Chronic myelogenous leukaemia* OR Chronic granulocytic leukaemia* OR Chronic Myeloid Leukaemia* OR Myelogenous leukaemia* OR Myeloid Leukaemia* OR Granulocytic Leukaemia* OR leukemia, myeloid[MeSH Terms] OR leukemia[MeSH Terms]	279,306
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,377,750
#4	#1 AND #2 AND #3	84
Time filter	#1 AND #2 AND #3 Filter: 2012–2022	67
ClinicalTrial.gov		
Search	Chronic Myelogenous Leukemia OR Chronic myeloid leukemia OR Chronic granulocytic leukemia OR CML OR CGL OR Granulocytic Leukemia OR Myeloid Leukemia OR Myelogenous Leukemia OR Myelocytic Leukemia OR Chronic Monocytic Leukemia	Bosulif OR Bosutinib
Filters	Phase 2, 3, 4 + Not applicable	
Results		26

Brentuximab Vedotin

PubMed		
#1	(Adcetris)) OR (Brentuximab vedotin)	1,208
#2	Hodgkins Lymphoma OR Hodgkin disease OR Hodgkin disease* OR Hodgkin's Granuloma OR Hodgkins Granuloma OR Malignant Lymphogranuloma OR Malignant Lymphogranuloma* OR Hodgkin Lymphoma OR Hodgkin's Disease OR Hodgkin's Disease* OR Adult Hodgkin Lymphoma OR Lymphocyte Depletion Hodgkin's Lymphoma OR Hodgkin's Lymphoma OR Hodgkins Disease OR Hodgkin Granuloma OR Malignant Granuloma OR Malignant Granuloma* OR Nodular Lymphocyte-Predominant Hodgkin's Lymphoma OR Nodular Lymphocyte Predominant Hodgkin's Lymphoma OR Nodular Sclerosing Hodgkin's Lymphoma OR Lymphocyte-Rich Classical Hodgkin's Lymphoma OR Lymphocyte Rich Classical Hodgkin's Lymphoma OR Mixed Cellularity Hodgkin's Lymphoma OR lymphoma	281,489
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,378,208
#4	#1 AND #2	1,023
#5	#1 AND #2 AND #3	164
Time filter	#1 AND #2 AND #3 Filter: 2012–2022	154
ClinicalTrial.gov		
Search	Hodgkins Lymphoma OR Hodgkin disease OR Hodgkin's Granuloma OR Hodgkins Granuloma OR Malignant Lymphogranuloma OR Hodgkin Lymphoma OR Hodgkin's Disease OR Adult Hodgkin Lymphoma OR Lymphocyte Depletion Hodgkin's Lymphoma OR Hodgkin's Lymphoma OR Hodgkins Disease OR Hodgkin Granuloma OR Malignant Granuloma OR Nodular Lymphocyte-Predominant Hodgkin's Lymphoma OR Nodular Lymphocyte Predominant Hodgkin's Lymphoma OR Nodular Sclerosing Hodgkin's Lymphoma OR Lymphocyte-Rich Classical Hodgkin's Lymphoma OR Lymphocyte Rich Classical Hodgkin's Lymphoma OR Mixed Cellularity Hodgkin's Lymphoma OR lymphoma	Adcetris OR Brentuximab Vedotin
Filters	Phase 2, 3, 4 + Not applicable	
Results		77

Cabozantinib

PubMed		
#1	Cometriq OR Cabozantinib	1,221
#2	Thyroid cancer OR Thyroid Neoplasm OR Thyroid Carcinoma OR (Cancer of Thyroid) OR (Cancer of the Thyroid) OR Thyroid Adenoma OR thyroid diseases[MeSH Terms] OR Thyroid cancer* OR Thyroid Neoplasm* OR Thyroid Carcinoma* OR Thyroid Adenoma*	187,186
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,376,841
#4	#1 AND #2 AND #3	57
Time filter	#1 AND #2 And #3 Filters: 2013–2021	48

ClinicalTrial.gov		
Search	Thyroid cancer OR Thyroid Neoplasm OR Thyroid Carcinoma OR Thyroid Adenoma	Cometriq OR Cabozantinib
Filters	Phase 2, 3, 4 + Not applicable	
Results		14

Ceritinib

PubMed		
#1	Zykadia OR ceritinib	579
#2	Non-small Cell Lung Cancer OR Non-small Cell Lung Cancer* OR Non-Small-Cell Lung Carcinoma OR Non-Small-Cell Lung Carcinoma* OR Non Small Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma* OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung Carcinoma* OR Nonsmall Cell Lung Cancer OR Nonsmall Cell Lung Cancer* OR Adenocarcinoma OR Adenocarcinoma* OR Squamous cell carcinoma OR Squamous cell carcinoma* OR Large cell carcinoma OR Large cell carcinoma* OR lung neoplasms[MeSH Terms] OR lung neoplasm[MeSH Terms] OR carcinoma, bronchogenic[MeSH Terms] OR NSCLC	874,462
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,377,750
#4	#1 AND #2	468
#5	#1 AND #3	76
#6	#1 AND #2 AND #3	70
Time-Filter	#1 AND #2 AND #3 Filters: 2014–2022	69
ClinicalTrial.gov		
Search	Non Small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Adenocarcinoma OR Squamous cell carcinoma OR Large cell carcinoma	Zykadia OR ceritinib
Filters	Phase 2, 3, 4 + Not applicable	
Results		17

Dabrafenib

PubMed		
#1	Tafinlar OR Dabrafenib	1,445
#2	Melanoma OR Melanoma* OR Malignant Melanoma OR Malignant Melanoma* OR nevi and melanomas[MeSH Terms] OR skin cancer OR neuroectodermal tumors[MeSH Terms]	516,622
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,377,996
Time filter	#1 AND #2 AND #3 Filter: 2013–2022	143
ClinicalTrial.gov		
Search	Melanoma OR Malignant Melanoma OR skin cancer OR neuroectodermal tumors	Tafinlar OR Dabrafenib
Filters	Phase 2, 3, 4 + Not applicable	
Results		64

Everolimus

PubMed		
#1	(afinitor) OR (Everolimus)	8,186
#2	Renal cell carcinoma OR Renal cell carcinoma* OR renal cell cancer* OR nephroid carcinoma OR nephroid carcinoma* OR adenocarcinoma kidney OR adenocarcinoma kidney* OR Renal Cell Cancer OR Renal Cell Cancer* OR Renal Adenocarcinoma OR Renal Adenocarcinoma* OR Renal Carcinoma OR Renal Carcinoma* OR Renal Cell Adenocarcinoma OR Renal Cell Adenocarcinoma* OR Chromophobe Renal Cell Carcinoma OR Chromophobe Renal Cell Carcinoma* OR Sarcomatoid Renal Cell Carcinoma OR Sarcomatoid Renal Cell Carcinoma* OR Papillary Renal Cell Carcinoma OR Papillary Renal Cell Carcinoma* OR Chromophil Renal Cell Carcinoma OR Chromophil Renal Cell Carcinoma* OR Clear Cell Renal Carcinoma OR Clear Cell Renal Carcinoma* OR Grawitz Tumor OR Clear Cell Renal Cell Carcinoma OR Clear Cell Renal Cell Carcinoma* OR Hypernephroid Carcinoma OR Hypernephroid Carcinoma* OR Hypernephroma OR Hypernephroma* OR Collecting Duct Carcinoma Kidney OR Collecting Duct Carcinoma* Kidney OR Collecting Duct Carcinoma of the Kidney OR Renal Collecting Duct Carcinoma OR Renal Collecting Duct Carcinoma* OR Collecting Duct Carcinoma OR Collecting Duct Carcinoma* OR RCC OR kidney neoplasm OR kidney neoplasm*	155,136
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,378,208
#4	#1 AND #2	1,21
#5	#1 AND #2 AND #3	345
Time filter	#1 AND #2 AND #3 AND Filters: 2009–2022	328
ClinicalTrial.gov		
Search	Renal cell carcinoma OR nephroid carcinoma OR adenocarcinoma kidney OR Renal Cell Cancer OR Renal Adenocarcinoma OR Renal Carcinoma OR Renal Cell Adenocarcinoma OR Chromophobe Renal Cell Carcinoma OR Sarcomatoid Renal Cell Carcinoma OR Papillary Rena	Afinitor OR Everolimus
Filters	Phase 2, 3, 4 + Not applicable	
Results		66

Fulvestrant

PubMed		
#1	Faslodex OR fulvestrant	3,483
#2	Breast cancer OR Breast cancer* OR Breast Neoplasm OR Breast Neoplasm* OR Breast Tumor OR Breast Tumor* OR Mammary Cancer OR Mammary Cancer* OR (Malignant Neoplasm of Breast) OR Breast Malignant Neoplasm OR Breast Malignant Neoplasm* OR (Malignant Tumor of Breast) OR Breast Malignant Tumor OR Breast Malignant Tumor* OR Cancer of Breast OR Cancer of the Breast OR Human Mammary Carcinoma OR Human Mammary Carcinoma* OR Human Mammary Neoplasm OR Human Mammary Neoplasm* OR Breast Carcinoma OR Breast Carcinoma*	477,447
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,377,603
#4	#1 AND #2	1,999
#5	#1 AND #2 AND #3	402
Time-filter	#1 AND #2 AND #3 Filters: 2017–2022	184
ClinicalTrial.gov		
Search	Breast cancer OR Breast Neoplasm OR Breast Tumor OR Mammary Cancer OR Breast Malignant Neoplasm OR Breast Malignant Tumor OR Cancer of Breast OR Cancer of the Breast OR Human Mammary Carcinoma OR Human Mammary Neoplasm OR Breast Carcinoma	Faslodex OR fulvestrant
Filters	Phase 2, 3, 4 + Not applicable	
Results		283

Idelalisib

	PubMed	
#1	Zydelig OR Idelalisib	733
#2	(Follicular Lymphoma OR Follicular Lymphoma* OR Non-Hodgkin Lymphoma OR Non-Hodgkin Lymphoma* OR Giant Follicular Lymphoma OR Giant Follicular Lymphoma* OR Nodular Lymphoma OR Nodular Lymphoma* OR Brill-Symmers Disease OR Brill Symmers Disease OR Follicular Lymphoma, Grade 1 OR Follicular Mixed-Cell Lymphoma OR Follicular Mixed Cell Lymphoma OR Follicular Mixed Cell Lymphoma* OR Lymphoma, Follicular, Small and Large Cleaved Cell OR Lymphoma, Nodular, Mixed Lymphocytic Histiocytic OR Lymphoma, Nodular, Mixed Small and Large Cell OR Lymphoma, Follicular, Small and Large Cleaved-Cell OR Lymphoma, Follicular, Mixed Small and Large Lymphoid OR Follicular Lymphoma, Grade 3 OR Nodular Histiocytic Lymphoma OR Nodular Histiocytic Lymphoma* OR Nodular Large Follicular Center-Cell Lymphoma OR Nodular Large Follicular Center Cell Lymphoma OR Follicular Large-Cell Lymphoma OR Follicular Large-Cell Lymphoma* OR Small Follicular Center-Cell Lymphoma OR Small Follicular Center Cell Lymphoma OR Small Follicular Center Cell Lymphoma* OR Lymphocytic Lymphoma, Nodular, Poorly Differentiated OR Follicular Lymphoma, Grade 2 OR Small Cleaved Cell Lymphoma, Follicular OR Lymphoma, Small Follicular Center Cell) OR (lymphoma, non hodgkin [MeSH Terms]) OR lymphoma, non hodgkin* OR Indolent Non-Hodgkin Lymphoma	128,082
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,376,899
#4	#1 AND #2	179
#5	#1 AND #2 AND #3	30
Time-filter	#1 AND #2 AND #3 Filters: 2014–2021	27

	ClinicalTrial.gov
Search	Zydelig OR Idelalisib
Filters	Phase 2, 3, 4 + Not applicable
Results	40

Larotrectinib

PubMed		
#1	Vitakvi OR larotrectinib	234
#2	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,378,208
#3	#1 AND #2	26
Time filter	#1 AND #2 Filter: 2019–2022	22

ClinicalTrial.gov		
Search	Vitakvi OR larotrectinib	
Filters	Phase 2, 3, 4 + Not applicable	
Results		8

Lorlatinib

PubMed		
#1	lorviqua OR lorlatinib OR lorbrena	315
#2	Non-small Cell Lung Cancer OR Non-small Cell Lung Cancer* OR Non-Small-Cell Lung Carcinoma OR Non-Small-Cell Lung Carcinoma* OR Non Small Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma* OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung Carcinoma* OR Nonsmall Cell Lung Cancer OR Nonsmall Cell Lung Cancer* OR Adenocarcinoma OR Adenocarcinoma* OR Squamous cell carcinoma OR Squamous cell carcinoma* OR Large cell carcinoma OR Large cell carcinoma* OR lung neoplasms[MeSH Terms] OR lung neoplasm[MeSH Terms] OR carcinoma, bronchogenic[MeSH Terms] OR NSCLC	877,460
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,381,875
#4	#1 AND #2	266
#5	#1 AND #3	26
Time filters:	#1 AND #3 Filters: From 2018–2022	21
ClinicalTrial.gov		
Search	Non Small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Adenocarcinoma OR Squamous cell carcinoma OR Large cell carcinoma	lorviqua OR lorlatinib OR lorbrena
Filters	Phase 2, 3, 4 + Not applicable	
Results		16

Nilotinib

PubMed		
#1	tasigna OR nilotinib	2,525
#2	Chronic Myelogenous Leukemia OR Chronic myeloid leukemia OR Chronic granulocytic leukemia OR CML OR CGL OR Granulocytic Leukemia OR Myeloid Leukemia OR Myelogenous Leukemia OR Myelocytic Leukemia OR Chronic Monocytic Leukemia OR Chronic Myelogenous Leukemia* OR Chronic myeloid leukemia* OR Chronic granulocytic leukemia* OR Granulocytic Leukemia* OR Myeloid Leukemia* OR Myelogenous Leukemia* OR Myelocytic Leukemia* OR Chronic Monocytic Leukemia* OR Monocytic Leukemia* OR Chronic myelogenous leukaemia* OR Chronic granulocytic leukaemia* OR Chronic Myeloid Leukaemia* OR Myelogenous leukaemia* OR Myeloid Leukaemia* OR Granulocytic Leukaemia* OR leukemia, myeloid[MeSH Terms] OR leukemia[MeSH Terms]	279,306
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,377,750
#4	#1 AND #2 AND #3	254
Time filter	#1 AND #2 AND #3 Filters: 2010–2021	203
ClinicalTrial.gov		
Search	Chronic Myelogenous Leukemia OR Chronic myeloid leukemia OR Chronic granulocytic leukemia OR CML OR CGL OR Granulocytic Leukemia OR Myeloid Leukemia OR Myelogenous Leukemia OR Myelocytic Leukemia OR Chronic Monocytic Leukemia	tasigna OR nilotinib
Filters	Phase 2, 3, 4 + Not applicable	
Results		97

Niraparib

PubMed		
#1	Zejula OR niraparib	358
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,378,208
#4	#1 AND #3	91
Time filter	#1 AND #3 Filters: 2018–2022	82
ClinicalTrial.gov		
Search	Ovarian Cancer OR Ovarian Neoplasm OR Ovary Neoplasm OR Ovary Cancer OR Cancer of the Ovary OR Epithelial Ovarian Cancer OR Ovarian Epithelial Cancer OR Ovarian Epithelial Carcinoma OR Epithelial Ovarian Carcinoma OR Fallopian Tube Neoplasm OR Fallop	Zejula OR niraparib
Filters	Phase 2, 3, 4 + Not applicable	
Results		46

Olaparib

Pubmed		
#1	Lynparza OR Olaparib	2,050
#2	Ovarian Cancer OR Ovarian Cancer* OR Ovarian Neoplasm OR Ovarian Neoplasm* OR Ovary Neoplasm OR Ovary Neoplasm* OR Ovary Cancer OR Ovary Cancer* OR (Cancer of Ovary) OR (Cancer of the Ovary) OR Epithelial Ovarian Cancer OR Epithelial Ovarian Cancer* OR Ovarian Epithelial Cancer OR Ovarian Epithelial Cancer* OR Ovarian Epithelial Carcinoma OR Ovarian Epithelial Carcinoma* OR Epithelial Ovarian Carcinoma OR Epithelial Ovarian Carcinoma* OR Ovarian Carcinoma, Epithelial OR Ovarian Carcinoma*, Epithelial OR Fallopian Tube Neoplasm OR Fallopian Tube Neoplasm* OR Fallopian Tube Cancer OR Fallopian Tube Cancer* OR (Cancer of the Fallopian Tube) OR Peritoneal Neoplasm OR Peritoneal Neoplasm* OR Peritoneal Surface Malignancy OR Peritoneal Surface Malignancies* OR Peritoneal Carcinomatosis OR Peritoneum cancer OR Peritoneum cancer* OR Peritoneal Carcinomatoses*	177,180
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,378,208
#4	#1 AND#3 AND #4	183
Time filter	#1 AND #3 AND #4 Filters: From 2018–2022	110
ClinicalTrial.gov		
Search	Ovarian Cancer OR Ovarian Neoplasm OR Ovary Neoplasm OR Ovary Cancer OR Cancer of the Ovary OR Epithelial Ovarian Cancer OR Ovarian Epithelial Cancer OR Ovarian Epithelial Carcinoma OR Epithelial Ovarian Carcinoma OR Fallopian Tube Neoplasm OR Fallopian Tube Cancer OR Cancer of the Fallopian Tube OR Peritoneal Neoplasm OR Peritoneal Surface Malignancy OR Peritoneal Carcinomatosis OR Peritoneum cancer	Lynparza OR Olaparib
Filters	Phase 2, 3, 4 + Not applicable	
Results		73

Osimertinib

Pubmed		
#1	Tagrisso OR Osimertinib	1,789
#2	Non-small Cell Lung Cancer OR Non-small Cell Lung Cancer* OR Non-Small-Cell Lung Carcinoma OR Non-Small-Cell Lung Carcinoma* OR Non Small Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma* OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung Carcinoma* OR Nonsmall Cell Lung Cancer OR Nonsmall Cell Lung Cancer* OR Adenocarcinoma OR Adenocarcinoma* OR Squamous cell carcinoma OR Squamous cell carcinoma* OR Large cell carcinoma OR Large cell carcinoma* OR lung neoplasms[MeSH Terms] OR lung neoplasm[MeSH Terms] OR carcinoma, bronchogenic[MeSH Terms] OR NSCLC	874,462
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,377,750
#4	#1 AND #2	1,615
#5	#1 AND #2 AND #3	134
Time-filter	#1 AND #2 AND #3 Filters: 2016–2022	129
ClinicalTrial.gov		
Search	Non Small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Adenocarcinoma OR Squamous cell carcinoma OR Large cell carcinoma	Tagrisso OR Osimertinib
Filters	Phase 2, 3, 4 + Not applicable	
Results		136

Palbociclib

Pubmed		
#1	Ibrance OR Palbociclib	1,364
#2	Breast cancer OR Breast cancer* OR Breast Neoplasm OR Breast Neoplasm* OR Breast Tumor OR Breast Tumor* OR Mammary Cancer OR Mammary Cancer* OR (Malignant Neoplasm of Breast) OR Breast Malignant Neoplasm OR Breast Malignant Neoplasm* OR (Malignant Tumor of Breast) OR Breast Malignant Tumor OR Breast Malignant Tumor* OR Cancer of Breast OR Cancer of the Breast OR Human Mammary Carcinoma OR Human Mammary Carcinoma* OR Human Mammary Neoplasm OR Human Mammary Neoplasm* OR Breast Carcinoma OR Breast Carcinoma*	477,447
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,377,603
#4	#1 AND #2	881
#5	#1 AND #2 AND #3	212
Time filter	#1 AND #2 AND #3 Filters: 2016–2022	193
ClinicalTrial.gov		
Search	Breast cancer OR Breast Neoplasm OR Breast Tumor OR Mammary Cancer OR Breast Malignant Neoplasm OR Breast Malignant Tumor OR Cancer of Breast OR Cancer of the Breast OR Human Mammary Carcinoma OR Human Mammary Neoplasm OR Breast Carcinoma	Ibrance OR Palbociclib
Filters	Phase 2, 3, 4 + Not applicable	
Results	135	
New trial included		1

Ponatinib

	PubMed	
#1	Iclusig OR Ponatinib	864
#2	Chronic Myelogenous Leukemia OR Chronic myeloid leukemia OR Chronic granulocytic leukemia OR CML OR CGL OR Granulocytic Leukemia OR Myeloid Leukemia OR Myelogenous Leukemia OR Myelocytic Leukemia OR Chronic Monocytic Leukemia OR Chronic Myelogenous Leukemia* OR Chronic myeloid leukemia* OR Chronic granulocytic leukemia* OR Granulocytic Leukemia* OR Myeloid Leukemia* OR Myelogenous Leukemia* OR Myelocytic Leukemia* OR Chronic Monocytic Leukemia* OR Monocytic Leukemia* OR Chronic myelogenous leukaemia* OR Chronic granulocytic leukaemia* OR Chronic Myeloid Leukaemia* OR Myelogenous leukaemia* OR Myeloid Leukaemia* OR Granulocytic Leukaemia* OR leukemia, myeloid[MeSH Terms] OR leukemia[MeSH Terms]	279,170
#3	Acute Lymphoblastic Leukemia OR Acute Lymphoblastic Leukemia* OR Acute Lymphoblastic Leukaemia OR Acute Lymphocytic Leukemia OR Acute Lymphocytic Leukemia* OR Acute Lymphocytic Leukaemia OR Precursor Cell Lymphoblastic Leukemia Lymphoma OR Lymphoblastic Leukemia OR Lymphoblastic Lymphoma OR Lymphoblastic Lymphoma* OR Acute Lymphoid Leukemia OR L1 Lymphocytic Leukemia OR L2 Lymphocytic Leukemia OR Lymphoblastic Leukemia, Acute, L1 OR Leukemia, Lymphocytic, Acute, L2 OR Leukemia, Lymphoblastic, Acute, Philadelphia-Positive OR leukemia, lymphoid[MeSH Terms] OR leukaemia, lymphoid	108,508
#4	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,376,973
#5	#1 AND #2 AND #4	66
Time-filter	#1 AND #2 AND #4 Filters: 2014–2021	53
#8	#1 AND #3 AND #4	17
Time-filter	#1 AND #3 AND #4 Filters: 2014–2021	12

ClinicalTrial.gov		
Search	Chronic Myelogenous Leukemia OR Chronic myeloid leukemia OR Chronic granulocytic leukemia OR CML OR CGL OR Granulocytic Leukemia OR Myeloid Leukemia OR Myelogenous Leukemia OR Myelocytic Leukemia OR Chronic Monocytic Leukemia	Iclusig OR Ponatinib
Filters	Phase 2, 3, 4 + Not applicable	
Results		27
ClinicalTrial.gov		
Search	Acute Lymphoblastic Leukemia OR Acute Lymphoblastic Leukaemia OR Acute Lymphocytic Leukemia OR Acute Lymphocytic Leukaemia OR Precursor Cell Lymphoblastic Leukemia Lymphoma OR Lymphoblastic Leukemia OR Lymphoblastic Lymphoma OR Acute Lymphoid Leukemia OR L1 Lymphocytic Leukemia OR L2 Lymphocytic Leukemia	Iclusig OR Ponatinib
Filters	Phase 2, 3, 4 + Not applicable	
Results		26

Ribociclib

PubMed		
#1	Kisqali OR ribociclib	510
#2	Breast cancer OR Breast cancer* OR Breast Neoplasm OR Breast Neoplasm* OR Breast Tumor OR Breast Tumor* OR Mammary Cancer OR Mammary Cancer* OR (Malignant Neoplasm of Breast) OR Breast Malignant Neoplasm OR Breast Malignant Neoplasm* OR (Malignant Tumor of Breast) OR Breast Malignant Tumor OR Breast Malignant Tumor* OR Cancer of Breast OR Cancer of the Breast OR Human Mammary Carcinoma OR Human Mammary Carcinoma* OR Human Mammary Neoplasm OR Human Mammary Neoplasm* OR Breast Carcinoma OR Breast Carcinoma*	477,507
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,377,750
#4	#1 AND #2 AND #3	133
Time-filter	#1 AND #3 Filters: From 2017–2022	121
ClinicalTrial.gov		
Search	Breast cancer OR Breast Neoplasm OR Breast Tumor OR Mammary Cancer OR Breast Malignant Neoplasm OR Breast Malignant Tumor OR Cancer of Breast OR Cancer of the Breast OR Human Mammary Carcinoma OR Human Mammary Neoplasm OR Breast Carcinoma	Kisqali OR ribociclib
Filters	Phase 2, 3, 4 + Not applicable	
Results		50

Venetoclax

	PubMed	
#1	Venclyxto OR venetoclax	1,807
#2	Chronic Lymphocytic Leukemia OR Chronic Lymphocytic Leukemia* OR Chronic Lymphocytic Leukaemia OR CLL OR Small Lymphocytic Lymphoma OR Small Lymphocytic Lymphoma* OR Lymphoma, Small Lymphocytic, Plasmacytoid OR CLL Lymphoplasmacytoid Lymphoma OR CLL Lymphoplasmacytoid Lymphoma* OR Small Lymphocytic Lymphoma OR Small Lymphocytic Lymphoma* OR Lymphoma, Small Lymphocytic, Plasmacytoid OR Small-Cell Lymphoma OR Small-Cell Lymphoma* OR Small Cell Lymphoma OR Small Cell Lymphoma* OR Chronic Lymphoblastic Leukemia OR Chronic Lymphoblastic Leukemia* OR Chronic Lymphocytic Leukemia OR Chronic Lymphocytic Leukemia* OR Lymphocytic Lymphoma OR Lymphocytic Lymphoma* OR Well-Differentiated Lymphocytic Lymphoma OR Well-Differentiated Lymphocytic Lymphoma* OR B-Cell Chronic Lymphocytic Leukemia OR B-Cell Chronic Lymphocytic Leukemia* OR B Cell Chronic Lymphocytic Leukemia OR B Cell Chronic Lymphocytic Leukemia* OR Chronic B-Cell Leukemia OR Chronic B-Cell Leukemia* OR B-Cell Malignancy, Low-Grade OR Chronic B-Lymphocytic Leukemia OR Chronic B-Lymphocytic Leukemia* OR Chronic Lymphocytic Leukemia OR Chronic Lymphocytic Leukemia* OR Diffuse Well-Differentiated Lymphocytic Lymphoma OR Diffuse Well-Differentiated Lymphocytic Lymphoma* OR Diffuse Well Differentiated Lymphocytic Lymphoma OR Diffuse Well Differentiated Lymphocytic Lymphoma* OR (Disrupted B-Cell Malignancy) OR (Disrupted B-Cell Malignancy*) OR Leukemia, Chronic Lymphatic OR leukemia, b cell[MeSH Terms] OR leukemia, lymphoid[MeSH Terms]	142,474
#3	randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR clinical trials as topic [mesh: noexp] OR randomly[Title/Abstract] NOT (animals [mh] NOT humans [mh])	1,381,875
#4	#1 AND#2 AND #3	96
Time filter	#1 AND #2 AND #3 Filters: 2019–2022	64

	ClinicalTrial.gov	
Search	Chronic Lymphocytic Leukemia OR Chronic Lymphocytic Leukaemia OR CLL OR Small Lymphocytic Lymphoma OR CLL Lymphoplasmacytoid Lymphoma OR Lymphoma Small Lymphocytic Plasmacytoid OR Small-Cell Lymphoma OR Small Cell Lymphoma OR Chronic Lymphoblastic Leukemia OR Chronic Lymphocytic Leukemia OR Lymphocytic Lymphoma OR Well-Differentiated Lymphocytic Lymphoma OR B-Cell Chronic Lymphocytic Leukemia OR B Cell Chronic Lymphocytic Leukemia OR Chronic B-Cell Leukemia OR B-Cell Malignancy, Low-Grade OR Chronic B-Lymphocytic Leukemia OR Chronic Lymphocytic Leukemia OR Diffuse Well-Differentiated Lymphocytic Lymphoma OR Diffuse Well Differentiated Lymphocytic Lymphoma OR Disrupted B-Cell Malignancy	Venclyxto OR venetoclax
Filters	Phase 2, 3, 4 + Not applicable	
Results		82

Table S22. Summary of findings: drugs with continued lack of evidence of improvements in OS and QoL

Trial	Setting	Start	Cutoff	Sample	Drugs	HR (95% CI)	P-value	Intervention MOS	Control MOS	QoL Analysis	Instrument	QoL Result	P-value
ALECTINIB 1													
<i>Patients with ALK+ non-small cell lung cancer who have been previously treated with crizotinib</i>													
ALUR NCT02604342 ¹	13 countries	11/2015	09/2018	119	Alectinb vs chemotherapy	0.91 (0.49–1.70)	0.76	27.8 (18.2–NE)	NE (8.6–NE)	NR	NR	NR	NR
AXITINIB													
<i>Patients with advanced RCC after failure of prior treatments with sunitinib or cytokines</i>													
AXIS NCT00678392 ²	22 countries	09/2008	11/2011	723	Axitinib vs sorafenib	0.97 (0.8–1.17)	0.374	20.1 (16.7–23.4)	19.2 (17.5–22.3)	Yes	FKSI-15 FKSI-DRS	No difference	0.492
NCT02639182 ³	NR	NR	08/2019	133	Axitinib vs AGS-16C3F	0.93 (0.59–1.47)	0.747	15.4 (12.5–21.6)	13.1 (10.1–23.0)	NR	NR	NR	NR
NCT00920816 ⁴	7 countries	09/2009	10/2011	204	Axitinib vs sorafenib	0.96 (0.60–1.51)	0.42	NE	NE	Yes	FKSI-15 FKSI-DRS EQ-5D	No difference	NR
BOSUTINIB ^a													
<i>Patients with Ph+ CML in chronic, accelerated or blast phase previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.</i>													
No trials identified													
BRENTUXIMAB VEDOTIN													
<i>Patients with recurrent or refractory CD30+ Hodgkin's Lymphoma; following ASCT or following at least two prior therapies when ASCT or chemotherapy is not a treatment option or will be doing a ASCT (used as neo-adjuvant treatment</i>													
AETHERA NCT01100502 ^{5, 6}	America, Europe	04/2010	08/2014	329	Brentuximab vedotin vs placebo	1.15 (0.67–1.97)	0.6204	NE	NE	Yes	EQ-5D-3L EQ VAS	No difference	No

Table S22. Summary of findings: drugs with continued lack of evidence of improvements in OS and QoL (continued)

Trial	Setting	Start	Cutoff	Sample	Drugs	HR (95% CI)	P-value	Intervention MOS	Control MOS	QoL Analysis	Instrument	QoL Result	P-value
CABOZANTINIB													
<i>Patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma</i>													
EXAM NCT00704730 ⁷	23 countries	09/2008	08/2014	330	Cabozantinib vs placebo	0.85 (0.64–1.12)	0.24	26.6 (NR)	21.1 (NR)	No	NR	NR	NR
DABRAFENIB													
<i>Patients with unresectable or metastatic melanoma with a BRAF V600 mutation</i>													
BREAK-3 NCT01227889 ^{8,9}	12 countries	12/2010	12/2012	250	Dabrafenib vs dacarbazine	0.76 (0.48–1.21)	NR	18.2 (16.2–NR)	15.6 (NR)	Yes	EORT QLQ C30	No difference	NR
FULVESTRANT													
<i>Patients with ER+ locally advanced or metastatic breast cancer in postmenopausal women not previously treated with endocrine therapy</i>													
FALCON NCT01602380 ¹⁰	20 countries	10/2012	NR	462	Fulvestrant vs Anastrozole	NR	NR	NR	NR	Yes	FACT-B	No difference	NR
IDELASILIB ^a													
<i>Patient with follicular lymphoma that is refractory to two previous treatments</i>													
No trials identified													
LAROTREKTINIB													
<i>Treatment of patients with solid tumors with NTRK-gene fusion with locally advanced or metastatic disease or where surgical resection is likely to result in severe morbidity or who have no satisfactory treatment options.</i>													
No trials identified													

Table S22. Summary of findings: drugs with continued lack of evidence of improvements in OS and QoL (continued)

Trial	Setting	Start	Cutoff	Sample	Drugs	HR (95% CI)	P-value	Intervention MOS	Control MOS	QoL Analysis	Instrument	QoL Result	P-value
LORLATINIB <i>Patients with ALK+ non-small cell lung cancer whose disease has progressed after treatment with alectinib or ceritinib as first ALK tyrosine kinase inhibitor therapy; or crizotinib and at least another ALK TKI</i>													
No trials identified													
PONATINIB 1^a <i>Patients with CML in chronic, accelerated or blast phase, who are resistant to dasatinib or nilotinib; or who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not appropriate; or who have a T315I mutation</i>													
No trials identified													
PONATINIB 2^a <i>Patients with Ph+ Acute lymphocytic leukemia who are resistant to dasatinib and for whom subsequent treatment with imatinib is not appropriate; or who have T315I mutation</i>													
No trials identified													
NILOTINIB <i>Newly diagnosed patients with Ph+ CML</i>													
ENESTnd NCT00471497 ¹¹	NR	09/2007	08/2019	846	Nilotinib vs imatinib	0.79 (0.46–1.36)	0.4	NR	NR	NR	NR	NR	NR
LASOR NCT00802841 ¹²	Latin America, Europe, Asia	07/2009	07/2014	191	Nilotinib vs imatinib	0.54 (0.16–1.86)	0.31	NR	NR	NR	NR	NR	NR

Table S22. Summary of findings: drugs with continued lack of evidence of improvements in OS and QoL (continued)

Trial	Setting	Start	Cutoff	Sample	Drugs	HR (95% CI)	P-value	Intervention MOS	Control MOS	QoL Analysis	Instrument	QoL Result	P-value
ENESTchina NCT01275196 ¹²	Kina	04/2011	05/2013	267	Nilotinib vs Imatinib	NR	NR	NR	NR	NR	NR	NR	NR
NIRAPARIB													
<i>As maintenance treatment for patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response after platinum-based chemotherapy</i>													
ENGOT OV16 NCT01847276 ¹³	4 countries	08/2013	NR	553	Niraparib vs placebo	NR	NR	NR	NR	Yes	FOSI EQ-5D-5L EQ-VAS	No difference	NR
NORA NCT03705156 ¹⁴	China	09/2017	02/2020	265	Niraparib vs placebo	0.64 (0.29–1.49)	0.267	NR	NR	No	NR	NR	NR
VENETOCLAX													
<i>In combination with obinutuzumab for the treatment of adults with previously untreated CLL</i>													
CLL14 NCT02242942 ¹⁵¹⁶	21 countries	08/2015	09/2020	432	Venetoclax + obinutuzumabs vs obinutuzumabs + chlorambucil	0.85 (0.54–1.35)	0.49	NE	NE	Yes	EORTC QLQ-C30, MDASI-CLL	No difference	NR

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-3L, European Quality of Life 5 Dimensions 3 Level Version; EQ-VAS, European Quality of Life Visual Analogue Scale; FKSI-15, Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index 15 Items, FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – Disease-related symptoms; MDASI-CLL, MD Anderson Symptom Inventory, with the CLL module

Table S23. Studies with adjustments for cross-over, different doses, and alternative comparators within trials

	Trial	Article	Setting	Start	Cutoff	Sample	Drugs	HR (95% CI)	P-value	Intervention MOS	Control MOS
<i>Cross-over adjustment</i>											
Everolimus	RECORD-1 NCT00410124	Korhonen et al. ¹⁷	5 countries	12/2006	11/2008	416	Everolimus vs placebo	0.60 (0.22–1.65)	NR	NR	NR
Dabrafenib	BREAK-3 NCT01227889	Latimer et al. ⁸	12 countries	12/2010	12/2012	250	Dabrafenib vs dacarbazine	0.5 (0.15– 1.64)	NR	18.2 (16.6–NE)	15.6 (NR)
Nilotinib	ENESTnd, NCT00471497	Kantarjian et al. ¹¹	NR	09/2007	08/2019	846	Nilotinib* vs Imatinib	1.07 (0.64–1.76)	0.8	NR	NR
Osimertintib	AURA3 NCT02151981	Papadimitrakopoulou et al. ²²	18 countries	08/2014	02/2019	419	Osimertinib vs Pemetrexed + Carboplatin or Cisplatin	0.54 (0.18–1.6)	0.277	26.8 (23.5– 31.5)	22.5 (20.2–28.8)
<i>Alternative doses</i>											
Olaparib	SOLO2 NCT01874353	Poveda et al. ²⁰	16 countries	09/2013	02/2020	295	Olaparib vs placebo	0.56 (0.35–0.97)	NR	51.7 (41.5–59.1)	38.8 (31.4–48.6)
<i>Alternative comparator</i>											
Everolimus	NCT02724020	Choueiri et al. ¹⁹	35 countries	06/2016	02/2020	96	Everolimus vs Sapanisertib + TAK-117	0.67 (0.34–1.30)	0.546	18.1 (6.2–23.4)	22.4 (8.2–NE)

Table S24. Pooled estimates of the effects on OS from fixed effects meta-analyses

	Alectinib	Everolimus	Palbociclib	Axitinib	Olaparib	Osimertinib	Nilotinib
HR	0.73	1.23	1.05	0.96	0.73	0.83	0.74
(95% CI)	(0.56–0.96)	(1.10–1.36)	(0.87–1.26)	(0.82 – 1.13)	(0.60–0.90)	(0.70–0.97)	(0.45–1.22)
[P-value]	[0.022]	[<0.001]	[0.624]	[0.646]	[0.003]	[0.023]	[0.239]
I ²	72.83	78.75	47.75	0	0	0	0
Confirms primary results	Yes	No	Yes	Yes	Yes	Yes	Yes

Note: Pooled hazard ratios from fixed-effects inverse variance meta-analyses for drug indications with multiple trials (n=7) and reported summary estimates of the effects on OS.

Table S25. List of all reports and trials included in the review

Drug, trial	Primary reports OS, QoL	Preceding reports	Subgroup-analyses, reports
<i>Alectinib 1</i>			
ALUR NCT02604342	Wolf et al. 2022 ¹	Novello et al. (2018) ²⁴	
<i>Alectinib 2</i>			
ALEX NCT02075840	Mok et al. 2020 ²⁵	Peters et al. 2017 ²⁶	
	Pérol et al. 2019 ²⁷	Camidge et al. 2019 ²⁸	
J-ALEX number JapicCTI-132316	Hotta et al. 2022 ²⁹	Hida et al. 2017 ³⁰	
		Nakagawa et al. 2020 ³¹	
ALESIA, NCT02838420	Zhou et al. 2019 ³²		
No trial registration code	Li et al. 2021 ³³		
<i>Axitinib</i>			
AXIS, NCT00678392	Motzer et al. 2013 ²	Cella et al. 2013 ³⁴	Ueda et al. 2013 ³⁵
			Escudier et al. 2014 ³⁶
			Bracarda et al. 2019 ³⁷
Studie NCT02639182	Kollmannsberger et al. 2021 ³		
Studie NCT00920816.	Qin et al. 2015 ⁴		
<i>Brentuximab Vedotin</i>			
AETHERA NCT01100502	Moskowitz et al. 2015 ⁵		
	Ramsey et al. 2016 ⁶		
<i>Cabozantinib</i>			
EXAM NCT00704730	Schlumberger et al 2017 ⁷	Elisei et al. 2013 ³⁸	

Table S24. List of all reports and trials included in the review (continued)

Drug, trial	Primary reports OS, QoL	Preceding reports	Subgroup-reports
<i>Ceritinib</i>			
ASCEND-5 NCT01828112	Shaw et al. 2017 ³⁹	Kiura et al. 2018 ⁴⁰	
<i>Dabrafenib</i>			
BREAK-3 NCT01227889	Hauschild et al. 2020 ⁴¹		
	Latimer et al. 2015 ⁸		
	Grob et al. 2014 ⁹		
<i>Everolimus</i>			
METEOR NCT01865747	Motzer et al. 2018 ⁴²	Choueiri et al. 2015 ⁴³	Donskov et al. 2020 ⁴⁴
	Cella et al. 2018 ⁴⁵	Choueiri et al. 2016 ⁴⁶	Escudier et al. 2018 ⁴⁷
			Powles et al. 2021 ⁴⁸
			Schmindiger et al. 2022 ⁴⁹
RECORD-1 NCT00410124	Motzer et al. 2010 ⁵⁰	Korhonen et al. 2012 ¹⁷	Porta et al. 2012 ⁵¹
	Beumont et al. 2011 ¹⁸		Tsukamoto et al. 2011 ⁵²
CheckMate025 NCT0166878	Motzer et al. 2020 ⁵³	Motzer et al. 2015 ⁵⁴	Escudier et al. 2017 ⁵⁵
		Cella et al. 2016 ⁵⁶	Tomita et al. 2017 ⁵⁷
		Shah et al. 2019 ⁵⁸	Tomita et al. 2019 ⁵⁹
ZEBRA EUDRACT no. 2008-005614- 44	Powles et al. 2016 ⁶⁰		
ROVER, NCT01442090.	Powles et al. 2016 ⁶¹		
NCT01136733	Motzer et al. 2015 ⁶²		
NCT02724020	Choueiri et al. 2022 ¹⁹		
NCT01239342	Jonasch et al. 2017 ⁶³		

Table S24. List of all reports and trials included in the review (continued)

Trial	Primary reports OS, QoL	Preceding reports	Subgroup-analyses, reports
<i>Fulvestrant</i>			
FALCON NCT01602380	Robertson et al. 2018 ¹⁰		
<i>Nilotinib</i>			
LASOR, NCT00802841	Cortes et al. 2016 ¹²		
ENESTnd, NCT00471497	Kantarjian et al. 2021 ¹¹	Kantarjian et al. 2011 ⁶⁴ Larson et al. 2012 ⁶⁵ Hughes et al. 2014 ⁶⁶ Hochhaus et al. 2016 ⁶⁷	
ENESTchina, NCT01275196	Wang et al. 2015 ⁶⁸		Yu et al. 2018 ⁶⁹
<i>Niraparib</i>			
ENGOT-OV16/NOVA NCT01847274	Oza et al. 2018 ¹³		Fabbro et al. 2019 ⁷⁰ Del Campo et al. 2019 ⁷¹
NORA NCT03705156	Wu et al. 2021 ¹⁴		
<i>Olaparib</i>			
SOLO2 (ENGOT Ov-21) NCT01874353	Proveda et al. 2021 ²⁰ Friedl et al. 2018 ²¹		Liu et al. 2022 ⁷² Trillsch et al. 2022 ⁷³
SOLO3, NCT02282020	Penson et al. 2020 ⁷⁴		
Study 19, NCT00753545	Friedl et al. 2018 ⁷⁵		
NCT02446600	Liu et al. 2022 ⁷⁶		
<i>Osimertinib</i>			
FLAURA, NCT02296125	Ramalignam et al. 2020 ⁷⁷ Leighl et al. 2020 ⁸⁰	Soria et al. 2018 ⁷⁸	Cho et al. 2018 ⁷⁹ Ohe et al. 2019 ⁸¹

Table S24. List of all reports and trials included in the review (continued)

Trial	Primary reports	Preceding reports	Subgroup-reports
AURA3, NCT02151981	Papadimitrakopoulou et al 2020 ²² Lee et al. 2018 ²³	Mok et al. 2017 ⁸³	Cheng et al. 2021 ⁸²
NCT02959749	Nie et al. 2018 ⁸⁴		
<i>Palbociclib</i>			
PALOMA-2 NCT01740427	Rugo et al. 2019 ⁸⁵	Rugo et al. 2018 ⁸⁶ Rugo et al. 2018 ⁸⁸	Turner et al. 2018 ⁸⁷
PENELOPE-B NCT01864746	Loibl. et al. 2021 ⁸⁹	NR ⁹⁰	
PALLAS NCT02513394	Gnant et al. 2021 ⁹¹	Mayer et al. 2021 ⁹²	
PEARL NCT02028507	Martin et al. 2021 ⁹³		
PALOMA-4 NCT02297438	Xu et al. 2022 ⁹⁴ Results from Clinicaltrial.gov ⁹⁵		
<i>Ribociclib</i>			
MONALEESA-2	Hortobagyi et al.2022 ⁹⁶ Janni et al. 2018 ⁹⁹	Hortobagyi et al. 2018 ⁹⁷ Verma et al. 2018 ¹⁰⁰	Yardley et al. 2019 ⁹⁸
<i>Venetoclax</i>			
CLL14, NCT02242942	Al-Sawaf et al. 2021 ¹⁵ Al-Sawaf et al. 2021 ¹⁶	Fisher et al. 2019 ¹⁰¹ Al-Sawaf et al. 2020 ¹⁰²	

Note: List of included reports for each drug and trial. Primary reports concern the main reports used to retrieve data on OS and QoL. All included reports as well as study information from Clinicaltrial.gov was additionally used to extract information on trial characteristics.

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