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Federal Department of Home Affairs
Federal Office of Public Health FOPH
Health and Accident Insurance Directorate
Section Health Technology Assessment

Health Technology Assessment (HTA)

Scoping Report

Title	Palbociclib (Ibrance®) for the treatment of hormone receptor (HR)-positive, human epidermal growth factor (HER2)-negative advanced breast cancer
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Technology	Palbociclib (Ibrance®)
Date	14 July 2020
Type of Technology	Pharmaceuticals

Executive Summary (max. 250 words):

Inhibitors of cyclin-dependent kinases 4/6 (CDK4/6) are a relatively recent addition to the treatment options available for patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative locally advanced or metastatic breast cancer. Three CDK4/6 inhibitors – palbociclib, ribociclib and abemaciclib – are now available in Switzerland. The clinical and economical effectiveness of palbociclib has been questioned.

This scoping report evaluates the feasibility of a health technology assessment (HTA), assessing 1) the efficacy, effectiveness, safety and cost effectiveness of palbociclib compared with other CDK4/6 inhibitors and endocrine therapies, 2) the costs of palbociclib and the budget impact of a potential change in reimbursement status of palbociclib, 3) related legal, social, ethical and organisational issues.

Few clinical trials compare palbociclib with relevant alternative treatments. The available body of evidence from randomised controlled trials for the assessment of efficacy, effectiveness and safety appears sufficient to perform indirect comparisons through network meta-analysis. Further, a number of observational studies provide additional safety data on palbociclib.

To assess cost effectiveness, it will be necessary to adapt and substantially extend an existing Swiss model. Cost data and other relevant model parameters will have to be gathered from several sources. The budget impact analysis will include changes in overall drug costs; several scenarios are proposed in consultation with the FOPH and clinical experts.

Sufficient literature is available to address the defined relevant ethical and organisational issues. Evidence to appropriately address the defined relevant legal and social issues is scarce or lacking.

Following the expert review, the suggested PICO, the title and the key questions for the full HTA report have been extended to include all CDK 4/6 inhibitors as interventions. For reasons of feasibility the number of comparators has been reduced and it was decided not to address legal and social issues.

Zusammenfassung:

Inhibitoren der cyclinabhängigen Kinasen 4 und 6 (CDK4/6) sind eine relativ neue Therapieoption für Patientinnen mit einem lokal fortgeschrittenen oder metastasierenden hormonrezeptorpositiven, für den humanen epidermalen Wachstumsfaktor-Rezeptor 2 negativen Mammakarzinom. Unterdessen sind in der Schweiz drei CDK4/6-Inhibitoren verfügbar: Palbociclib, Ribociclib und Abemaciclib. Die klinische Wirksamkeit und die Wirtschaftlichkeit von Palbociclib wurden in Frage gestellt.

Mit diesem Scoping-Bericht wird die Durchführbarkeit einer Gesundheitstechnologiebewertung (HTA) abgeklärt, mit der die folgenden Aspekte beurteilt werden: 1) die Wirksamkeit unter idealen Bedingungen und unter Alltagsbedingungen sowie die Verträglichkeit und die Kosteneffizienz von Palbociclib im Vergleich zu anderen CDK4/6-Inhibitoren und Hormontherapien, 2) die Kosten von Palbociclib und die budgetären Auswirkungen einer potenziellen Änderung des Kostenerstattungsstatus von Palbociclib, 3) die damit verbundenen rechtlichen, sozialen, ethischen und organisatorischen Fragen.

Es liegen nur wenige klinische Studien vor, in denen Palbociclib mit anderen einschlägigen Therapien verglichen wird. Die verfügbaren evidenzbasierten Daten aus randomisierten kontrollierten Studien zur Bewertung der Wirksamkeit unter idealen Bedingungen und unter Alltagsbedingungen sowie der Verträglichkeit erscheinen ausreichend, um über Netzwerk-Metaanalysen indirekte Vergleiche durchzuführen. Zudem werden mehrere Beobachtungsstudien zusätzliche Daten zur Verträglichkeit von Palbociclib liefern.

Zur Beurteilung der Kosteneffizienz muss ein bestehendes schweizerisches Modell angepasst und erheblich erweitert werden. Die Daten zu den Kosten sowie weitere relevante Modellparameter müssen aus verschiedenen Quellen zusammengetragen werden. In die Ausgaben-Einfluss-Analyse werden Veränderungen der gesamten Arzneimittelkosten aufgenommen; in Absprache mit dem BAG und klinischen Expertinnen und Experten werden verschiedene Szenarien vorgeschlagen.

Für die Bearbeitung der festgelegten relevanten ethischen und organisatorischen Fragen ist ausreichend Literatur verfügbar. Hingegen liegen nur wenige oder gar keine evidenzbasierten Daten vor, um die festgelegten relevanten rechtlichen und sozialen Fragen angemessen anzugehen.

Nach der Überprüfung durch Expertinnen und Experten wurden das vorgesehene PICO-Schema, der Titel und die zentralen Fragen für den ausführlichen HTA-Bericht ergänzt, indem alle CDK4/6-

Inhibitoren als Interventionen aufgenommen wurden. Im Hinblick auf die Durchführbarkeit wurde die Zahl der Vergleichssubstanzen verringert. Zudem wurde beschlossen, auf die Bearbeitung der rechtlichen und sozialen Fragen zu verzichten.

Synthèse:

Les inhibiteurs des kinases dépendantes des cyclines 4/6 (inhibiteurs CDK 4/6 pour *cyclin-dependant kinases*) constituent une nouvelle option thérapeutique pour les patientes atteintes d'un cancer du sein positif aux récepteurs hormonaux, négatif aux récepteurs 2 du facteur de croissance épidermique humain et localement avancé ou métastatique. Trois inhibiteurs CDK 4/6 – le palbociclib, le ribociclib et l'abémaciclib – sont désormais disponibles en Suisse. L'efficacité clinique et l'économicité du palbociclib ont été remises en question.

Le présent rapport détermine la faisabilité d'une évaluation des technologies de la santé (ETS ou HTA pour *health technology assessment*) pour apprécier 1) l'efficacité, la sécurité et l'économicité du palbociclib en comparaison avec d'autres inhibiteurs CDK 4/6 et traitements endocriniens, 2) les coûts du palbociclib et l'impact budgétaire d'un éventuel changement dans son remboursement, 3) les aspects légaux, sociaux, éthiques et organisationnels y relatifs.

Peu d'essais cliniques ont comparé le palbociclib à des traitements alternatifs pertinents. Le corpus de preuves issues d'essais contrôlés randomisés concernant l'efficacité théorique et pratique ainsi que la sécurité semble suffisant pour effectuer des comparaisons indirectes à l'aide de méta-analyses en réseau. De plus, diverses études d'observation fournissent des données supplémentaires sur la sécurité du palbociclib.

En ce qui concerne l'évaluation de l'économicité, il sera nécessaire d'adapter et d'étendre considérablement un modèle suisse existant. Les données sur les coûts devront être réunies à partir de plusieurs sources, de même que divers paramètres de modèles pertinents. L'analyse de l'impact budgétaire inclura des changements dans les coûts totaux des médicaments ; elle proposera plusieurs scénarios, en concertation avec l'OFSP et les experts cliniques.

La littérature est suffisamment abondante pour aborder les aspects éthiques et organisationnels pertinents tels que définis. Il n'existe en revanche que peu, voire pas de documentation permettant de répondre de manière appropriée aux questions légales et sociales définies.

Conformément à l'évaluation des experts, le protocole PICO, le titre et les questions clés du rapport ETS complet ont été étendus à tous les inhibiteurs CDK 4/6. Pour des raisons de faisabilité, il a été décidé de réduire le nombre de comparateurs et de ne pas aborder les aspects légaux et sociaux.

Sintesi:

Gli inibitori delle chinasi ciclina-dipendenti (CDK4/6) rappresentano un'opzione di trattamento relativamente recente per pazienti con carcinoma mammario localmente avanzato o metastatico positivo al recettore degli ormoni e negativo al recettore 2 per il fattore di crescita epidermico umano. In Svizzera sono disponibili tre inibitori delle CDK4/6: palbociclib, ribociclib e abemaciclib. L'efficacia clinica ed economica di palbociclib è stata messa in discussione.

Il presente rapporto di scoping valuta la fattibilità di un Health Technology Assessment (HTA) che verifichi 1) efficacia, sicurezza ed efficienza dal punto di vista dei costi di palbociclib rispetto ad altri inibitori delle CDK4/6 e terapie endocrine; 2) il costo di palbociclib e le ripercussioni sul budget di un potenziale cambiamento dello stato della rimunerazione di palbociclib; 3) questioni collegate di natura legale, sociale, etica e organizzativa.

Pochi studi clinici confrontano palbociclib a trattamenti alternativi rilevanti. Gli elementi di prova disponibili derivanti da studi controllati randomizzati per la valutazione dell'efficacia, dell'efficienza e della sicurezza appaiono sufficienti per effettuare confronti indiretti attraverso meta-analisi «a rete». Inoltre, una serie di studi di osservazione fornisce ulteriori dati sulla sicurezza di palbociclib.

Per valutare l'efficienza dal punto di vista dei costi sarà necessario adattare ed estendere considerevolmente un modello svizzero esistente raccogliendo da varie fonti dati relativi ai costi e altri parametri del modello rilevanti. L'analisi dell'impatto sul budget comprenderà le variazioni dei costi complessivi del medicamento; d'intesa con l'UFSP ed esperti clinici, saranno proposti diversi scenari.

La letteratura disponibile è sufficiente per rispondere alle questioni di natura etica e organizzativa rilevanti e definite. Tuttavia, scarseggiano o sono assenti evidenze per affrontare in maniera appropriata le questioni di natura legale e sociale.

Come suggerito dalla revisione degli esperti, lo schema PICO proposto, il titolo e le domande chiave per il rapporto HTA completo sono stati estesi per includere tutti gli inibitori delle CDK4/6 impiegati come trattamento. Per motivi di fattibilità, il numero di comparatori è stato ridotto e si è deciso di non affrontare le questioni legali e sociali.

Table of contents

List of tables

List of figures

Abbreviations and acronyms

ABC	Advanced breast cancer
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie e.V.
AI	Aromatase inhibitor
CDK	Cyclin-dependent kinase
CTCAE	Common Terminology Criteria for Adverse Events
ESO-ESMO	European School of Oncology – European Society for Medical Oncology
ET	Endocrine therapy
FOPH	Federal Office of Public Health
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HR	Hazard ratio
HR+	Hormone receptor-positive
HER2-	Human epidermal growth factor receptor 2-negative
HrQoL	Health related quality of life
HTA	Health Technology Assessment
IQWiG	Institute for Quality and Efficiency in Health Care
LABC	Locally advanced breast cancer
LA/MBC	Locally advanced or metastatic breast cancer
LHRH	Luteinising hormone-releasing hormone
LYG	Life-year gained
MA	Meta-analysis
MBC	Metastatic breast cancer
N.A.	Not applicable
NMA	Network meta-analysis
NRS	Non-randomised study
OKP	Mandatory health insurance (obligatorische Krankenpflegeversicherung)
OS	Overall survival
PFS	Progression-free survival
PICO	Patients, Interventions, Comparators, Outcomes
PICO (EO)	Population, intervention, comparator, outcome (economic outcomes)
PR	Progesterone receptor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient reported outcome
QALY	Quality adjusted life-year
QoL	Quality of life
Rb	Functional retinoblastoma
RCT	Randomised controlled trial
SL	List of specialties (Spezialitätenliste)
SR	Systematic review
SERD	Selective oestrogen receptor degrader
SERM	Selective oestrogen receptor modulator
TTP	Time to progression

Short forms for interventions

ABE	Abemaciclib
ANA	Anastrozole
EXE	Exemestane
LET	Letrozole
FUL	Fulvestrant
PAL	Palbociclib
pbo	Placebo
RIB	Ribociclib
RoB	risk of bias
TAM	Tamoxifen

Objective of the HTA scoping report

The objective of the scoping report is to conduct a systematic literature search and to synthesise the available evidence base addressing the main health technology assessment (HTA) domains, i.e. clinical effectiveness/safety, costs/budget impact/cost effectiveness, legal/social/ethical and organisational issues. In the report, the analytical methods are described that are to be used if an HTA is pursued. Based on the quantity and quality of the extracted evidence, the feasibility of pursuing an HTA is judged. An analysis of the individual study outcomes is not the objective of the scoping report.

1 Policy question and context

Each HTA topic entails a policy and a research question. In healthcare, a ***policy question*** is a request to regulate a reimbursement policy and is aimed at securing financing of health technologies. Such a request, related to a particular health technology, typically addresses an existing controversy around a technology. The controversy is brought forward by the applicant of the HTA topic. This HTA report addresses the following policy question:

In 2017, the Swiss Agency for Therapeutic Products (Swissmedic) granted marketing authorisation for palbociclib (PAL) for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced (LABC) or metastatic breast cancer (MBC) in combination with an aromatase inhibitor (AI) or in combination with fulvestrant (FUL) in women who had received prior endocrine therapy (ET). In pre- or perimenopausal women, ET should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.[1] Currently, the mandatory health insurance (OKP) reimburses PAL 1) as a first-line treatment in combination with AIs if the disease-free interval has lasted for more than 12 months after completion of a neoadjuvant or adjuvant therapy with anastrozole (ANA) or letrozole (LET); 2) in combination with FUL as a first-line treatment for relapse during neoadjuvant or adjuvant ET or within 12 months of completion of adjuvant ET; 3) in combination with FUL as a second-line therapy after ET was already used as a first-line therapy in the metastatic stage.

Results from clinical studies in patients with HR+/HER2- locally advanced or metastatic breast cancer (LA/MBC) suggest that PAL in combination with FUL prolongs progression-free survival[2] but has no statistically significant effect on the overall survival (OS)[3] of these patients. This would render PAL the only drug in its class that has not been shown to statistically significantly prolong OS in combination with FUL. Furthermore, conflicting data concerning the role of PAL in improving health-related quality of life and the incidence of haematological adverse events during PAL therapy exist.[2 4-6] Lastly, different HTA reports and cost effectiveness studies in other countries suggest an unfavourable cost effectiveness ratio for PAL in combination with LET or FUL when compared with LET or FUL monotherapy.[7-9] Therefore, it was proposed that an HTA is conducted to review the efficacy, safety and cost effectiveness of PAL compared with similar drugs within the same drug class or endocrine monotherapy for treating patients with HR+/HER2- LA/MBC.

2 Research question

To answer a policy question, the research question has to be defined and answered first. The ***research question*** is an answerable inquiry into the HTA topic, which requires data collection and analysis. Research questions are specific and narrow. This HTA report addresses the following research question:

What is the efficacy, effectiveness, safety, cost effectiveness and budgetary impact of PAL 1) in combination with an AI in women with HR+/HER2- LA/MBC who have not received prior ET for advanced-stage disease and 2) in combination with FUL in women with disease progression following ET for advanced-stage disease, compared with alternative treatment options (as defined, for example, in guidelines)?

Are there any legal, social, ethical or organisational issues associated with the use of PAL in this context?

3 Medical background

Breast cancer commonly develops from an uncontrolled growth of epithelial cells lining the milk ducts or lobules, or both, caused by dysregulation of the cell cycle. Aberrant hormone and growth factor signalling also contributes to the development of breast cancer. Lifestyle-related factors like decreased childbearing, an increase in obesity, decreased physical activity and others may play a role in increasing breast cancer rates as well.[10]

Breast cancer is the most commonly diagnosed cancer in women (in both transitioned and transitioning countries), with over 5'700 newly diagnosed cases every year in Switzerland. It is also the leading cause of cancer deaths worldwide in women. In Switzerland, around 1'400 patients die each year from the disease.[11] (These numbers derive from an epidemiologic analysis of the years 2008 to 2012.)

Initial signs of breast cancer may include a lump in the breast, a change in the size or shape of the breast, skin irritation, and breast or nipple pain. The stage of breast cancer is determined by the cancer's characteristics, such as tumour size and receptor status. Primary invasive cancers are investigated as a matter of routine for expression of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). Since 2007, standardised methods have been implemented for testing HER2 expression in invasive breast cancer to improve the accuracy of HER2 testing and its utility as a predictive marker.[12] Tumours expressing either ER, PR or both are termed hormone receptor (HR)-positive, with HR-positive cancers accounting for approximately 65 per cent and 80 per cent of breast cancers in pre- and postmenopausal women, respectively.[13] Breast cancers are then classified with respect to the presence or absence of receptors as luminal A (HR-positive and HER2-negative), luminal B (HR-positive and HER2-positive), HER2-enriched (HR-negative and HER2-positive) or basal-like (HR-negative and HER2-negative; triple negative breast cancer).[14] [15] HR-positive and HER2-negative (luminal A type) is the most common subtype, accounting for 78 per cent of all breast cancers.[16]

Tumour biology influences the prognosis for breast cancer patients and determines treatment options. The preferred treatment for HR+/HER2- breast cancers is ET. Traditional ET agents include the selective oestrogen receptor modulator (SERM) tamoxifen (TAM), the selective oestrogen receptor degrader (SERD) FUL as well as several AIs, including the steroidal AI exemestane (EXE) and the non-steroidal aromatase inhibitors (NSAIs) LET and ANA.[17] Even with early-stage disease and optimal treatment, many patients will develop recurrent or progressive disease and ultimately require treatment with cytotoxic chemotherapeutics.[18] Approximately 20 to 30 per cent of patients with early-stage disease will relapse with distant metastatic disease.[19] [20]

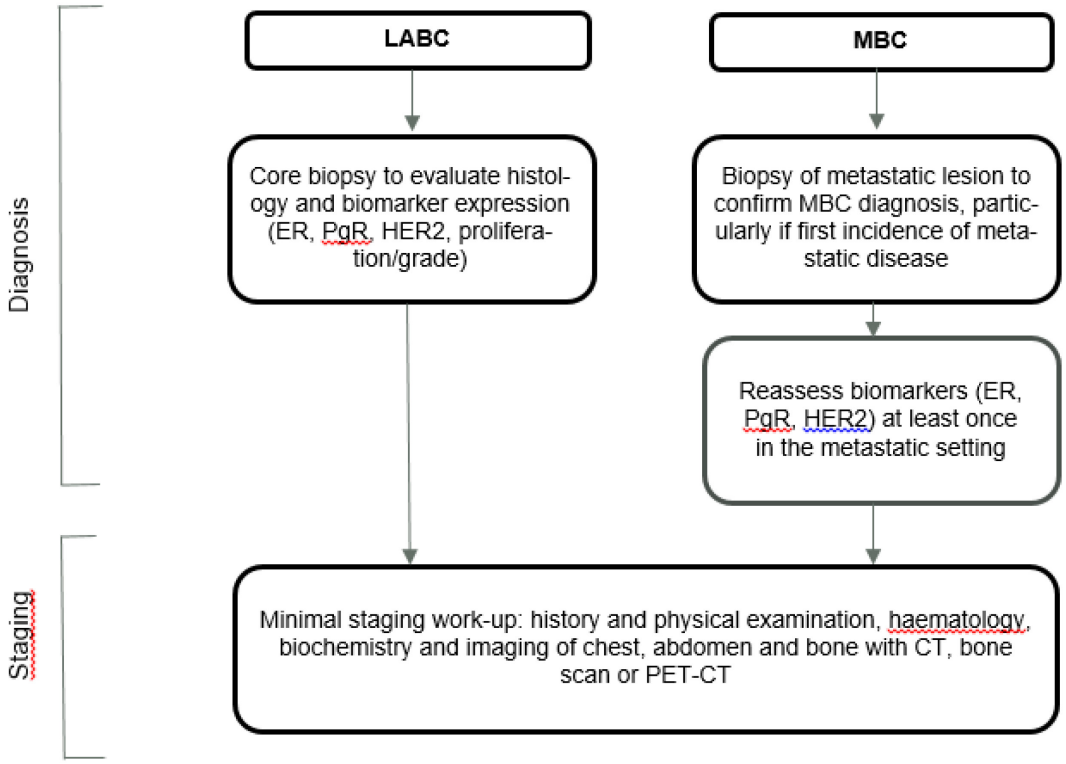
Advanced breast cancer (ABC) generally comprises both locally advanced breast cancer (LABC) and metastatic breast cancer (MBC).[21] In this context, according to the guidelines of the European School

of Oncology (ESO) and the European Society for Medical Oncology (ESMO), LABC is defined as inoperable locally advanced disease (stage IIIB, IIIC) that has not yet spread to distant sites.[22] Metastatic breast cancer (MBC) is a treatable but incurable disease with a median overall survival (OS) of around 3 years and a 5-year OS rate of only around 25 per cent.[23 24] As the research questions for the planned HTA apply equally to LABC and MBC, we will refer to both disease manifestations collectively using the term LA/MBC. Current treatments for LA/MBC focus on prolonging life, relieving symptoms and improving and maintaining the quality of life (QoL). Treatment-associated toxicities must be outweighed by the potential benefits.[19]

According to clinical guidelines relevant for the Swiss context, endocrine-based therapy (including combination therapies with CDK4/6-inhibitors) should be considered first choice in women with hormone receptor-positive LA/MBC (HER2-negative), irrespective of their menopausal status.[25] Monochemotherapy is the treatment of choice in slowly progressing disease or if secondary resistance to ET arises. Combination chemotherapy is recommended in the case of a visceral crisis or if clinical remission needs to be achieved urgently.[26]

Diagnostic and treatment algorithms for LA/MBC taken from the ESO–ESMO International Consensus Guidelines are provided in Figure 1 and Figure 2, respectively.[21]

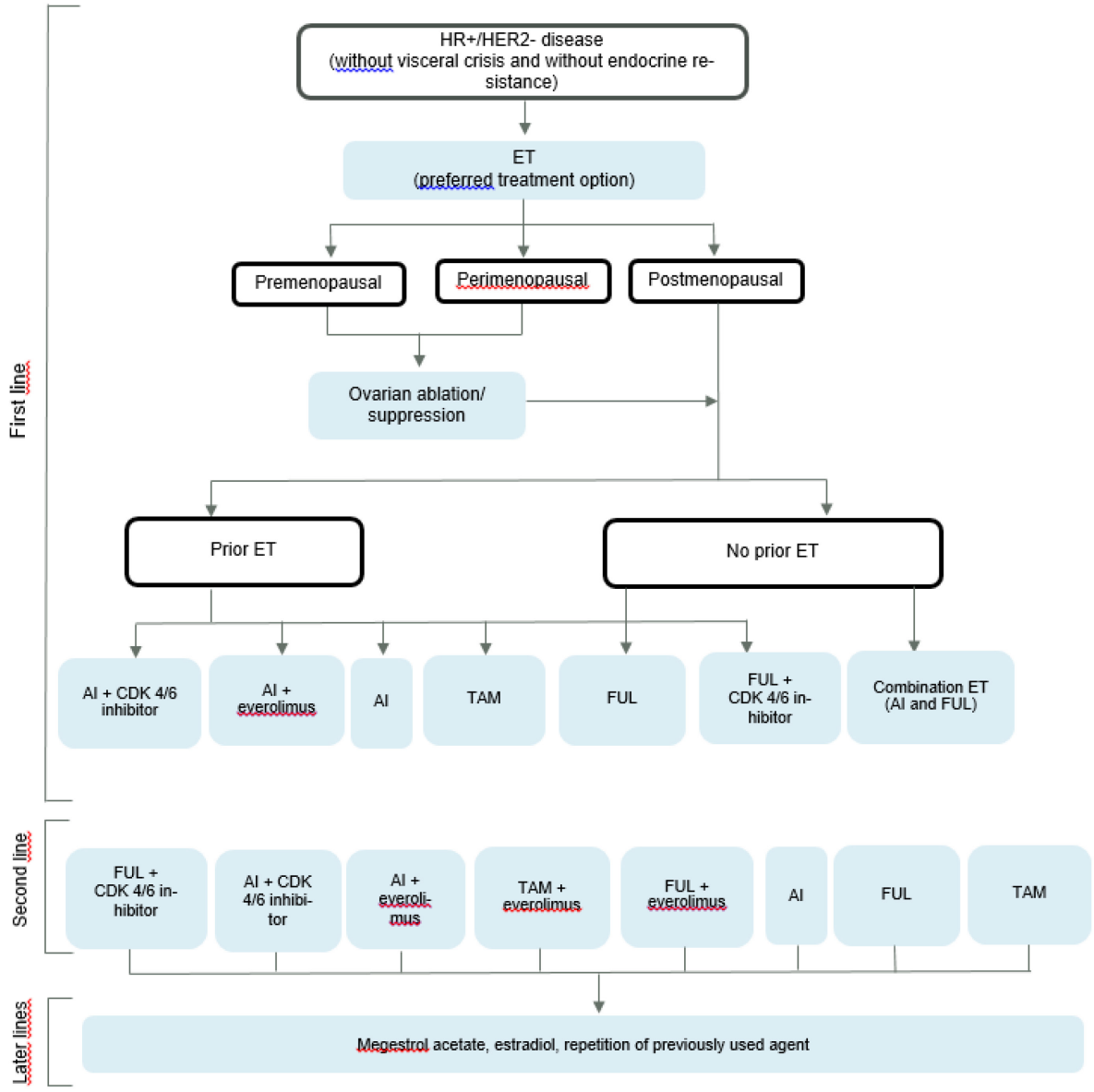
Figure 1: Diagnosis and staging of LA/MBC



CT=computed tomography; ER=oestrogen receptor; HER2=human epidermal growth factor 2; LABC=locally advanced breast cancer; MBC=metastatic breast cancer; PET-CT=positron emission computed tomography; PgR=progesterone receptor

Source: Modified from Cardoso et al. 2018[21]

Figure 2: Treatment of HR+/HER2- LA/MBC



AI=aromatase inhibitor; CDK=cyclin-dependent kinase; ET=endocrine therapy; FUL=fulvestrant; HR=hormone receptor; HER2=human epidermal growth factor 2; TAM=tamoxifen

Source: Modified from Cardoso et al. 2018[21]

4 Technology

4.1 Technology description

In recent years, a novel class of drugs that prevent cell cycle progression has been tested for the treatment of LA/MBC. This class of drugs targets the two key cell cycle regulators cyclin-dependent kinases 4 and 6 (CDK4/6) and, to date, comprises three small-molecule inhibitors: palbociclib (PAL), ribociclib (RIB) and abemaciclib (ABE). The effects of CDK4/6 inhibitors are dependent on the presence of a functional retinoblastoma (Rb) protein.[27] Highly selective oral CDK4/6 inhibitors like PAL can inhibit the proliferation of Rb-positive tumour cells and show dose-dependent growth inhibition in animal models of HR+ breast cancer.[28 29]

PAL (Ibrance®) is available as capsules (75 mg, 100 mg and 125 mg). The recommended dose is 125 mg once a day for 21 consecutive days, followed by a 7-day break to complete a 28-day treatment cycle.[30] Treatment should be started and supervised by a doctor experienced in the use of cancer medication. PAL is indicated for the treatment of HR+/HER2- LA/MBC in combination with an AI or in combination with FUL in women who have received prior ET. In pre- or perimenopausal women, ET should be combined with an LHRH agonist.[1] Treatment is continued as long as there is a clinical benefit and the side effects are tolerable. If treatment-associated side effects occur, treatment may need to be interrupted or stopped or the dose may need to be reduced.

The most common severe side effects of PAL are reduced blood cell counts (neutropenia, leukopenia, anaemia), tiredness and infections. Contraindications are hypersensitivity to the active substance or to any of the excipients and use of preparations containing St. John's Wort. The product contains lactose; therefore, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not be treated with PAL. Women of childbearing potential or their male partners must use a highly effective method of contraception while taking this medicine.[30]

PAL is primarily metabolised by Cytochrome P450 3A4 (CYP3A4) and sulfotransferase 2A1 (SULT2A1).[31] Concomitant treatment with strong inhibitors of CYP3A4 may lead to increased toxicity and their use during treatment with PAL should be avoided.[32] If co-administration with a strong CYP3A4 inhibitor is unavoidable, a dose reduction to 75 mg once daily is required. Co-administration of CYP3A4 inducers may lead to decreased PAL exposure and consequently to a risk of inefficacy. Therefore, concomitant use of PAL with strong CYP3A4 inducers should be avoided.[30]

4.2 Alternative technologies

The recommended first-line treatment for HR+/HER2- LA/MBC is ET, which may be combined with a CDK4/6 inhibitor (see Figure 2). The different CDK4/6 inhibitors and ET agents approved in Switzerland are listed in Table 1.

The recommended dose of RIB is 600 mg per day, adhering to the same schedule as for PAL (28-day cycle), while the recommended dose of ABE is 150 mg continuously. The three CDK4/6 inhibitors have similar safety profiles but also some unique side effects.[33] [34] A high incidence of grade 3 and 4 neutropenia has been reported for PAL, RIB has a potential for QT interval prolongation, whereas ABE is associated with less haematological toxicity but more gastrointestinal symptoms and a higher rate of fatigue.[33]

Different types of ET are available for breast cancer. They typically act either by lowering oestrogen levels or by inhibiting the pro-proliferative effect of oestrogen on breast cancer cells.

The oral SERM TAM acts as an oestrogen receptor antagonist in breast tissue. Commonly reported side effects of TAM include hot flashes, nausea, vaginal dryness and discharge. The recommended dose for the patient population studied in this report is 20 mg to 40 mg orally per day.

The SERD FUL achieves oestrogen receptor degradation and is administered by intramuscular injection. In the first month of treatment, the injections are given 2 weeks apart. After that, they are given once a month. The recommended dose of FUL is 500 mg per injection. Common side effects of FUL include injection site reactions (pain, swelling, redness), nausea, vomiting, loss of appetite, constipation, diarrhoea, muscle pain and musculoskeletal complaints.[35]

Third-generation AIs have become the standard of care for the treatment of postmenopausal women with HR+ LA/MBC. LET and ANA are non-steroidal AIs that reversibly and competitively bind aromatase whereas EXE, a steroidal AI, irreversibly deactivates the enzyme. All three AIs are taken orally once per day, with recommended doses of 1 mg for ANA, 2.5 mg for LET and 25 mg for EXE. The side effects of AIs include hot flashes, weight gain, insomnia, musculoskeletal complaints, mood changes, vaginal dryness and vaginal discharge.

Table 1: List of preparations of the assessed interventions available in Switzerland

Substance class	ATC Code	Substance	Preparation	Authorisation holder	Reim-bursed by OKP
CDK4/6 inh.	L01XE33	Palbociclib	Ibrance	Pfizer AG	L*
CDK4/6 inh.	L01XE42	Ribociclib	Kisqali	Novartis Pharma Schweiz AG	L*
CDK4/6 inh.	L01XE50	Abemaciclib	Verzenios	Eli Lilly (Suisse) SA	L†
AI	L02BG06	Exemestane	Aromasin	Pfizer PFE Switzerland GmbH	yes
AI	L02BG06	Exemestane	Exemestan Devatis	Devatis AG	yes
AI	L02BG06	Exemestane	Exemestan Mylan	Mylan Pharma GmbH	yes
AI	L02BG06	Exemestane	Exemestan Sandoz	Sandoz Pharmaceuticals AG	yes
AI	L02BG04	Letrozole	Femara	Novartis Pharma Schweiz AG	yes
AI	L02BG04	Letrozole	Letrozol Devatis	Devatis AG	yes
AI	L02BG04	Letrozole	Letrozol Helvepharm	Helvepharm AG	yes
AI	L02BG04	Letrozole	Letrozol Labatec	Labatec Pharma SA	yes
AI	L02BG04	Letrozole	Letrozol Mepha	Mepha Pharma AG	no
AI	L02BG04	Letrozole	Letrozol Mylan	Mylan Pharma GmbH	yes
AI	L02BG04	Letrozole	Letrozol Sandoz	Sandoz Pharmaceuticals AG	yes
AI	L02BG04	Letrozole	Letrozol Teva	Teva Pharma AG	yes
AI	L02BG03	Anastrozole	Anastrozol Devatis	Devatis AG	yes
AI	L02BG03	Anastrozole	Anastrozol Helvepharm	Helvepharm AG	yes
AI	L02BG03	Anastrozole	Anastrozol Orion	Orion Pharma AG	yes
AI	L02BG03	Anastrozole	Anastrozol Sandoz	Sandoz Pharmaceuticals AG	yes
AI	L02BG03	Anastrozole	Anastrozol Teva	Teva Pharma AG	yes
AI	L02BG03	Anastrozole	Arimidex	AstraZeneca AG	yes
SERM	L02BA01	Tamoxifen	Nolvadex	AstraZeneca AG	yes
SERM	L02BA01	Tamoxifen	Tamec	Sandoz Pharmaceuticals AG	yes
SERM	L02BA01	Tamoxifen	Tamoxifen Farmos	Orion Pharma AG	yes
SERD	L02BA03	Fulvestrant	Faslodex	AstraZeneca AG	L‡
SERD	L02BA03	Fulvestrant	Fulvestrant Mylan	Mylan Pharma GmbH	no
SERD	L02BA03	Fulvestrant	Fulvestrant Sandoz	Sandoz Pharmaceuticals AG	L‡
SERD	L02BA03	Fulvestrant	Fulvestrant Teva	Teva Pharma AG	no

AI=aromatase inhibitor; CDK4/6 inh.=cyclin-dependent kinase 4/6 inhibitor; L=limitation; OKP=mandatory health insurance; SERD=selective oestrogen receptor degrader; SERM=selective oestrogen receptor modulator;
* Indicated in combination with an AI in patients who have not relapsed or progressed on prior ET and if ET monotherapy is not indicated. Indicated in combination with fulvestrant in patients who relapsed or progressed during or within 12 months after adjuvant ET or during ET for advanced-stage disease.
† Same indications as palbociclib and ribociclib. In addition, indicated as monotherapy in patients who have relapsed or progressed during ET as well as during at least one chemotherapy regimen.
‡ Indicated for postmenopausal patients who have relapsed or progressed during treatment with a different ET agent.

5 PICO

Note: During the expert review, the FOPH was strongly advised to include all CDK 4/6 inhibitors in their evaluation. The revised title, PICO and research questions suggested for the conduct of a full HTA are provided in Chapter 10.

Table 2: PICO 1

P:	Pre/peri- (under ovarian suppression) or postmenopausal women with HR+/HER2- LA/MBC who have not relapsed or progressed during or within 12 months after adjuvant ET and have not received prior ET for advanced-stage disease
I:	PAL (Ibrance®) in combination with an AI (ANA, LET or EXE)
C:	- AI (ANA, LET or EXE) - FUL - TAM - RIB in combination with an AI (ANA, LET or EXE) - ABE in combination with an AI (ANA, LET or EXE) - RIB in combination with FUL - ABE in combination with FUL - PAL in combination with FUL
O:	Efficacy and effectiveness - HrQoL (critical outcome) - OS (critical outcome) - PFS (important outcome*) Safety - Treatment-related AEs (critical outcome) - Treatment discontinuation due to AEs (critical outcome) Economics - Costs for complete treatment path including costs after stopping treatment with PAL - Costs of (severe) side effects - Budget impact - ICER, incremental/total costs, QALYs and LYG

ABE=abemaciclib; AE=adverse event; AI=aromatase inhibitor; ANA=anastrozole; ET=endocrine therapy; EXE=exemestane; FUL=fulvestrant; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; HrQoL=health-related quality of life; ICER =incremental cost effectiveness ratio; LET=letrozole; LYG=life years gained; OS=overall survival; PAL=palbociclib; PFS=progression-free survival; PICO=population, intervention, comparator, outcome; PROM=patient-reported outcome measure; QALY=quality-adjusted life year; RIB=ribociclib; TAM=tamoxifen
* PFS can be seen as a surrogate parameter and was therefore ranked as important (but not critical).

Table 3: PICO 2

P:	Pre/peri- (under ovarian suppression) or postmenopausal women with HR+/HER2- LA/MBC who have relapsed or progressed during or within 12 months after adjuvant ET or during ET for advanced-stage disease
I:	PAL (Ibrance®) in combination with FUL
C:	- FUL - AI (ANA, LET or EXE) - TAM - RIB in combination with FUL - ABE in combination with FUL - RIB in combination with an AI (ANA, LET or EXE) - ABE in combination with an AI (ANA, LET or EXE) - PAL in combination with an AI (ANA, LET or EXE)
O:	Efficacy and effectiveness - HrQoL (critical outcome) - OS (critical outcome) - PFS (important outcome*) Safety - Treatment-related AEs (critical outcome) - Treatment discontinuation due to AEs (critical outcome) Economics - Costs for complete treatment path including costs after stopping treatment with PAL - Costs of (severe) side effects - Budget impact - ICER, incremental/total costs, QALYs and LYG

ABE=abemaciclib; AE=adverse event; AI=aromatase inhibitor; ANA=anastrozole; ET=endocrine therapy; EXE=exemestane; FUL=fulvestrant; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; HrQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; LET=letrozole; LYG=life years gained; OS=overall survival; PAL=palbociclib;; PFS=progression-free survival; PICO=population, intervention, comparator, outcome; PROM=patient-reported outcome measure; QALY=quality-adjusted life year; RIB=ribociclib; TAM=tamoxifen

* PFS can be seen as a surrogate parameter and was therefore ranked as important (but not critical).

6 HTA key questions

Note: During the expert review, the FOPH was strongly advised to include all CDK 4/6 inhibitors in their evaluation. The revised title, PICO and research questions suggested for the conduct of a full HTA are provided in Chapter 10.

To evaluate the technology, the following key questions were addressed covering central HTA domains as designated by the EUnetHTA Core Model® (clinical efficacy and effectiveness, safety, costs, cost effectiveness, budget impact, legal, social, ethical and organisational aspects):

1. Is PAL in combination with an AI (ANA, LET or EXE) in women with HR+/HER2- LA/MBC who have not received prior ET for advanced-stage disease effective/efficacious compared with alternative treatment options*?
2. Is PAL in combination with FUL in women with HR+/HER2- LA/MBC with disease progression/recurrence during/after prior ET effective/efficacious compared with alternative treatment options*?
3. Is PAL in combination with an AI (ANA, LET or EXE) in women with HR+/HER2- LA/MBC who have not received prior ET for advanced-stage disease safe compared with alternative treatment options*?
4. Is PAL in combination with FUL in women with HR+/HER2- LA/MBC with disease progression/recurrence during/after prior ET safe compared with alternative treatment options*?
5. What are the costs of PAL?
6. What is the budget impact of a potential change in the reimbursement status of PAL in the two above-mentioned combinations and indications†?
7. How cost-effective is PAL in the two above-mentioned combinations and indications compared with alternative treatment options*?
8. Are there legal, social or ethical issues related to PAL in the two above-mentioned combinations and indications‡?
9. Are there organisational issues related to PAL in the two above-mentioned combinations and indications‡?

* We defined alternative treatment options in accordance with international guidelines and in consultation with a Swiss clinical oncology expert which are listed in detail in PICO (see Chapter 5).

† The scenarios that might have to be analysed are to be defined during conduct of a full HTA based on the results of the cost effectiveness analysis.

‡ We refined and specified this question during the scoping phase in consultation with the FOPH; see Section 6.1 for detailed questions on the issue(s).

6.1 Additional question(s)

Note: During the expert review, the FOPH was strongly advised to include all CDK 4/6 inhibitors in their evaluation. The revised title, PICO and research questions suggested for the conduct of a full HTA are provided in Chapter 10.

6.1.1 Ethical issues

In consultation with the FOPH, we identified the following question from the EUnetHTA Core Model® ontology as being relevant.[36] The original question was rephrased according to PICO.

What are the ethical consequences of the choice of endpoints in the assessment as well as in the included clinical studies?

6.1.2 Social issues

In consultation with the FOPH, we identified the following question from the EUnetHTA Core Model® ontology as being relevant.[36] The original question was rephrased according to PICO.

What expectations and wishes do patients have with regard to PAL combination therapy (either with an AI or with FUL as indicated) and possible alternative treatment options?

6.1.3 Organisational issues

In consultation with the FOPH, we identified the following question from the EUnetHTA Core Model® ontology as being relevant.[36] The original question was rephrased according to PICO.

How does PAL combination therapy (either with an AI or with FUL as indicated) modify the need for other technologies and use of resources?

6.1.4 Legal issues

With respect to legal issues, the FOPH raised the following question as being relevant:

What are the consequences of a disinvestment decision regarding patient access (for example, reimbursement “on a case-by-case basis” according to article 71a-d of the Swiss regulation on health insurance)?[37]

7 Methodology literature search

7.1 Databases and search strategy

7.1.1 Palbociclib versus comparators: clinical effectiveness and safety

7.1.1.1 Systematic literature search

We performed systematic literature searches in the following databases: Ovid MEDLINE, EMBASE, The Cochrane Library and CRD. Ongoing studies were identified automatically through the inclusion of Cochrane CENTRAL (as part of The Cochrane Library), which contains the entries from ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP; WHO registry), which in turn contains the entries from the EU Clinical Trials Register (EUCTR) and the International Standard Randomised Controlled Trial Number (ISRCTN) registry. The searches were built using the PICO framework. Search strings were applied on 'Population', 'Intervention' and 'Comparators'. The search was restricted to RCTs, meta-analyses (MAs) and systematic reviews (SRs) as well as to human subjects without restriction on date of publication. The searches in Ovid MEDLINE and EMBASE were restricted to publications in English, German or French. Searches for publications in English and German were conducted between 14 and 17 November 2019 and searches for publications in French between 24 and 27 January 2020. The search strings for the different databases are included in Appendix 12.1.

7.1.1.2 Selection procedure

RCTs were filed separately from SRs and MAs. Relevant RCTs were included in the synthesis of the evidence base regarding the assessment of clinical effectiveness and safety to be used in the planned network meta-analysis (NMA). Reference lists of relevant SRs and (N)MAs were reviewed for additional RCTs which might have been missed in the systematic literature search.

The search results from the different databases were compiled and organised in EndNote version X8.2. Automatic duplicate removal was performed and complemented with a manual check for remaining duplicates. The resulting list of publications was then uploaded in Covidence[38] and divided into two groups: articles published before or after 2007 (when standardised HER2-testing was implemented; see Chapter 3). Two reviewers independently screened the titles and abstracts of articles published from 2007 onwards and selected all potentially relevant articles for full-text review while articles that did not seem to contain relevant data were excluded (see Table 4 for selection criteria). Articles published up to 2006 were screened by one reviewer to identify studies that reported participants' HER2-status.

During the full-text acquisition phase, some articles that were found to be conference abstracts or published in a non-included language were excluded immediately by one reviewer. Two reviewers then

independently assessed the relevance of the remaining full-text articles based on the inclusion and exclusion criteria (see Table 4). Discrepancies between the two reviewers regarding inclusion or exclusion reasons were discussed and decided among the reviewers. One reviewer coordinated this work and was responsible for documenting the selection process and compilation of articles in the final EndNote library. When several articles analysed the same patient cohort and presented identical outcome measures (interim analyses, for example), only the articles reporting data from the most recent cut-off date or the most complete data were included. Articles that analysed mixed cohorts (for example HER2+ and HER2- or different ETs within one study arm) were included if they provided reliable subgroup analyses. Articles that reported on mixed cohorts and did report the numbers of patients in each group (for example, numbers of HER2+ and HER2- patients) but did not provide separate outcome data or subgroup analyses were included on the proviso that additional data will have to be requested from the authors during the HTA phase.

Currently ongoing clinical trials that were identified through the searches in registries (see Subsection 7.1.1.1) were checked for relevance to the research questions of this HTA.

7.1.1.3 Inclusion and exclusion criteria

Table 4 lists the inclusion and exclusion criteria for selecting the studies to be included in a potential NMA for the assessment of clinical effectiveness and safety.

Table 4: Selection criteria for the systematic review of clinical effectiveness and safety

Criteria	Inclusion	Exclusion
Publication date	No restriction	
Country of study	All countries	
Language	English, German or French	**Other language**
Publication type	Full study publication	Conference abstract, study protocol
Study design/type	Randomised controlled trials (RCTs)	**Other study type**
Intervention or comparator at least one of the therapies has to be either intervention or comparator	- PAL, RIB or ABE in combination with AI (LET, ANA, EXE) or FUL - AI (ANA, LET or EXE) - FUL - TAM	**No treatment of interest included** e.g. PAL, RIB or ABE as monotherapy
Study population	- HR+/HER2- inoperable LA/MBC - Pre/peri- (under ovarian suppression) or postmenopausal women - For PICO 1: no prior ET for advanced-stage disease - For PICO 2: disease progression during/after ET for advanced-stage disease	**Other study population** e.g. HR-, HER2+ or HER2 status unknown, early breast cancer, LABC amenable to curative operative treatment, pre/perimenopausal women without ovarian suppression, males
Study outcomes	Data on at least one of the outcomes listed in the PICO schemes must be reported	**None of the defined study outcomes included**

ABE=abemaciclib; AI=aromatase inhibitor; ANA=anastrozole; EXE=exemestane; FUL=fulvestrant; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; LET=letrozole; PAL=palbociclib; PICO=population, intervention, comparator, outcome; RCT=randomised controlled trial; RIB=ribociclib; TAM=tamoxifen

7.1.1.4 Data extraction

The study characteristics of the included publications were extracted and summarised using a data extraction template in Excel. Extracted items included: trial identifier, first article author, year of publication, population, interventions, reported outcomes and trial sponsor. One reviewer extracted study characteristics that were cross-checked by another reviewer. The individual publications were grouped by the clinical trials they reported on.

7.1.2 Palbociclib: extended safety assessment, economic, ethical, social, legal and organisational issues

7.1.2.1 Systematic literature search

To include all available evidence on PAL regarding safety (non-randomised studies such as cohort studies and case reports) as well as to cover the other five assessment domains, we conducted a second literature search. In this search we applied search strings on ‘Population’ and ‘Intervention’ to limit the search to breast cancer and PAL. There were no restrictions on study types or the date of publication. Literature searches were performed in the following databases: Ovid MEDLINE, EMBASE, TRIP-database, The Cochrane Library, Scopus and CRD using the PICO framework. The searches in Ovid MEDLINE, EMBASE and Scopus were restricted to publications in English, German or French.

Searches for publications in English and German were conducted between 4 and 8 November 2019 and searches for publications in French between 21 and 24 January 2020. The search strings for the databases are included in Appendix 12.2.

A supplementary search in the EconLit database yielded no hits. The search strings for the search in EconLit are included in Appendix 12.2.4.

7.1.2.2 Selection procedure

The search results were compiled and organised in EndNote version X8.2. Automatic duplicate removal was performed and complemented with a manual check for remaining duplicates.

The titles and abstracts of the resulting list of publications were initially screened by one reviewer, who tagged publications that reported on relevant patient populations (see PICO) and on PAL indicating their relevance for specific assessment domains. This first overview supported the formulation of specific additional research questions (see Section 6.1). The initial selection of abstracts was then cross-checked by a second reviewer with regard to the selected research questions.

The second reviewer also oversaw the whole process and, in a second step, integrated publications from the literature search on clinical effectiveness described in Subsection 7.1.1 that were tagged as being relevant for the other domains (checked for duplicates). The resulting publications were organised into groups corresponding to the individual assessment domains. Full-text screening was then performed by the second reviewer and the results were checked by a third reviewer.

7.1.2.3 Inclusion and exclusion criteria

The inclusion and exclusion criteria regarding the extended safety assessment and economic studies are laid out in Table 5 and Table 6, respectively. With regard to ethical, social, organisational and legal issues, all articles that were deemed to give relevant information for one of the four selected research questions listed in Section 6.1 were included within the full-text review.

Table 5: Selection criteria for the extended safety assessment of PAL

Criteria	Inclusion	Exclusion
Language	English, German or French	**Other language**
Country of study	All countries	
Study design/type	Observational studies and case reports/series reporting relevant outcomes*	**Inappropriate study design** e.g. narrative reviews, in-vitro studies
Study population	HR+ LA/MBC	**Other study population** e.g. HR-, early breast cancer, males
Study intervention	- PAL in combination with an AI (LET, ANA, EXE) or FUL - PAL monotherapy	**Other intervention**
Study outcomes	- Treatment-related AEs - Discontinuation due to AEs	**None of the defined study outcomes included**

AE=adverse event; AI=aromatase inhibitor; ANA=anastrozole; EXE=exemestane; FUL=fulvestrant; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; LA=locally advanced; LET=letrozole; MBC=metastatic breast cancer; PAL=palbociclib
* RCTs were tagged for inclusion in the clinical effectiveness and safety search (see Subsection 7.1.1) while SRs and MAs were tagged to be used as background information and for reference list screening.

Table 6: Selection criteria for the economic review

Criteria	Inclusion	Exclusion
Language	English, German or French	**Other language**
Country of study	All countries	
Study design/type	Cost effectiveness or cost-utility studies, budget impact analyses	**Other study type**
Study population	- HR+/HER2- inoperable LA/MBC - Pre/peri- (under ovarian suppression) or post-menopausal women	**Other study population** e.g. HR-, HER2+ or HER2 status unknown, early breast cancer, LABC amenable to curative operative treatment, pre/perimenopausal women without ovarian suppression, males
Study intervention	- PAL in combination with an AI (LET, ANA, EXE) or FUL	**Other intervention** e.g. PAL monotherapy
Study comparison (not applicable for budget impact analyses)	- AI (LET, ANA, EXE) - FUL - TAM - RIB in combination with an AI (LET, ANA, EXE) or FUL - ABE in combination with an AI (LET, ANA, EXE) or FUL	**Other comparator**
Study outcomes	- Costs for complete treatment path including costs after stopping treatment with PAL - Costs of severe side effects - Budget impact - Incremental cost effectiveness ratio, incremental/total costs, QALYs and LYG	**None of the defined study outcomes included**

ABE=abemaciclib; AI=aromatase inhibitor; ANA=anastrozole; EXE=exemestane; FUL=fulvestrant; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; LA=locally advanced; LET=letrozole; LYG=life years gained; MBC =metastatic breast cancer; PAL=palbociclib; QALY=quality-adjusted life years; RIB=ribociclib; TAM=tamoxifen

7.1.2.4 Data extraction

The study characteristics of the included publications were extracted and summarised by one reviewer using a data extraction template in Excel. Across all assessment domains, extracted items included: first author, year of publication and sponsor. Additional extracted items for the economic studies included: country, population, interventions, cost perspective and outcome measures. Additional extracted items for the other assessment domains included study design and relevant issues covered.

7.2 Other sources

The following additional sources were searched for relevant publications:

- EUnetHTA POP database (key word “palbociclib”)
- Project database of the German Institute for Quality and Efficiency in Health Care (IQWiG) (key word “palbociclib”)
- Reference lists of SRs and MAs

7.3 Quality of evidence assessment

A preliminary quality assessment of the included RCTs (see Subsection 7.1.1) was conducted by judging the risk of bias (RoB) in the following domains:

- random sequence generation
- allocation concealment
- blinding of participants and personnel
- blinding of outcome assessment.

The assessment was assisted by RobotReviewer, an open-source machine learning system for semi-automated RoB assessment.[39 40] The RoB assessments generated by RobotReviewer were checked by a reviewer and modified if necessary. Out of a total of 152 assessments (4 RoB domains assessed in 38 publications whereby 6 publications could not be processed by RobotReviewer), 27 (17.8%) had to be modified by the human reviewer. The final RoB assessments are shown in Appendix 12.3. During the HTA phase, an extended assessment covering all RoB domains will be conducted by human reviewers using the Cochrane RoB tool version 2.[41] In this preliminary quality assessment, only the outcome PFS/TTP was assessed. In the comprehensive quality assessment for the HTA report, outcome-specific RoB domains will be assessed for all included outcomes.

The quality of the included economic studies (see Subsection 7.1.2) was assessed using the Consensus Health Economic Criteria (CHEC) list.[42]

8 Synthesis of evidence base

8.1 Evidence base pertaining to efficacy, effectiveness and safety

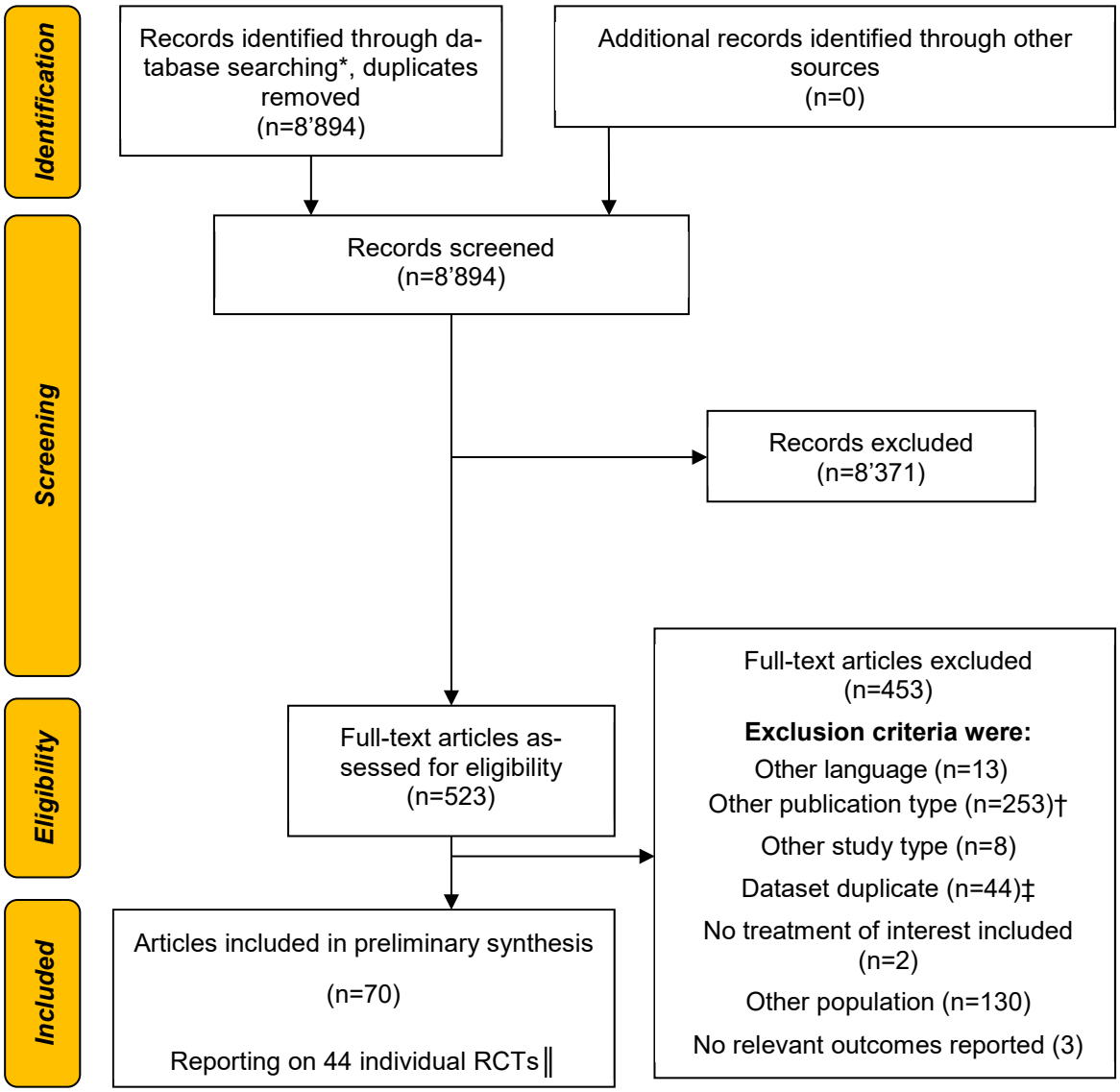
The evaluation of the overall effectiveness of the technology encompasses its efficacy, its effectiveness and its safety.

- Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (internal validity).
- Effectiveness is the extent to which a specific health technology, when applied in real-world circumstances in the target group, does what it is intended to do for a diagnostic or therapeutic purpose regarding the benefits compared with alternative technologies (external validity).
- Safety is a judgement of the harmful effects and their severity using the health technology. Relevant adverse events are those that result in death, are life-threatening, require inpatient hospitalisation or cause prolongation of existing hospitalisation (serious adverse events) and those that occur repetitively and the most frequent (highest rate).

8.1.1 PRISMA flow diagrams

Table 18 (Appendix 12.1.5) shows the number of hits retrieved through the systematic search described in Subsection 7.1.1.1 in MEDLINE, EMBASE, The Cochrane Library and CRD. After automatic removal of duplicates in Endnote, 9’739 hits remained. The remaining hits were further deduplicated manually and filtered for 1) RCTs and 2) SRs and (N)MAs, resulting in 8’894 RCTs and 845 SRs. Figure 3 shows the PRISMA flow chart for publications selected for the potential NMA of clinical effectiveness and safety.

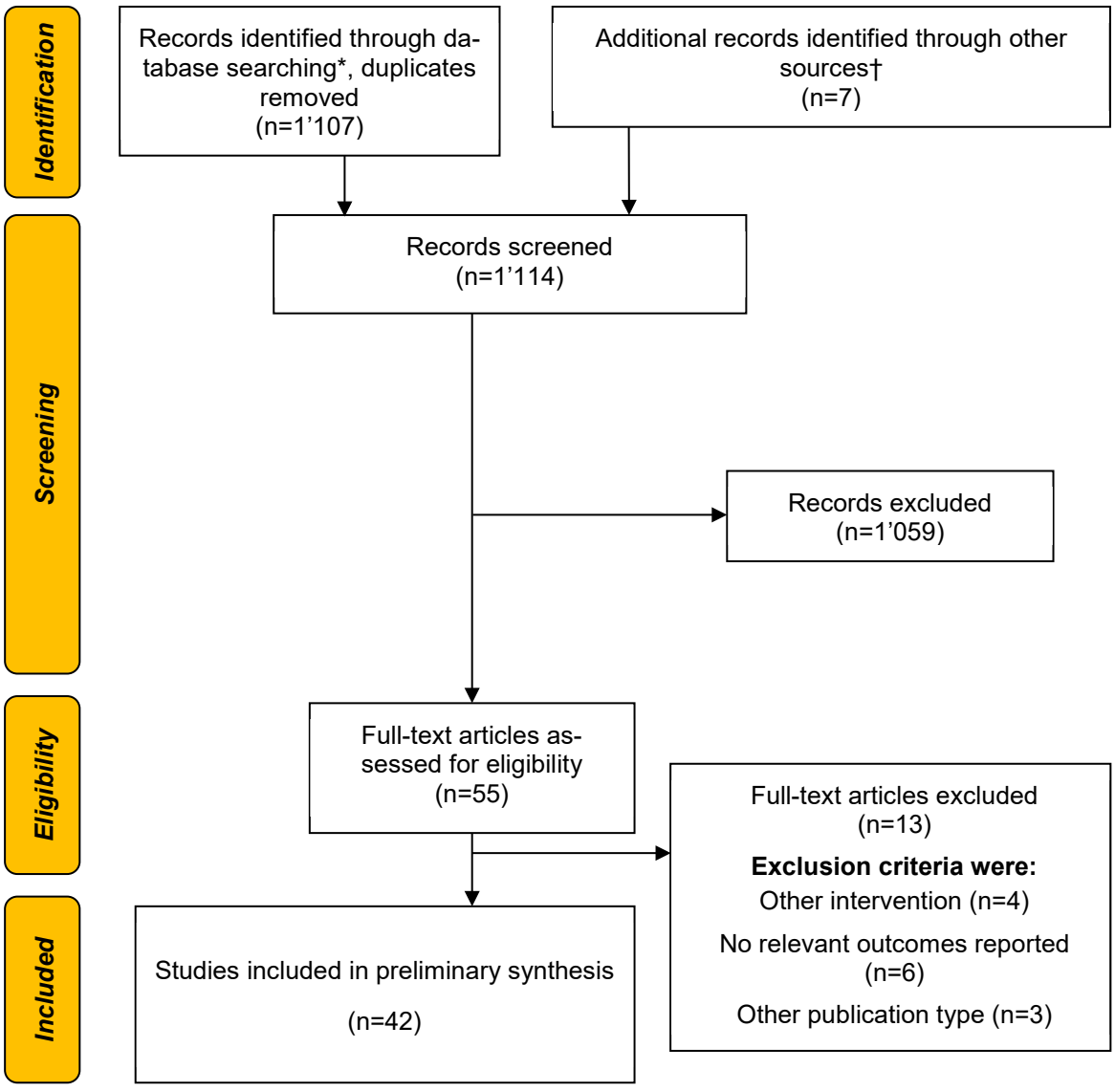
Figure 3: PRISMA flow chart for clinical effectiveness and safety studies (PAL versus comparators) – refers to HTA key questions 1-4



* Literature search efficacy, effectiveness and safety (RCTs).
† Publications other than complete primary articles, for example: conference abstracts (except for conference abstracts reporting on PALOMA trials, which were also checked for relevant unique data), study protocols (which were collected separately and checked for relevant ongoing studies), letters to editors, book chapters.
‡ Articles presenting only data that is also presented in another, more complete or more recent article.
‖ Of the 44 included RCTs, 13 are included on the condition that supplementary data can be obtained from the study authors during the HTA report.
¶ Refers to the literature search for safety (extended analysis) and health economics as well as ethical, social, legal and organisational aspects plus other sources described in Section 7.2.

Table 19 (Appendix 12.2.8) shows the number of hits retrieved through the systematic search described in Subsection 7.1.2.1 in MEDLINE, EMBASE, The Cochrane Library, CRD, Scopus and TRIP database. After removal of duplicates in Endnote, 1'107 hits remained. Figure 4 shows the PRISMA flow chart for publications selected for the extended safety assessment (see Subsection 7.1.2.1).

Figure 4: PRISMA flow chart for additional safety studies (extended analysis) – refers to HTA key questions 3 and 4



* Literature search for safety (extended analysis) and health economics as well as ethical, social, legal and organisational aspects.
† Refers to the literature search for efficacy, effectiveness and safety (RCTs) as well as to other sources described in Section 7.2.

8.1.2 Evidence tables

We sorted the selected relevant RCTs into two groups, based on whether they provide sufficient data to be included in a potential NMA (Table 7) or whether supplementary data need to be requested from the study authors (Table 8) (see Subsection 8.1.3 for further explanation). The extracted characteristics of studies included for the extended safety analysis of PAL are presented in Table 9.

Table 7: Evidence table for included RCTs with sufficient data – refers to HTA key questions 1-4

Trial	Author Year	Size* (pts)	Population		Intervention	Comparator	Outcome measures‡	Sponsor
			Prior ET†	HER2				
NCT00721409 PALOMA-1 (Phase 2)	Finn et al. 2017[43]	165	unclear	negative	PAL 125 mg + LET 2.5 mg	LET 2.5 mg	OS (median, 95% CI; HR, 95% CI, P)	Pfizer
	Bell et al. 2016[44]						QoL (BPI, mean, SE, P)	
	Finn et al. 2015[45]						PFS (median, 95% CI; HR, 95% CI, P) AEs (n; %) Dis (n)	
NCT01740427 PALOMA-2 (Phase 3)	Rugo et al. 2019[46]	666	no	negative	PAL 125 mg + LET 2.5 mg	pbo + LET 2.5 mg	PFS (median; HR, 95% CI, P) AEs (n; %) QoL (FACT-B, overall cfb, HR, 95% CI, P)	Pfizer
	Rugo et al. 2018[47]						QoL (FACT-B and EQ-5D, several measures)	
	Dieras et al. 2019[48]						AEs (n; %; Risk Diff, 95% CI, P)	
	Durairaj et al. 2018[49]						QTc (ms, LSM, cfb, SE, 90% CI)	
	Finn et al. 2016[4]						PFS (median, 95% CI; HR, 95% CI, P) AEs (n; %) Dis (n; %)	

Trial	Author Year	Size* (pts)	Population		Intervention	Comparator	Outcome measures‡	Sponsor
			Prior ET†	HER2				
NCT01942135 PALOMA-3 (Phase 3)	Harbeck et al. 2016[5]	521	yes	negative	PAL 125 mg + FUL 500 mg	pbo + FUL 500 mg	QoL (EORTC: TTD in pain scores, 95% CI, HR, P)	Pfizer
	Verma et al. 2016[50]						AEs (n; %; RD, %, 95% CI)	
	Turner et al. 2018[3]						PFS (median, 95% CI; HR, 95% CI, P) OS (median; HR, 95% CI, P; subgroup) AEs (n; %)	
	Loibl et al. 2016[51]						QoL (VAS, EQ-5D index, mean (SD), P)	
	Cristofanilli et al. 2018[52]						PFS (median, 95% CI; HR, 95% CI, P)	
	Cristofanilli et al. 2016[2]						PFS, outdated (median, 95% CI; HR, 95% CI, P) Dis (n; %) AEs (n; %)	
NCT01958021 MONALEESA-2 (Phase 3)	Hortobagyi et al. 2016[53]	668	no	negative	RIB 600 mg + LET 2.5 mg	pbo + LET 2.5 mg	PFS (median; HR, 95% CI, P) Dis (n; %) AEs (n; %)	Novartis
	Janni et al. 2018[54]						QoL (EORTC pain score: cfb, median %, mean)	
	Hortobagyi et al. 2018[55]						PFS (median; HR, 95% CI, P) OS (n; %, median, HR, 95% CI) Dis (n; %) AEs (n; %)	
	Verma et al. 2018[56]						QoL (EORTC; LSM, cfb, SEM; TTD, HR, 95% CI, P)	
NCT02422615 MONALEESA-3 (Phase 3)	Slamon et al. 2018[57]	726	mixed (sg av.)	negative	RIB 600 mg + FUL 500 mg	pbo + FUL 500 mg	PFS (median, 95% CI, P; HR, 95% CI, P) Dis (n) AEs (n; %)	Novartis

Trial	Author Year	Size* (pts)	Population		Intervention	Comparator	Outcome measures‡	Sponsor
			Prior ET†	HER2				
NCT02107703 MONARCH 2 (Phase 3)	Sledge et al. 2017[58]	669	yes	negative	ABE 200/150 mg + FUL 500 mg	pbo + FUL 500 mg	PFS (median; HR, 95% CI, P), outdated AEs, outdated (n; %) Dis (n; %)	Eli Lilly
	Kaufman et al. 2019[59]						QoL (mBPI-sf, EORTC: TTD: median; HR, 95% CI)	
	Sledge et al. 2019[60]						OS (median; HR, 95% CI, P) PFS (median; HR, 95% CI) AEs (n; %)	
NCT00863655 BOLERO-2 (Phase 3)	Yardley et al. 2013[61]	724	yes	negative	EVE 10 mg + EXE 25 mg	pbo + EXE 25 mg	PFS (median; HR, 95% CI, P) Dis (n; %) AEs (n; %)	Novartis
	Piccart et al. 2014[62]						OS (median; HR, 95% CI, P) AEs (n; %)	
	Burris et al. 2013[63]						Dis (%) QoL (EORTC, TTD; median, 95% CI, P)	
	Campone et al. 2013[64]						QoL (EORTC; LSM, cfb, SE, 95% CI; LSM difference, HR, 95% CI)	
NCT01610284 BELLE-2 (Phase 3)	Baselga et al. 2017[65]	1'147	yes	negative	BUP 100 mg + FUL 500 mg	pbo + FUL 500 mg	PFS (median, 95% CI; HR, 95% CI, P) Dis (n; %) AEs (n; %)	Novartis
	Campone et al. 2018[66]						OS (median, 95% CI; HR, 95% CI, P) AEs (n; %) Dis (%)	
NCT01633060 BELLE-3 (Phase 3)	Di Leo et al. 2018[67]	432	yes	negative	BUP 100 mg + FUL 500 mg	pbo + FUL 500 mg	PFS (median, 95% CI; HR, 95% CI, P) AEs (n; %) Dis (n)	Novartis
NCT01602380 FALCON (Phase 3)	Robertson et al. 2018[68]	462	no	negative	FUL 500 mg	ANA 1 mg	QoL (FACT-B: cfb, mean, SD; TTD, median, HR, 95% CI, P)	AstraZeneca
	Robertson et al. 2016[69]						PFS (n; %, median; HR, 95% CI, P)AEs (n; %)	

Trial	Author Year	Size* (pts)	Population		Intervention	Comparator	Outcome measures‡	Sponsor
			Prior ET†	HER2				
NCT01266213 FLAG (Phase 2)	Kim et al. 2018[70]	138	unclear	negative	FUL 500 mg + GOS 3.6 mg	Comparator 1: ANA 1 mg + GOS 3.6 mg Comparator 2: GOS 3.6 mg	TTP (median, 95% CI; HR, 95% CI) OS (HR, 95% CI, P) AEs (n; %, P) Dis (n)	AstraZeneca
NCT00073528 (Phase 3)	Johnston et al. 2009[71]	1'286	no	mixed (sg av.)	LAP 1500 mg + LET 2.5 mg	pbo + LET 2.5 mg	PFS (median; HR, 95% CI, P) AEs (n; %)	GSK
NCT00075764 (Phase 3)	Mehta et al. 2019[72]	694	no	mixed (sg av.)	ANA 1 mg + FUL 500/250 mg	ANA 1 mg	PFS (median; HR, 95% CI, P), no subgroups OS (median; HR, 95% CI, P), no subgroups	AstraZeneca NCI
	Mehta et al. 2012[73]						PFS (median, 95% CI, P; HR, 95% CI, P), outdated OS (median, 95% CI, P; HR, 95% CI, P), no subgroups Dis (n, P)	
NCT00229697 (Phase 2)	Osborne et al. 2011[74]	290	mixed (sg av.)	mixed (sg av.)	GEF 250 mg + TAM 20 mg	pbo + TAM 20 mg	PFS (median; HR, 95% CI, P), subgroup only for HER2+ AEs (n; %) Dis (n)	AstraZeneca
NCT00253422 NCT00944918 SoFEA (Phase 3)	Johnston et al. 2013[75]	723	mixed (sg av.)	mixed (sg av.)	ANA 1 mg + FUL 500/250 mg	Comparator 1: pbo + FUL 500/250 mg Comparator 2: EXE 25 mg	PFS (median, 95% CI; HR, 95% CI, P) OS (median, 95% CI; HR, 95% CI, P), no subgroups AEs (n, P; %) Dis (n)	NHS, ICR AstraZeneca
NCT00390455 (Phase 3)	Burstein et al. 2014[76]	291	unclear	mixed (sg av.)	LAP 1500 mg + FUL 500 mg	pbo + FUL 500 mg	PFS (median; HR, 95% CI, P) OS (median; HR, 95% CI, P), no subgroups Dis (n; %)	NCI
NCT00545077 LEA (Phase 3)	Martin et al. 2015[77]	380	unclear	negative	BEV 15 mg/kg + LET 2.5 mg or BEV 15 mg/kg +FUL 500 mg	LET 2.5 mg or FUL 500 mg	PFS (median, 95% CI, P; HR, 95% CI, P), subgroups per ET OS (median; HR, 95% CI, P), no subgroups AEs (n; %, P), no subgroups Dis (n), no subgroups	Roche

Trial	Author Year	Size* (pts)	Population		Intervention	Comparator	Outcome measures‡	Sponsor
			Prior ET†	HER2				
NCT00696072 (Phase 2)	Paul et al. 2019[78]	120	mixed (sg av.)	negative	DAS 100 mg + LET 2.5 mg	pbo + LET 2.5 mg	PFS exploratory (median; HR, 95% CI) OS (median) AEs (n; %) Dis (n; %)	BMS
NCT00770354 (Phase 2)	Ibrahim et al. 2011[79]	110	no	negative	AS1402 9 mg/kg + LET 2.5 mg	LET 2.5 mg	PFS (estimated HR, 95% CI) AEs (n; %)	Antisoma
NCT01142401 (Phase 2)	Adelson et al. 2016[80]	118	mixed (no sg av.)	negative	BOR 1.6 mg + FUL 500 mg	FUL 500 mg	PFS (median; HR, 95% CI, P) Dis (n; %) AEs (n; %)	NCI
NCT01151215 MINT (Phase 2)	Johnston et al. 2016[81]	359	no	negative	AZD8931 20 mg + ANA 1 mg	Comparator 1: AZD8931 40 mg + ANA 1 mg Comparator 2: pbo + ANA 1 mg	PFS (median; HR, 95% CI, P) AEs (n; %) Dis (n)	AstraZeneca
NCT01160718 (Phase 2)	Zaman et al. 2015[82]	46	unclear	negative	SEL 75 mg + FUL 500 mg	pbo + FUL 500 mg	PFS (median, 95% CI) AEs (n; %)	AstraZeneca
NCT01234857 (Phase 2)	Baselga et al. 2017[83]	115	yes	negative	RID 30 mg + DAL 10 mg	EXE 25 mg	PFS (median, 95% CI; HR, 95% CI, P) Dis (n; %) AEs (n; %)	Merck
NCT01437566 FERGI (Phase 2)	Krop et al. 2016[84]	229	yes	negative	PIC 340/260 mg + FUL 500 mg	pbo + FUL 500 mg	PFS (median, 95% CI; HR, 95% CI, P) AEs (n; %) Dis (n)	Roche
NCT01528345 (Phase 2)	Musolino et al. 2017[85]	97	yes	negative	DOV 500 mg + FUL 500 mg	pbo + FUL 500 mg	PFS (median, 95% CI; HR, 95% CI) OS (HR, 95% CI; premature) AEs (n; %) Dis (n)	Novartis

Trial	Author Year	Size* (pts)	Population		Intervention	Comparator	Outcome measures‡	Sponsor
			Prior ET†	HER2				
NCT02216786 MANTA (Phase 2)	Schmid et al. 2019[86]	333	yes	negative	VIS 50 mg + FUL 500 mg	Comparator 1: VIS 125 mg + FUL 500 mg Comparator 2: EVE 10 mg + FUL 500 mg Comparator 3: FUL 500 mg	PFS (median, 95% CI; HR, 95% CI, P) OS (HR, 95% CI, P; premature) AEs (n; %) Dis (n)	AstraZeneca NIH CRUK QMUL
NCT02437318 (Phase 3)	Andre et al. 2019[87]	572	mixed (sg av.)	negative	ALP 300 mg + FUL 500 mg	pbo + FUL 500 mg	PFS (median, 95% CI; HR, 95% CI, P) Dis (n; %) AEs (n; %)	Novartis
NCT02482753 ACE (Phase 3)	Jiang et al. 2019[88]	365	yes	negative	TUC 30 mg + EXE 25 mg	pbo + EXE 25 mg	PFS (median, 95% CI; HR, 95% CI, P) AEs (n; %) Dis (n)	Chipscreen
NCT02592746 KCSG-BR15-10 (Phase 2)	Park et al. 2019[89]	184	mixed (no sg av.)	negative	PAL 125 mg + EXE 25 mg	CAP 1250 mg	PFS (median, 95% CI; HR, 95% CI, P) AEs (n; %) Dis (n)	Pfizer Shinpoong Daewoong Takeda
N/A (Phase 3)	Lipton et al. 2008[90]	522	mixed (no sg av.)	mixed (sg av.)	LET 2.5 mg	TAM 20 mg	TTP (HR, 95% CI, P) OS (HR, 95% CI, P)	none declared
N/A (Phase 2)	Bachelot et al. 2012[91]	111	yes	negative	EVE 10 mg + TAM 10 mg	TAM 10 mg	TTP (median, 95% CI; HR, 95% CI) Dis (n) AEs (n; %)	Novartis

ABE=abemaciclib; AE=adverse event; ANA=anastrozole; BEV=bevacizumab; BMS=Bristol-Myers Squibb; BOR=bortezomib; BPI=brief pain inventory; BUP=buparlisib; CAP=capecitabine; cfb=change from baseline; CI=confidence interval; CRUK=Cancer Research UK; DAL=dalotuzumab; DAS=dasitinib; Dis=discontinuation due to adverse event; DOV=dovitinib; EORTC=European Organisation for Research and Treatment; ET=endocrine therapy; EVE=everolimus; EXE=exemestane; FUL=fulvestrant; GEF=gefitinib; GnRH=gonadotropin-releasing hormone agonist; GOS=gosereline; GSK=GlaxoSmithKline; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; ICR=The Institute of Cancer Research, London; LAP=lapatinib; LET=letrozole; LSM=least squares mean; mBPI-sf=modified Brief Pain Inventory short form; ms=milliseconds; n=number of patients; N/A=not applicable; NCI=National Cancer Institute; NIH=National Institutes of Health; OS=overall survival; P=p-value; PAL=palbociclib; pbo=placebo; PFS=progression-free survival; PIC=pictilisib; pts=patients; QMUL=Queen Mary University of London; QoL=quality of life; QTc=corrected QT-interval; RD=risk difference; RIB=ribociclib; RID=ridaforolimus; SD=standard deviation; SE=standard error; SEM=standard error of the mean; sg av.=subgroup available; TAM=tamoxifen; TTD=time to deterioration; TTP=time to progression; TUC=tucidinostat; VAS=visual analogue scale; VIS=vistusertib

* Total number of patients in trial.
† In line with the population defined in the PICO schemes, “prior ET" means that a patient has relapsed or progressed during or within 12 months after adjuvant ET or during ET for advanced-stage disease.
‡ If an outcome is listed as “outdated” it means that this article reports data on this outcome but they are not the most recent, as another article on this trial reports data on the same outcome from a more recent data cut-off.

Table 8: Evidence table for RCTs for which supplementary data needs to be requested – refers to HTA key questions 1-4

Trial	Author Year	Size* (pts)	Population		Intervention	Comparator	Outcome measures	Sponsor
			Prior ET	HER2†				
NCT00721409 NCT01740427 NCT01942135 PALOMA-1/2/3‡	Dieras et al. 2019[92]	1343	mixed (no sg av.)	negative	PAL 125 mg + LET 2.5 mg or PAL 125 mg + LET 2.5 mg or PAL 125 mg + FUL 500 mg	LET 2.5 mg or pbo + LET 2.5 mg or pbo + FUL500 mg	AEs, most recent data cut-off but mixed LET/FUL (n; %;) Dis (n; %)	Pfizer
NCT02278120 MONALEESA-7 (Phase 3)	Tripathy et al. 2018[93]	672	yes	negative	RIB 600 mg + LET 2.5 mg or RIB 600 mg + ANA 1 mg or RIB 600 mg + TAM 20 mg	pbo + LET 2.5 mg or pbo + ANA 1 mg or pbo + TAM 20 mg	PFS (median; HR, 95% CI, P) subgroups NSAI vs. TAM AEs (n; %) Dis (n; %) QoL (EORTC: TTD, median, HR, 95% CI, P)	Novartis
	Im et al. 2019[94]	672					OS (n; %, median, HR, 95% CI, P,) subgroups NSAI vs. TAM Dis (n; %) AEs (n; %)	
NCT02246621 MONARCH 3 (Phase 3)	Johnston et al. 2019[95]	493	no	negative	ABE 150 mg + LET 2.5 mg or ABE 150 mg + ANA 1 mg	pbo + LET 2.5 mg or pbo + ANA 1 mg	PFS (median; HR, 95% CI, P) subgroup per ET unclear AEs (n; %) Dis (n; %)	Eli Lilly

Trial	Author Year	Size* (pts)	Population		Intervention	Comparator	Outcome measures	Sponsor
			Prior ET	HER2†				
NCT00305448 FINDER1 (Phase 2)	Ohno et al. 2010[96]	143	yes	mixed (no sg av.)	FUL 250 mg	Comparator 1: FUL 250/500 mg Comparator2: FUL 500 mg	TTP (median) AEs (n; %) Dis (n; %)	AstraZeneca
NCT00313170 FINDER2 (Phase 2)	Pritchard et al. 2010[97]	144	yes	mixed (no sg av.)	FUL 250 mg	Comparator 1: FUL 250/500 mg Comparator2: FUL 500 mg	TTP (median) AEs (n; %) Dis (n)	AstraZeneca
NCT00274469 FIRST (Phase 2)	Ellis et al. 2015[98]	205	no	mixed (no sg av.)	FUL 500/250 mg	ANA 1 mg	OS (median; HR, 95% CI, P) AEs (n; %)	AstraZeneca
	Robertson et al.2012[99]	205					TTP (median; HR, 95% CI, P)	
	Robertson et al. 2009[100]	205					TTP (median; HR, 95% CI, P) AEs (n; %, P) Dis (n; %)	
NCT00050141 (Phase 2)	Johnston et al. 2008[101]	121	unclear	mixed (no sg av.)	TIP 300 mg + LET 2.5 mg	pbo + LET 2.5 mg	TTP (median, 95% CI) AEs (n; %)	J&J
NCT00066378 (Phase 2)	Tryfonidis et al. 2016[102]	71	mixed (sg av.)	mixed (no sg av.)	GEF 250 mg + ANA 1 mg	pbo + ANA 1 mg	PFS (% at 1 year, 95% CI) AEs (n; %)	AstraZeneca EORTC
NCT00083993 (Phase 3)	Wolff et al. 2013[103]	1112	no	mixed (no sg av.)	TEM 30 mg + LET 2.5 mg	pbo + LET 2.5 mg	PFS (median, 95% CI; HR, 95% CI, P) OS, premature, trial terminated (HR, 95% CI, P) AEs (n; %)	Pfizer (Wyeth) NIH
NCT00601900 CALGB 40503 (Phase 3)	Dickler et al. 2016[104]	348	yes	mixed (no sg av.)	LET 2.5 mg + BEV 15 mg/kg	pbo + LET 2.5 mg	PFS (n; %, median; HR, 95% CI, P) OS (n; %, median; HR, 95% CI, P) Dis (n; %) AEs (n; %)	Genentech Novartis

Trial	Author Year	Size* (pts)	Population		Intervention	Comparator	Outcome measures	Sponsor
			Prior ET	HER2†				
NCT00626106 (Phase 2)	Robertson et al. 2013[105]	156	yes	mixed (no sg av.)	GAN 12 mg/kg + FUL 500 mg or GAN 12 mg/kg + EXE 25 mg	pbo + FUL 500 mg or pbo + EXE 25 mg	PFS (median, 80% CI, IQR; HR, 80% CI, P) subgroup per ET OS, premature (HR, 80% CI, P) AEs (n; %) Dis (n; %)	Amgen
NCT00676663 (Phase 2)	Yardley et al. 2013[106]	130	mixed (no sg av.)	mixed (no sg av.)	ENT 5 mg + EXE 25 mg	pbo + EXE 25 mg	PFS (median, 95% CI; HR, 95% CI, P) OS, premature (HR, 95% CI, P) AEs (n; %)	Syndax
UMIN000010087 Hi-FAIR ex (Phase 2/3)	Yamamoto et al. 2013[107]	91	yes	mixed (no sg av.)	TOR 120 mg	EXE 25 mg	PFS (median; HR, 95% CI, P) OS (median; HR, 95% CI, P) Dis (n)	none declared
N/A (Phase 3)	Iwata et al. 2013[108]	298	unclear	mixed (no sg av.)	pbo + EXE 25 mg	pbo + ANA 1 mg	TTP (median, 96% CI; HR, 95% CI) OS, premature (median, 96% CI; HR, 95% CI) AEs (n; %) Dis (n; %)	Pfizer

ABE=abemaciclib; AE=adverse event; ANA=anastrozole; BEV=bevacizumab; CI=confidence interval; Dis=discontinuation due to adverse event; ENT=entinostat; EORTC=European Organisation for Research and Treatment of Cancer; ET=endocrine therapy; EXE=exemestane; FUL=fulvestrant; GAN=ganitumab; GEF=gefitinib; GOS=gosereline; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; J&J=Johnson&Johnson; LET=letrozole; LHRH=luteinising hormone-releasing hormone analogue; LSM=least squares mean; n=number of patients; N/A=not applicable; NIH=National Institutes of Health; NSAI=non-steroidal aromatase inhibitor; OS=overall survival; P=p-value; PAL=palbociclib; pbo=placebo; PFS=progression-free survival; pts=patients; QoL=quality of life; RIB=ribociclib; sg av.=subgroup available; TAM=tamoxifen; TEM=temsirolimus; TIP=tipifarnib; TOR=toremifene; TTD=time to deterioration; TTP=time to progression

* Total number of patients in trial.

† In line with the population defined in the PICO schemes, “prior ET" means that a patient has relapsed or progressed during or within 12 months after adjuvant ET or during ET for advanced-stage disease.

‡ Dieras et al. (2019)[92] provide a pooled long-term analysis of AEs in patients in the PALOMA-1, PALOMA-2 and PALOMA-3 trials. These represent the most recent AEs data from the three trials but the report does not provide a subgroup analysis based on the different ETs.

Table 9: Evidence table for extended safety analysis of PAL – refers to HTA key questions 3 and 4

Author Year	Study design	Size (pts)	Outcomes	Sponsor*	COI with Pfizer†	Country
Ban et al. 2018[109]	retr. cohort	24	various AEs	Pfizer (drug)‡	no	HR
Battisti et al. 2019[110]	retr. cohort	118	various AEs	Pfizer (drug)‡	yes	GB
Bromberg et al. 2016[111]	case series	2	hyperuricemia	not disclosed	not disclosed	US
Brufsky et al. 2019[112]	retr. cohort	126	dose reductions treatment interruptions	Pfizer	yes	US
Bui et al. 2019[113]	retr. cohort	46	various AEs dose reductions treatment interruptions	none	no	NL
Clifton et al. 2019[114]	retr. cohort	605	haematological AEs	none	yes	US
du Rusquec et al. 2018[115]	prosp. cohort	60	various AEs	none	yes	FR
Gao et al. 2015[116]	case report	1	neutropenia	Pfizer (drug)‡	yes	US
Gong et al. 2018[117]	retr. cohort	100	various AEs dose reductions	not disclosed	no	US
Gowarty et al. 2019[118]	case report	1	adverse drug interaction	none	no	US
Guerin et al. 2018[119]	retr. cohort	210	various AEs therapy duration	Novartis	no	US
Guillemois et al. 2018[120]	case report	1	leukocytoclastic vasculitis	not disclosed	no	FR
Harrold et al. 2019[121]	case report	1	reversible encephalopathy syndrome	not disclosed	no	IE
Herrscher et al. 2019[122]	retr. cohort	77	various AEs treatment interruptions dose reductions	not disclosed	yes	FR
Hoste et al. 2018[123]	retr. cohort	82	various AEs treatment interruptions dose reductions	Pfizer	no	NL
Iwamoto et al. 2018[124]	retr. cohort	26	various AEs treatment interruptions dose reductions	not disclosed	not disclosed	JP
Jazieh et al. 2019[125]	case report	1	drug-induced pneumonitis	none	no	US
Karagounis et al. 2018[126]	case report	1	Stevens-Johnson syndrome/toxic epidermal necrolysis	none	no	US

Author Year	Study design	Size (pts)	Outcomes	Sponsor*	COI with Pfizer†	Country
Kawamoto et al. 2019[127]	case report	1	adverse interaction with radiotherapy	not disclosed	no	JP
Kish et al. 2018[128]	retr. cohort	763	neutropenia dose modifications	Pfizer	yes	US
Masuda et al. 2018[129]	single arm	42	various AEs treatment interruptions dose reductions	Pfizer	yes	JP
Maurer et al. 2018[130]	retr. cohort	34	various AEs treatment interruptions dose reductions	Pfizer (drug)‡	yes	BE
Messer et al. 2019[131]	case report	1	adverse interaction with radiotherapy	none	no	US
Momper et al. 2019[132]	case report	1	adverse drug interaction	none	no	US
Nelson et al. 2017[133]	case report	1	adverse drug interaction	none	no	US
Nersesjan et al. 2019[134]	case report	1	adverse drug interaction	none	no	DK
Nwabudike et al. 2018[135]	case report	1	aplastic anaemia	not disclosed	no	US
Pinard et al. 2018[136]	case report	1	subacute cutaneous lupus erythematosus	none	yes	US
Pizzuti et al. 2019[137]	retr. cohort	423	various AEs	not disclosed	no	IT
Raiss et al. 2018[138]	case report	1	thrombotic microangiopathy	none	no	MA
Roberts et al. 2018[139]	case report	1	elevated liver function tests	not disclosed	no	US
Schickli et al. 2019[140]	retr. cohort	53	haematological AEs dose reductions	none	yes	US
Stearns et al. 2018[141]	prosp. cohort	334	various AEs treatment interruptions dose reductions	Pfizer	yes	US/CA
Tamura et al. 2016[142]	single arm	6	various AEs	Pfizer	yes	JP
Tang et al. 2017[143]	retr. cohort	10313	treatment disruptions after palbociclib approval	Novartis	no	US
Taylor-Stokes et al. 2019[144]	retr. cohort	652	dose modifications treatment discontinuations	Pfizer	yes	US
Varella et al. 2019[145]	retr. cohort	411	various AEs treatment interruptions dose reductions	not disclosed	no	US
Vuppalanchi et al. 2017[146]	case series	2	hepatic failure	not disclosed	yes	US

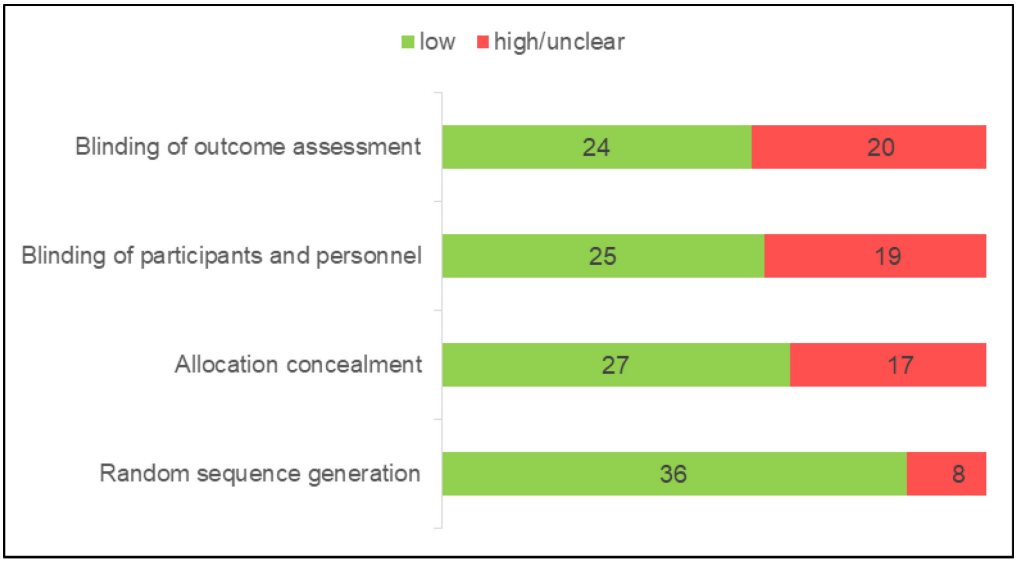
Author Year	Study design	Size (pts)	Outcomes	Sponsor*	COI with Pfizer†	Country
Waller et al. 2019[147]	retr. cohort	162	dose reductions treatment interruptions	Pfizer	yes	AR
Watson et al. 2019[148]	retr. cohort	64	various AEs treatment interruptions dose reductions	not disclosed	no	IE
Wilkie et al. 2019[149]	retr. cohort	70	neutropenia treatment interruptions dose reductions	not disclosed	yes	US
Xi et al. 2019[150]	retr. cohort	200	various AEs dose reductions	not disclosed	yes	US

AE=adverse event; AR=Argentina; BE=Belgium; CA=Canada; COI=conflict of interest; DK=Denmark; FR=France; GB=Great Britain; HR=Croatia; IE=Ireland; IT=Italy; JP=Japan; MA=Morocco; NL=The Netherlands; prosp.=prospective; pts=patients; retr.=retrospective; US=United States of America
* Refers to industry funding for the study/publication. “none” indicates that the authors declared that they did not receive industry funding for the study/publication. “not disclosed” indicates that no specific information on funding was provided in the publication.
† Refers to potential personal conflicts of interest of the authors which can arise, for example, from receiving consultation fees or serving on advisory boards. As the publications listed in this table pertain to safety data on PAL, we extracted declared COI of authors exclusively with the manufacturer Pfizer. “no” indicates that the authors declared that they did not have any COI with Pfizer. “not disclosed” indicates that no specific information on COI was provided in the publication.
‡ Pfizer provided PAL free of charge.

8.1.3 *Findings regarding efficacy, effectiveness and safety*

We identified 70 publications reporting on 44 individual RCTs providing evidence relevant to the assessment of clinical effectiveness and safety in a potential NMA.[2-6 43-46 48-108] Four trials included PAL in one treatment arm.[2 4 45 89] For two of the included trials, no information could be found on the locations of the trial centres.[91 108] The remaining trials recruited patients from a total of 61 countries, which are listed in Appendix 12.3. Six trials also recruited patients in Switzerland but none of those included PAL in a treatment arm.[57 58 65 82 93 105] All trials reported data on either PFS or TTP (two similar outcome measures, see discussion in Chapter 9). Most of the trials also reported AEs, while only a subset provided OS or QoL data. Of the 44 selected RCTs, 13 reported data on mixed patient cohorts (with regard to either HER2-status or treatment with different ET agents) without providing subgroup analyses.[93 95-97 100-108] These RCTs are included in the present evidence base; however, during the HTA phase, supplementary data will have to be requested from the study authors. Only if (sufficient) data can be obtained will these studies be included in the final study pool. A preliminary quality assessment of the 44 RCTs based on four RoB domains was performed and is presented in Table 20 (Appendix 12.3). High or unclear RoB was found in 45 per cent (20 of 44) of the RCTs regarding blinding of outcome assessment, in 43 per cent (19 of 44) of the RCTs regarding blinding of participants and personnel, in 39 per cent (17 of 44) of the RCTs regarding allocation concealment and in 18 per cent (8 of 44) of the RCTs regarding random sequence generation (see Figure 5).

Figure 5: Preliminary quality assessment of included RCTs



Numbers within the bars represent the numbers of trials in the categories concerned..

We identified 42 non-randomised studies (NRSs) providing relevant evidence for the extended safety assessment.[109-150] They comprised 15 single case reports, 2 case series, 2 prospective cohort studies,

21 retrospective cohort studies and 2 single arm trials. More than half of the studies were conducted in the US, 13 in Europe (none of them in Switzerland). The case reports mainly reported on rare AEs and adverse drug interactions. Almost all of the cohort studies and single arm trials reported on various AEs; most of them also reported on treatment disruptions and dose modifications due to AEs.

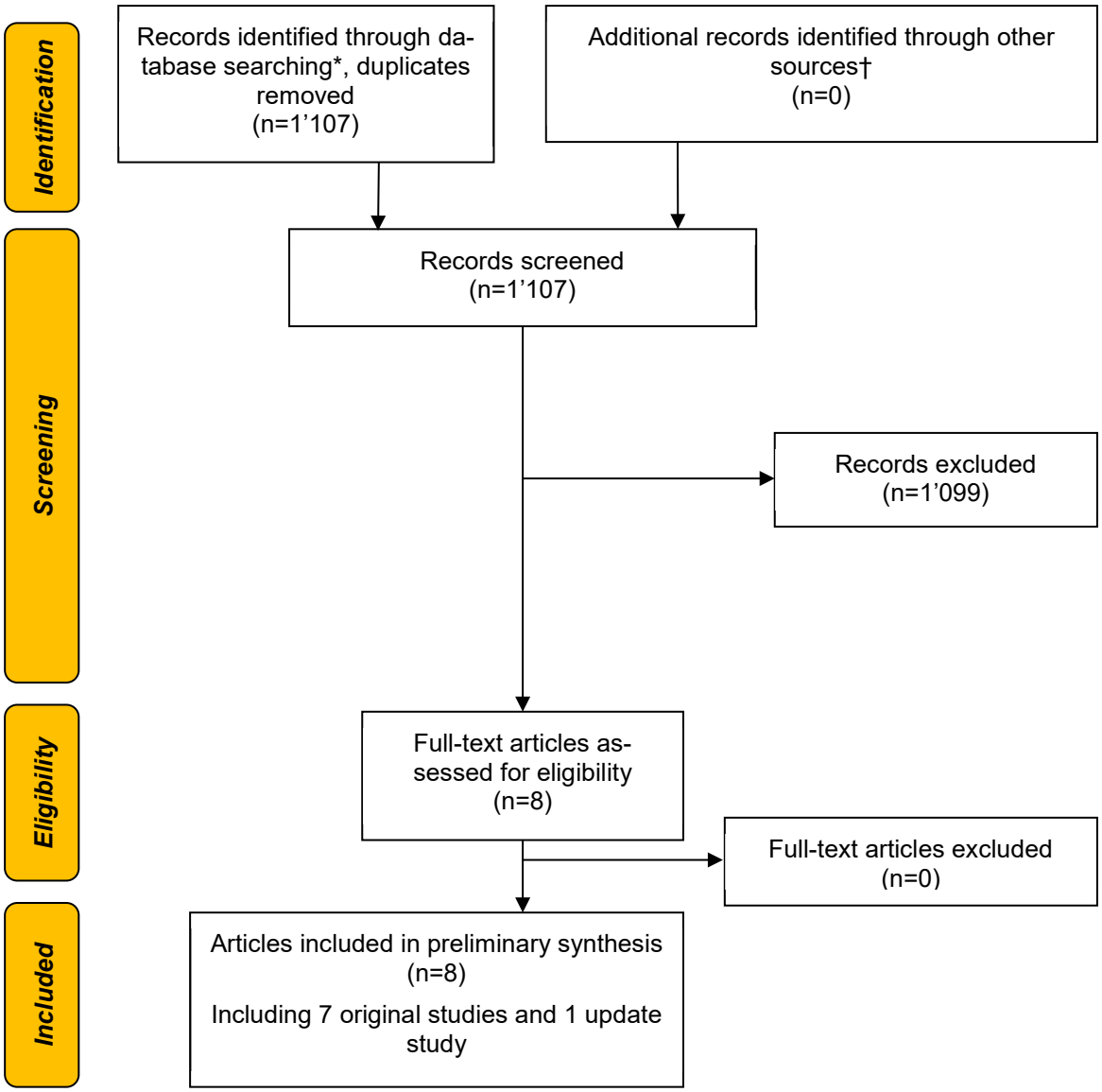
The extracted characteristics of relevant ongoing trials are presented in Table 28 in Appendix 12.6. Sixty-two ongoing trials have been identified that in the future might provide additional data on any of the treatments compared in the present assessment of clinical effectiveness and safety; thirteen of these include PAL in one or more treatment arms. Two ongoing single-arm trials have been identified that study relevant PAL combination therapies and might provide additional data on the safety of PAL (UMIN000029294 and NCT02692755). In addition, one RCT was identified that investigates the effect of eHealth support on the quality of life in patients treated with PAL and ET (EUCTR2016-004191-22-DE).

8.2 Evidence base pertaining to costs, cost effectiveness and budget impact

8.2.1 PRISMA flow diagram

Table 19 (Appendix 12.2.8) shows the number of hits retrieved through the systematic search described in Subsection 7.1.2.1 in MEDLINE, EMBASE, The Cochrane Library, TRIP database, CRD and Scopus. After removal of duplicates in Endnote, 1’107 hits remained. Figure 6 shows the PRISMA flow chart for economic studies.

Figure 6: PRISMA flow chart for economic studies – refers to HTA key questions 5-7



* Literature search for safety (extended analysis) and health economics as well as ethical, social, legal and organisational aspects.
† Refers to the literature search for efficacy, effectiveness and safety (RCTs) as well as other sources described in Section 7.2.

8.2.2 Evidence table

Eight relevant publications could be identified. They are described in Table 10.

Table 10: Evidence table for economic studies – refers to HTA key questions 5-7

Study (author/year)	Galve-Calvo et al. (2018)[151]	Mamiya et al. (2017)[7]	Mistry et al. (2018)[152]	Raphael et al. (2017)[153]	Matter-Walstra et al. (2016)[8]	Matter-Walstra et al. (2017)[154] – update	Zhang B.; Long, E.F. (2019)[155]	Zhang et al. (2019)[156]
Country/region	ES	US	US	CA	CH	CH	US	US, CN
Type of economic evaluation	CEA	CEA	CEA	CEA	CEA BIA	CEA	CEA	CEA
Perspective	Payer	Society‡	Payer	Payer	Payer	Payer	Not stated	US Payer CN Payer
Population	Hypothetical cohort of* postmenopausal women advanced HR+/HER2- first line without prior endocrine therapy	Hypothetical cohort of 10'000 postmenopausal women advanced HR+/HER2- Group A: first line without prior endocrine therapy Group B: second line with prior endocrine therapy	Hypothetical cohort of* postmenopausal women advanced HR+/HER2- first line without prior endocrine therapy	Hypothetical cohort of* postmenopausal women advanced HR+/HER2- first line without prior endocrine therapy	Hypothetical cohort of* postmenopausal women advanced HR+/HER2- first line without prior endocrine therapy	same as 2016	Hypothetical cohort of 10'000 postmenopausal women advanced HR+/HER2 - first line without prior endocrine therapy†	Hypothetical cohort of* postmenopausal women advanced HR+/HER2- second line with prior endocrine therapy
Intervention	RIB + LET (200 + 2.5 mg)	Group A: PAL + LET (125 + 2.5 mg) Group B: PAL + FUL dose*	RIB + LET (dose)*	PAL + LET (125 + 2.5 mg)	PAL + LET (125 + 2.5 mg)	same as 2016	PAL + LET (125 + 2.5 mg)	PAL + FUL (125 + 500 mg)
Comparator	PAL + LET (125, 100, 75 + 2.5 mg)	Group A: LET (dose)* Group B: FUL (dose)*	LET (dose)* PAL + LET (dose)*	LET (2.5 mg)	LET (2.5 mg)	same as 2016	RIB + LET (600 + 2.5 mg) LET (2.5 mg)	pbo + FUL (500 mg)

Table 10: Evidence table for economic studies (continued)

Outcome measures - EA	LYG, QALY; ICER, ICUR	QALY, ICER	LYG, QALY, ICER	QALYMs, ICER, INB	Healthcare costs, ICER, QALY	same as 2016	QALY, ICER	LYG, QALY, ICER
Model type/time	Partitioned survival model Time horizon: 15 years	Discrete event simulation model Time horizon: life time	Partitioned survival model Time horizon: 40 years	Discrete event simulation model Time horizon: 15 years	Markov cohort simulation Time horizon: life time	same as 2016	Markov model Time horizon: life time	Markov model Time horizon: 10 years
Costs included/Year	direct costs: drugs, administration, monitoring, treatment, adverse events, end-of-life care Year: 2017	direct costs: drugs, outpatient, laboratory, adverse events, hospice Year: 2015	direct costs: drugs, administration, monitoring, treatment, subsequent treatments, adverse of events, end-of-life care Year: 2016	direct costs: drugs, administration; treatment, monitoring, adverse events, subsequent treatment, death Year: not stated	direct costs: drugs‖, follow-up treatment, treating neutropenia Year: 2016	updated: drug costs for PAL valued with Swiss Public Prices 2017 Year: 2017	direct costs; drugs, treating severe neutropenia Year: 2016	direct costs: drugs, administration, pain medications, monitoring, serious adverse events, routine follow-up¶ Year: 2018
Data source EFF	Trials: MONALEESA-2, PALOMA-2, PALOMA-1§	Model-based (adverse events based on trials)	Trials: MONALEESA-2; PALOMA-1 Bayesian network meta-analysis	Trials: PALOMA-1 and PALOMA-2	Trial: PALOMA-1	same as 2016	Trials: PALOMA-1; MONALEESA-2	Trials: PALOMA-3 (PFS); CONFIRM-3 (OS)
Data source for utilities	MONALEESA-2 and literature	Literature	MONALEESA-2 and literature	literature	literature (LET)	same as 2016	literature	literature

Table 10: Evidence table for economic studies (continued)

Statistical validation	univariate sensitivity analysis, PSA	univariate sensitivity analysis, PSA	deterministic sensitivity analysis, PSA	PSA, CEAC	univariate sensitivity analysis, PSA	same as 2016	univariate sensitivity analysis	univariate sensitivity analysis, PSA
Sponsor(s)	Novartis	none declared	Novartis	none declared	Swiss State Secretariat for Education, Research and Innovation	same as 2016	none declared	Grants (National Natural Science Foundation; Key Science-Technology Research and Development Program)
COI	yes (consultancy fees, employment relationship)	none declared	yes (employment relationship)	none declared	none declared	same as 2016	none declared	none declared

BIA=budget-impact analysis; CEA=cost effectiveness analysis; CA=Canada; CEAC=cost effectiveness acceptability curve; CH=Switzerland; CN=China; COI=conflict of interest; EA=economic evaluation; ES=Spain; FUL=fulvestrant; ICER=incremental cost effectiveness- ratio; ICUR=incremental cost-utility ratio; INB=incremental net monetary benefit; LYG=life-years gained; NHS=national health service; OS=overall survival; pbo=placebo; PFS=progression-free survival; PSA=probabilistic sensitivity analysis; QALY=quality-adjusted life years; QUALMs=quality-adjusted life months; US=United States of America, WTP=willingness-to-pay
* (Number) not stated.
† Not explicitly mentioned.
‡ Stated by the authors; however, the perspective is not clear. As a limitation only the use of direct costs is mentioned.
§ PFS and OS for RIB and LET from MONALEESA-2; PFS for PAL + LET from PALOMA-2 and OS from PALOMA-1 trial, indirect comparisons.
‖ For PAL from USA, for LET Swiss drug costs.
¶ Radiography, computed or magnetic resonance tomography.

8.2.3 Findings regarding costs, cost effectiveness and budget impact

The systematic literature search for the economic domain retrieved eight cost effectiveness analyses[7 8 151-156], of which one study – Matter-Walstra et al. 2017[154] – was an update of the study by Matter-Walstra et al. from 2016.[8] Only one rough estimation of the budget impact was identified; it was included in the study for Switzerland[8 154] and estimated the annual budget impact for the treatment of PAL + LET versus LET alone.

- Galve-Calvo et al.[151] assessed RIB and LET versus PAL and LET in the first-line treatment of postmenopausal patients with HR+/HER2- advanced breast cancer using a cohort-based partitioned survival model. The analysis was performed from the perspective of the Spanish healthcare system. The efficacy data were based on the MONALEESA-2 study and PALOMA-1 and PALOMA-2. The utility values were taken from the MONALEESA-2 study and literature. The authors conducted a cost effectiveness analysis (CEA) taking the following direct costs into account: pharmaceuticals, administration costs, monitoring costs, adverse event costs (e.g. diarrhoea, infection, nausea, neutropenia, pulmonary embolism, vomiting) as well as end-of-life care (e.g. palliative care, acute hospital unit). One limitation of the study was that only indirect comparisons could be conducted as the two CDK4/6 inhibitors were not directly compared in head-to-head clinical trials.
- Mistry et al.[152] also compared RIB and LET versus PAL and LET as well as LET monotherapy as a first-line treatment in a hypothetical cohort of postmenopausal women with HR+/HER2 advanced breast cancer using a partitioned survival model. The analysis was performed from the perspective of a private third party payer in the US. The efficacy data were based on the MONALEESA-2 and PALOMA-1 trials. The utility values were taken from the MONALEESA-2 study and literature. The cost parameters included were similar to those in Galve-Calvo et al.[152] There were two imitations of the study: PFS and OS were taken from two different trials (indirect comparison) and healthcare resource use data were only available to a limited extent.
- Mamiya et al.[7] conducted a CEA for PAL and LET versus LET monotherapy (group A – without prior ET) and PAL and FUL versus FUL monotherapy (group B – with prior ET) with a discrete event simulation model. The authors stated that the analysis was performed from a "societal" perspective in the US. However, only direct costs were included (drugs, outpatient and laboratory costs, costs for adverse events and hospice). The efficacy data were based on clinical trials (MONALEESA-2, PALOMA-1) and the utility values came from the literature. Limitations of the study included 1) that therapies after PAL treatment were not reported in the trials and therefore a specific type and sequence of therapies after PAL treatment had to be assumed and 2) that only wholesale acquisition costs for drugs were available.

- Raphael et al.[153] compared PAL and LET versus LET monotherapy as a first-line treatment in a hypothetical cohort of postmenopausal women with advanced HR+/HER2- breast cancer using a discrete event simulation model. The CEA was carried out from the perspective of the Canadian healthcare system. The efficacy data were based on the PALOMA-1 and PALOMA-2 trials and the utility values were taken from the literature.[152] Some limitations of the study were that OS data were not fully reported and that overall probability of death may have been overestimated.
- Matter-Walstra et al.[8 154] also compared PAL and LET versus LET as first-line treatment in a hypothetical cohort of postmenopausal women with advanced HR+/HER2- breast cancer using a Markov model. The CEA was conducted from the perspective of the Swiss healthcare system. Furthermore the yearly budget impact for the Swiss healthcare system was calculated. The efficacy data were based on the PALOMA-1 trial and the utility data for LET came from the literature. Limitations included the fact that PAL utilities were not available and that only costs related to drug use, follow-up treatment and the treatment of neutropenia were included in the analysis.
- Zhang, B. and Long, E.F.[155] compared PAL and LET versus RIB and LET as well as LET monotherapy in a hypothetical cohort of postmenopausal women with advanced HR+/HER2- breast cancer without prior ET. They used a Markov model. The CEA was done from the perspective of the US healthcare system. The efficacy data came from clinical trials (PALOMA-1, MONALEESA-2) and the utility values were taken from the literature. Drug costs and treatment costs for severe neutropenia were included. Limitations of the study were that the median OS had to be simulated and some costs such as physician visits or hospital costs were not considered.
- Zhang et al.[156] assessed PAL and FUL versus placebo and FUL as second-line therapy (with prior ET) in a hypothetical cohort of postmenopausal women with advanced HR+/HER2- breast cancer using a Markov model. The analyses were performed from the perspective of the US and Canadian payers. The efficacy data were taken from the PALOMA-3 and CONFIRM trials and the utility values from the literature. Limitations were that the median OS was derived from another trial instead of the PALOMA-3 trial and that the utility values were obtained from the literature and were assumed to be equal in the same state of health.

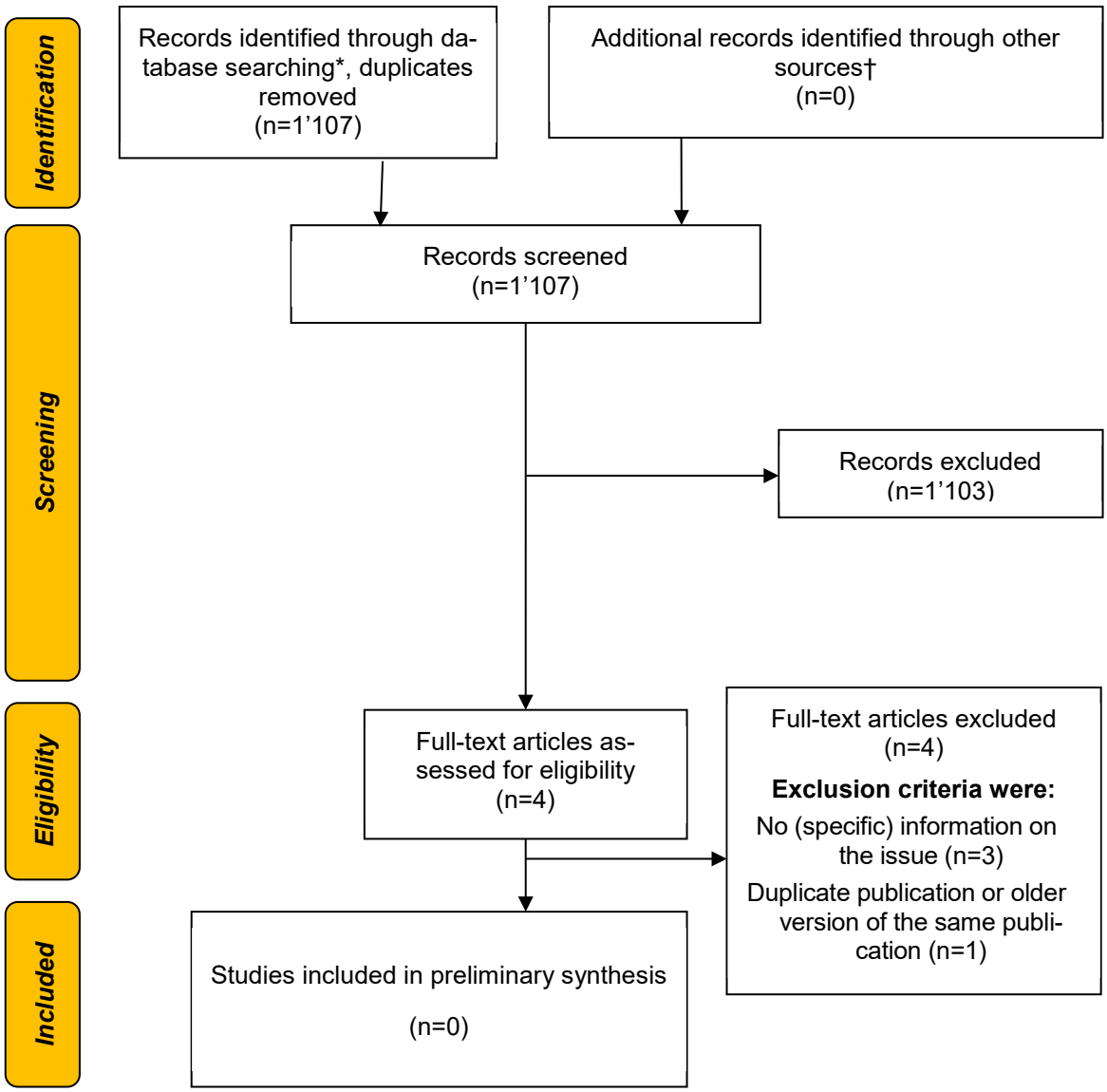
Overall the quality of the identified studies was moderate. They differed mainly with regard to the models used, the extent of included costs, the level of detail of the description of input and output parameters, the model descriptions and which secondary literature (in addition to the clinical trials) was used for unknown parameters. For a detailed quality assessment, see Appendix 12.5.

8.3 Evidence base pertaining to legal, social and ethical issues

8.3.1 PRISMA flow diagrams

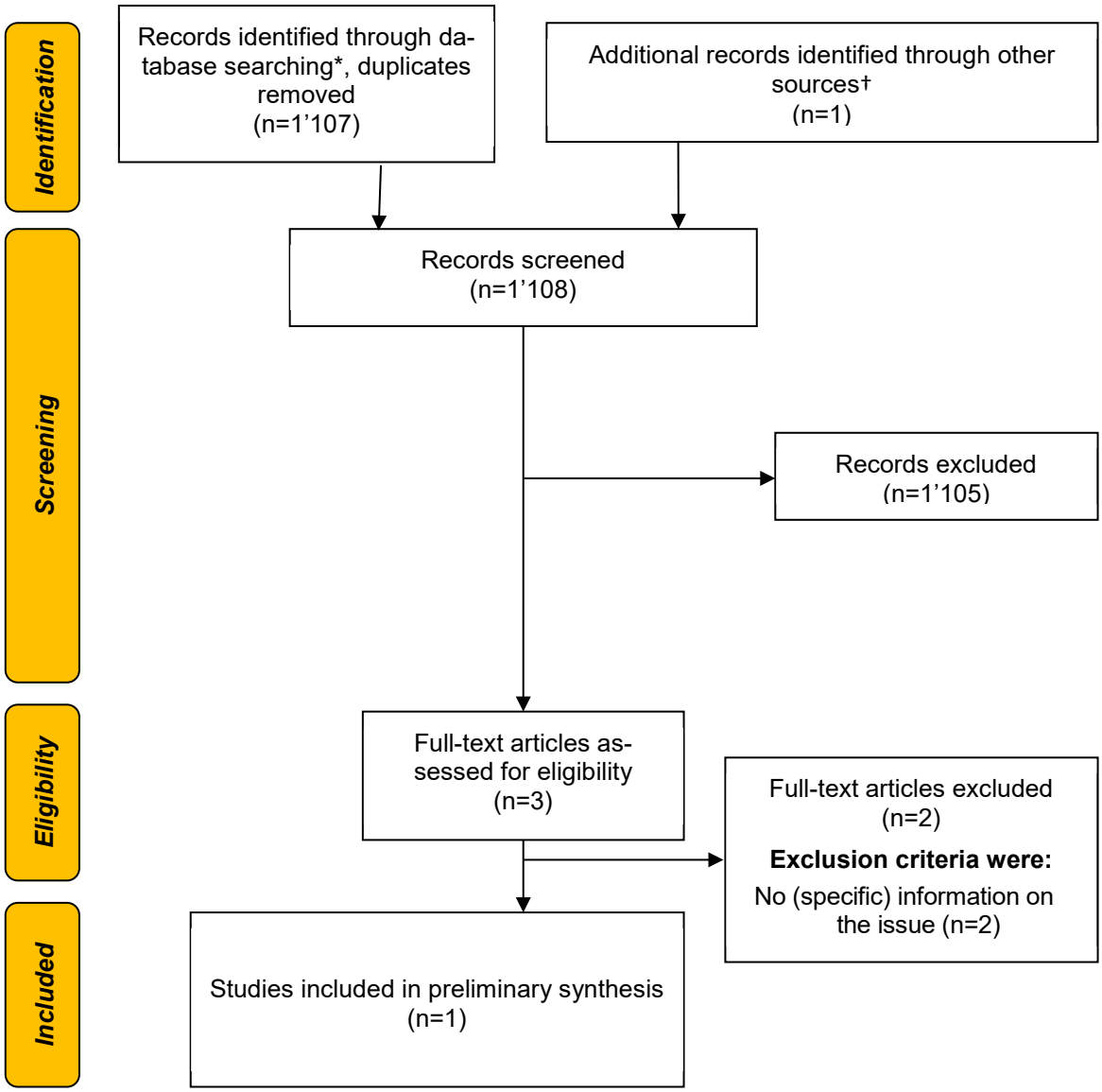
Table 19 (Appendix 12.2.8) shows the number of hits retrieved through the systematic search described in Subsection 7.1.2.1 in MEDLINE, EMBASE, The Cochrane Library, TRIP database, CRD and Scopus. After removal of duplicates in Endnote, 1’107 hits remained. Figure 7 to Figure 9 show the PRISMA flow charts for publications on legal, social and ethical issues.

Figure 7: PRISMA flow chart for publications on legal issues – refers to HTA key question 8 and legal issue Subsection 6.1.4



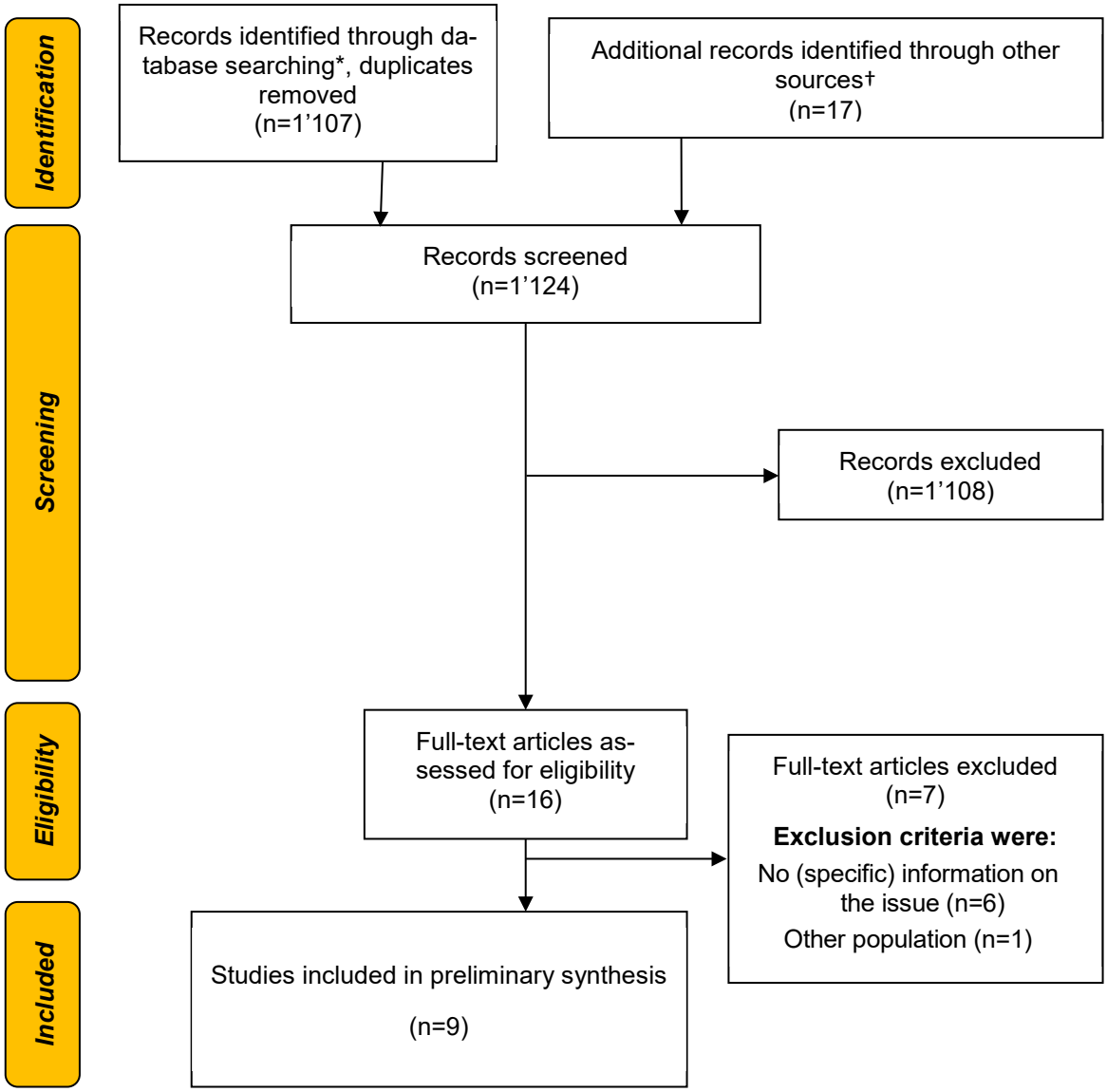
* Literature search for safety (extended analysis) and health economics as well as ethical, social, legal and organisational aspects.
† Refers to the literature search for efficacy, effectiveness and safety (RCTs) as well as other sources described in Section 7.2.

Figure 8: PRISMA flow chart for publications on social issues – refers to HTA key question 8 and social issue Subsection 6.1.2



* Literature search for safety (extended analysis) and health economics as well as ethical, social, legal and organisational aspects.
† Refers to the literature search for efficacy, effectiveness and safety (RCTs) as well as other sources described in Section 7.2.

Figure 9: PRISMA flow chart for publications on ethical issues – refers to HTA key question 8 and ethical issue Subsection 6.1.1



* Literature search for safety (extended analysis) and health economics as well as ethical, social, legal and organisational aspects.
† Refers to the literature search for efficacy, effectiveness and safety (RCTs) as well as other sources described in Section 7.2.

8.3.2 Evidence tables

8.3.2.1 Legal issues

No relevant publications could be identified.

8.3.2.2 Social issues

One relevant publication could be identified (Darden et al. 2018[157]). It is described in Subsection 8.3.3.2.

8.3.2.3 Ethical issues

Nine relevant publications could be identified. They are described in Table 11 and Table 12.

Table 11: Evidence table for systematic reviews on ethical issues – refers to HTA key question 8 and ethical issue Subsection 6.1.1

Author Year	Study design	Study aim	Search period	Included study designs	Number of included studies	Population	Intervention	Comparator	(Extracted) outcome measures	Sponsor(s)	Conflict of interest¶
Bottomley et al. 2002[158]	SR	systematic review of studies of HrQoL in patients with advanced breast cancer	1995 to 2001	RCTs that reported (patient reported) HrQoL results and included 50 patients or more	19	MBC	not (pre)specified	not (pre)specified	(patient reported) HrQoL	not disclosed	none declared
Forsythe et al. 2018[159]	SR	to assess PFS and other factors that influence OS and treatment response as well as HrQoL	January 2006 to January 2017	Phase II and III RCTs, observational studies in a "targeted search"	79 (RCTs)	HR+/HER2− MBC	not (pre)specified	not (pre)specified	PFS or TTP, OS (reported as either median survival or hazard ratios)	Novartis	yes (employment relationship)
Krohe et al. 2016[160]	SR	to examine how PROs are utilized as endpoints in industry-sponsored MBC clinical trials registered in the clinicaltrials.gov database	search date: mid-2015, no further information	Phase II and III RCTs sponsored by industry	38	MBC	24 selected MBC treatments*	not (pre)specified	PRO measures	Novartis	none declared

Table 11: Evidence table for systematic reviews on ethical issues (continued)

Lux et al. 2019[161]	SR + MA	to apply the methods proposed by IQWiG† in the indication of HR+/HER2− MBC to validate PFS as surrogate endpoint for OS	search date: mid-2016, no further information	RCTs (all phases)	26 (16 in quantitative analysis)	HR+/HER2- locally advanced‡ or metastatic breast cancer regardless of line of treatment	At least one study arm investigated: FUL, LET, TAM, EXE or ANA	Any drug intervention as single agent or in combination therapy	OS, PFS	Pfizer Deutschland GmbH	yes (honoraria, employment relationship)
Sherrill et al. 2008[162]	SR + MA	association between OS and TTP or PFS in MBC studies	1994 to 2007	RCTs (all phases) reporting both TTP (or PFS) and OS	67	MBC	not (pre)specified	not (pre)specified	TTP (or PFS) and OS	not disclosed	yes (employment relationship)
Templeton et al. 2015[163]	SR	to explore whether bias due to imbalanced censoring was present in reports of phase 3 trials for women with MBC; to compare correlation of OS and PFS/TTP as well as OS and TTF§	January 2001 to December 2012	phase 3 RCTs for MBC with at least 150 patients	34	MBC	not (pre)specified	not (pre)specified	PFS, TTP or OS as primary end point‖	Swiss Cancer Research Foundation	none declared

ANA=anastrozole; EXE=exemestane; FUL=fulvestrant; HR=hormone receptor; HER2=human epidermal growth factor receptor 2; HrQoL=health-related quality of life; IQWiG=Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; LET=letrozole; MA=meta-analysis; MBC=metastatic breast cancer; OS=overall survival; PFS=progression-free survival; PRO=patient reported outcome; RCT=randomized controlled trials; SR=systematic review; TAM=tamoxifen; TTF=the end point of time-to-treatment failure; TTP=time-to-progression
* Including hormonal agents for the ER+ patient population, HER2-targeted agents for the HER2+ patient population, chemotherapy for the triple-negative patient population, CDK 4/6 inhibitors, PI3K inhibitors.
† Methods for the validation of surrogate endpoints in HTA context (IQWiG rapid report from 2011, cited in Lux et al. 2019[161]).
‡ Mot amenable to resection or radiotherapy with curative intent.
§ Where discontinuation of study treatment for any reason is considered an event.
‖ With Kaplan–Meier curves for PFS/TTP showing numbers at risk at different follow-up times and reporting HRs for these outcomes.
¶ (Mainly) regarding pharmaceutical companies.

Table 12: Evidence table for other publication types on ethical issues – refers to HTA key question 8 and ethical issue Subsection 6.1.1

Author Year	Study title	Study design	Relevant ethical issues	Sponsor(s)	Conflict of interest*
Freidlin et al. 2013[164]	New challenges for comparative effectiveness in oncology: Choice of primary end points for randomized clinical trials	NR	PFS versus OS	not disclosed	none declared
Kaklamani 2016[165]	Clinical implications of the progression-free survival endpoint for treatment of hormone receptor-positive advanced breast cancer	NR	PFS versus OS	Novartis	yes (honoraria)
Korn et al. 2011[166]	Overall survival as the outcome for randomized clinical trials with effective subsequent therapies	commentary/theoretical article	how OS outcomes should be interpreted with increasing availability of effective therapies that can be given subsequently to the treatment assigned in an RCT	not disclosed	none declared

NR=narrative review; OS=overall survival; PFS=progression-free survival; RCT=randomized controlled trials
* (Mainly) regarding pharmaceutical companies.

8.3.3 Findings regarding legal, social and ethical issues

8.3.3.1 Legal issues

We did not identify any publication regarding the legal issue (see Subsection 6.1.4).

8.3.3.2 Social issues

Regarding the social issue (see Subsection 6.1.2), we identified one patient survey on treatment satisfaction (Darden et al. 2018[157]). The authors performed an observational, cross-sectional, web-based survey in patients with ABC or MBC receiving PAL plus an AI or PAL plus FUL in a real-world setting. They recruited 604 patients with self-reported HR+/HER2- ABC/MBC in six countries (Argentina, Canada, Denmark, Germany, the Netherlands and the USA). They used a self-designed questionnaire including 16 questions – on patient expectations of therapy, feelings about side effects and satisfaction with therapy – from the "Cancer Therapy Satisfaction Questionnaire" (cited in Darden et al.[157]). The study was conducted under the direction of Pfizer and also funded by Pfizer.

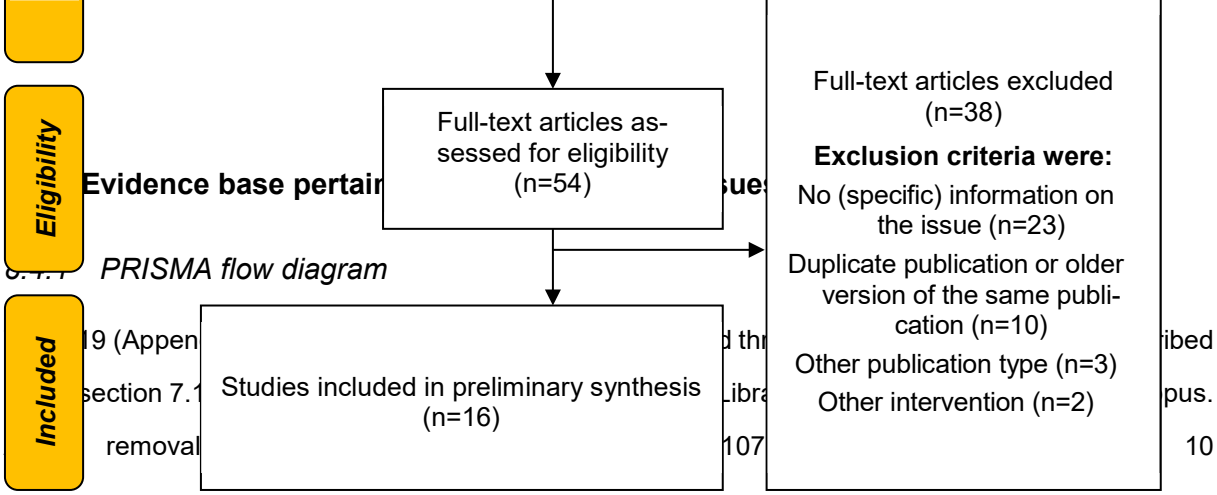
The survey may contribute to the social issue as it includes questions on patients' expectations of therapy and if expectations were met. However, the authors mainly reported overall findings and only selectively presented detailed results. As they did a cross-sectional survey, there was no follow-up. All participants were taking PAL + FUL or PAL + AI at the time of the survey, most of them for over half a year.

8.3.3.3 Ethical issues

We identified nine publications as evidence for the ethical issue (see Subsection 6.1.1). Four systematic reviews[159 161-163] and two narrative reviews[164 165] dealt with PFS as a surrogate outcome and the relation between PFS (or TTP) and OS (and HrQoL in one review). One systematic review[158] investigated the role of HrQoL as an endpoint in studies with ABC patients, another[160] the role of PRO in industry-sponsored MBC trials. One theoretical commentary investigated the role and interpretation of OS results when subsequent therapies are available.

The six systematic reviews are of mixed quality. The literature search strategy, databases included and study selection criteria were clearly described by most of the reviews. Two did not clearly state the aim of their study, and only four studies described the studies included in adequate detail.

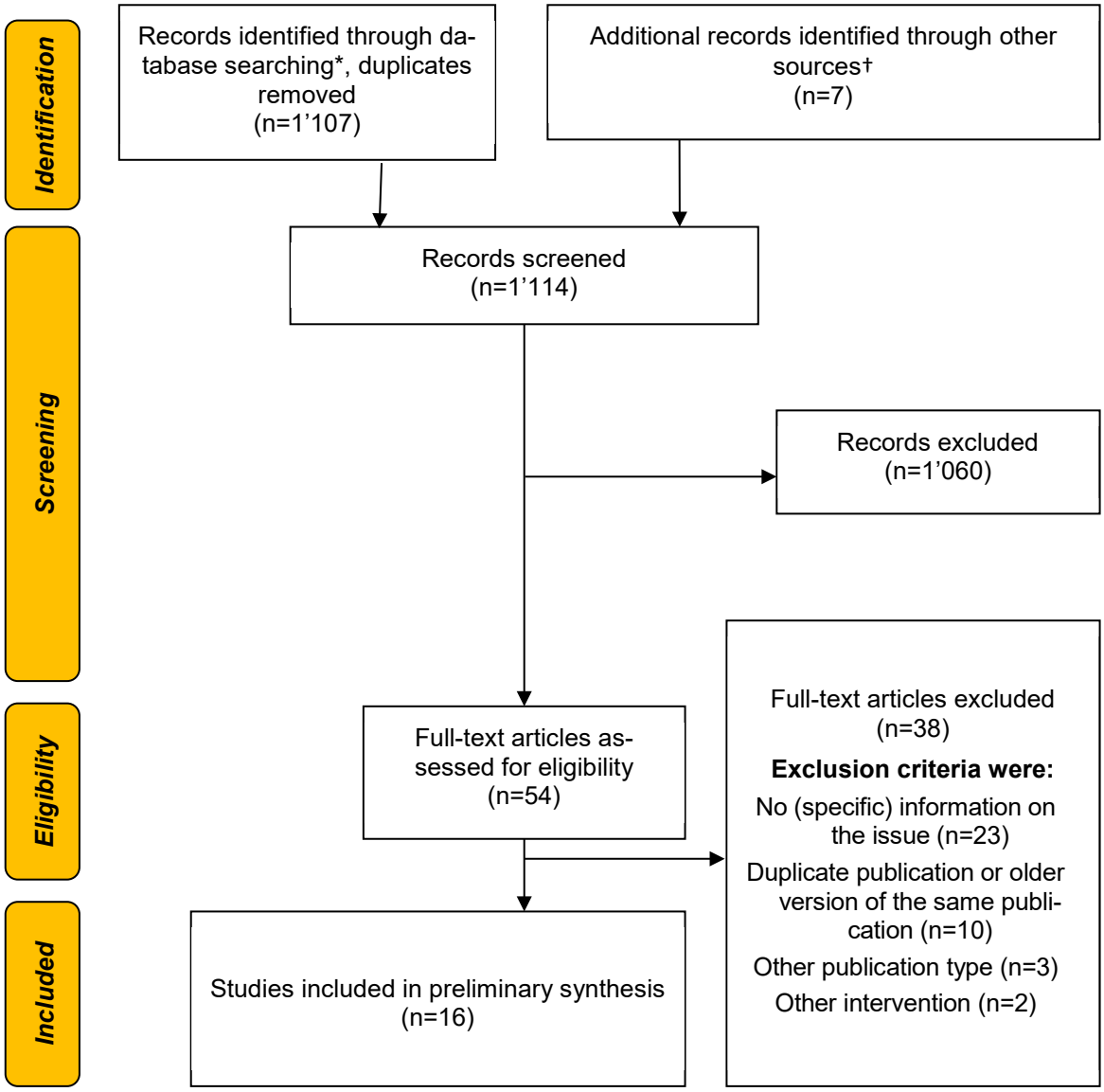
Not all of the publications specifically dealt with PAL, either because of the publication type (theoretical article) or because of the publication year or because of the date of literature search being too early in time.



PRISMA flow diagram

shows the PRISMA flow chart for publications on organisational issues.

Figure 10: PRISMA flow chart for publications on organisational issues – refers to HTA key question 9 and organisational issue Subsection 6.1.3



* Literature search for safety (extended analysis) and health economics as well as ethical, social, legal and organisational aspects.
† Refers to the literature search for efficacy, effectiveness and safety (RCTs) as well as other sources described in Section 7.2.

8.4.2 Evidence table

Sixteen publications could be identified. They are described in Table 13, Table 14 and Table 15.

Table 13: Evidence table for observational studies on organisational issues – refers to HTA key question 9 and organisational issue Subsection 6.1.3

Author Year	Title	Study design	Study size*	Relevant organisational issues	Sponsor(s)	Conflict of interest†
Goldschmidt et al. 2018[167]	Current Treatment Patterns Among Postmenopausal Women with HR+/HER2? Metastatic Breast Cancer in US Community Oncology Practices: An Observational Study	(Probably) retrospective cohort study	401	therapy duration and treatment sequencing	Novartis	yes (employment relationship, consulting)
Guerin et al. 2018[119]	Monitoring of Hematologic, Cardiac, and Hepatic Function in Post-Menopausal Women with HR+/HER2- Metastatic Breast Cancer	retrospective cohort study	401	management of toxicities and monitoring requirements	Novartis	yes (employment relationship, consulting)
Kish et al. 2018[128]	Real-world evidence analysis of palbociclib prescribing patterns for patients with advanced/metastatic breast cancer treated in community oncology practice in the USA one year post approval	retrospective cohort study	763	management of toxicities and monitoring requirements	Pfizer	yes (employment relationship)
Momper et al. 2019[132]	Interaction Between Cyclosporine and Palbociclib in a Renal Transplant Patient: Case Report and Pharmacokinetic Perspective	Case report	1	"Preemptive dose reductions of these immunosuppressive agents are warranted if palbociclib is initiated, followed by close monitoring of blood concentrations."	none declared	none declared
Rossi et al. 2019[168]	Clinical outcomes after palbociclib with or without endocrine therapy in postmenopausal women with hormone receptor positive and HER2-negative metastatic breast cancer enrolled in the TREnd trial	prospective cohort study	105	effectiveness of standard subsequent line therapies after PAL	Pfizer	yes (research funding, consulting)
Watson et al. 2019[148]	Real-World Experience of Palbociclib-Induced Adverse Events and Compliance With Complete Blood Count Monitoring in Women With Hormone Receptor-Positive/HER2-Negative Metastatic Breast Cancer	retrospective cohort study	64	management of toxicities and monitoring requirements	not disclosed	none declared

Table 13: Evidence table for observational studies on organisational issues (continued)

Xi et al. 2019[150]	Retrospective Analysis of Treatment Patterns and Effectiveness of Palbociclib and Subsequent Regimens in Metastatic Breast Cancer	retrospective cohort study	200	treatment sequencing (subsequent therapies after disease progression on PAL)	not disclosed	yes for some of the authors (research funding, honoraria)

PAL=palbociclib; HR=hormone receptor; HER2=human epidermal growth factor receptor 2; US=United States
* Number of patients.
† (Mainly) regarding pharmaceutical companies.

Table 14: Evidence table for narrative reviews on organisational issues - refers to HTA key question 9 and organisational issue Subsection 6.1.3

Author Year	Title	Relevant organisational issues	Sponsor(s)	Conflict of interest*
Boyle et al. 2018[169]	Hormone receptor positive, HER2 negative metastatic breast cancer: Impact of CDK4/6 inhibitors on the current treatment paradigm	management of toxicities and monitoring requirements	Novartis	yes for some of the authors (consulting, honoraria, etc.)
Spring et al. 2017[170]	Clinical Management of Potential Toxicities and Drug Interactions Related to Cyclin-Dependent Kinase 4/6 Inhibitors in Breast Cancer: Practical Considerations and Recommendations	management of toxicities and monitoring requirements	National Cancer Institute grant	none declared
Thill et al. 2018[34]	Management of adverse events during cyclin-dependent kinase 4/6 (CDK4/6) inhibitor-based treatment in breast cancer	management of toxicities and monitoring requirements	none declared	yes (consulting, honoraria)
Spring et al. 2019[171]	CDK 4/6 Inhibitors in Breast Cancer: Current Controversies and Future Directions	monitoring requirements and subsequent therapies	National Cancer Institute grant	not disclosed
Ettl 2019[172]	Management of adverse events due to cyclin-dependent kinase 4/6 inhibitors	management of toxicities and monitoring requirements	not disclosed	yes (honoraria, travel support)
Rossi et al. 2018[173]	Managing advanced HR-positive, HER2-negative breast cancer with CDK4/6 inhibitors in post-menopausal patients: is there a best sequence?	treatment sequencing	none declared	yes for some of the authors (consulting, grant)

CDK=cyclin-dependent kinase; HR=hormone receptor; HER2=human epidermal growth factor receptor 2
* (Mainly) regarding pharmaceutical companies.

Table 15: Evidence table for guidelines on organisational issues – refers to HTA key question 9 and organisational issue Subsection 6.1.3

Author Year	Title	Relevant organisational issues	Sponsor(s)	Conflict of interest*
Rugo et al.[174] 2016	Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline	Includes monitoring requirements	not disclosed	yes for some of the authors (research funding, honoraria, etc.)
Bellet et al.[32] 2019	Palbociclib and ribociclib in breast cancer: consensus workshop on the management of concomitant medication	Includes monitoring requirements	Novartis, Pfizer, Grünenthal, Esteve and Kyowa Hakko Kirin	yes (research funding, honoraria, etc.)
Cardoso et al.[21] 2018	4th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 4)	Management of toxicities	none declared	yes for some of the authors (research funding, honoraria, etc.)

ESO-ESMO=European School of Oncology – European Society for Medical Oncology; ABC=advanced breast cancer
* (Mainly) regarding pharmaceutical companies.

8.4.3 Findings regarding organisational issues

We identified 16 publications as evidence for the organisational issue (see Subsection 6.1.3). The ESO-ESMO international consensus guidelines[21] included a section with recommendations on supportive and palliative care including management of toxicities, the American Society of Clinical Oncology Guideline[174] included recommendations for PAL on dosing and blood count monitoring. The documentation of an expert consensus[32] gave a detailed overview of drug interactions of PAL (and RIB) and resulting management requirements. Six narrative reviews[34 169-173] were identified that also dealt with the management of toxicities, monitoring requirements and treatment sequencing, some in more detail. The seven included observational studies[119 128 132 148 150 167 168] (mostly retrospective cohort studies) added real-world data on monitoring frequency, dosing patterns/toxicity induced dose reductions and treatment sequencing.

9 Feasibility HTA

Despite the short time that PAL is available on the market, there is a substantial body of evidence to inform an HTA report. However, this is characterised by a small amount of direct evidence (Only two RCTs studied PAL in combination with LET and only one RCT studied PAL in combination with FUL.[2 4 45]) but a considerable amount of indirect evidence and secondary literature.

Efficacy, effectiveness and safety

In the light of this evidence, quantitative comparisons between the treatments of interest (see PICOs, Chapter 5) can only be done indirectly through NMAs. Covering the entire scope of the research questions on efficacy, effectiveness and safety – two PICOs (that differ with regard to population) and the five defined outcomes – requires ten separate NMAs. Data availability and feasibility issues for the NMAs with regard to outcomes can be summarised based on the preliminary extraction of study characteristics as follows:

- PFS and TTP were the most frequently reported outcomes in the included studies. PFS is usually defined as the time until tumour progression, death or censoring, whereas TTP only measures the time until tumour progression. NMA is feasible and we suggest combining PFS and TTP because: 1) trials in consideration for the potential NMA sometimes defined TTP as “time to progression or death“, similar to the definition of PFS; 2) PFS and TTP are often used interchangeably and recent MAs have also combined both outcomes.[175 176]
- About half of the studies under consideration reported OS data. Therefore, there is a risk that we cannot provide a full treatment network due to missing links between the studies.[1] We might have to include heterogeneous populations in the final NMA or combine different treatment dosages in one. However, such adjustments would increase the risk of violating transitivity and the risk of bias.
- QoL data are only reported in about 20 per cent of the studies under consideration. In addition, the instruments and reported subscales for measuring QoL differed substantially between the studies. If the individual scales are comparable (for example,. they measure the same factors, like pain), the results can be standardised and used in the NMA. The feasibility of constructing a meaningful treatment network for the outcome QoL remains to be determined in a detailed analysis of the trial data. The substantial heterogeneity between the included studies might produce a high risk of bias.

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[1] This refers to data availability only and does not imply any other consequences regarding this outcome. Even in the absence of a full treatment network, all OS analyses that are feasible, based on the available data, will be conducted.

- Most studies reported AEs. Consequently, an NMA will be possible. The validity of the results will depend on the definition of the AEs in the primary studies. It might be appropriate to conduct multiple NMAs on different grades of severity of individual AEs (further increasing the number of NMAs) or on different AEs pooled by grade of severity.
- Most studies also reported the rates of treatment discontinuations due to AEs. Since there are no severity levels, an NMA of discontinuation rates will be easier to conduct and will have a lower risk of bias than the analysis of AEs alone.

Our systematic literature review identified twelve NMAs that included PAL in one of the relevant combinations in their treatment networks and compared (a varying amount of) treatment alternatives for women with HR+/HER2- LA/MBC.[177-188] All NMAs used PFS as the main outcome, three also included OS (but could not assess it in an NMA), two also included QoL (but could not asses it in an NMA) and one also assessed AEs. None of the NMAs that included OS, QoL or AEs included all of the treatment alternatives relevant for the present assessment.

In conclusion, we can confirm that for most or at least some of the relevant outcomes, NMAs are feasible from a statistical point of view. However, the reliability and risk of bias of the results will vary depending on the outcomes and on the quality of the data provided in the primary studies.

With regard to the safety outcomes, the identified NRSs provide additional evidence for the assessment of PAL, such as rare side effects and adverse drug interactions. However, all but two of the cohort studies and all of the case reports, case series and single arm studies only included patients treated with PAL. The two studies that do include other treatment groups did not sufficiently fulfil the PICO definitions of this HTA report with regard to PAL treatment combinations or with regard to comparators.[119 143] Therefore, no comparative conclusions can be drawn from the NRSs. Rather, they might give a valuable additional insight into the safety profile of PAL by incorporating real-world data.

Costs, cost effectiveness and budget impact

With regard to the HTA key question on the costs of PAL, no published study with (current) drug prices and prescribing volumes for Switzerland has been identified (for the suggested approach to obtain these data, see Chapter 10). Neither was a study identified that precisely describes all medical resource consumption and unit costs potentially relevant for an economic modelling study (drug costs, inpatient and outpatient treatment costs, follow-up treatment costs, potential costs for hospitalisation, costs for side effects, etc.) for Switzerland.

With regard to cost effectiveness, several economic models are available but limited to the extent that they did not cover all comparators defined in PICO 1 and PICO 2. PAL plus LET (PICO 1) was compared

with either RIB plus LET or LET alone. PAL plus FUL (PICO 2) was covered in only one study and was compared with a pbo.[156] The only study that was conducted for the Swiss context used a Markov model comparing PAL plus LET with LET alone and included drug costs, follow-up treatment costs and costs of neutropenia.[8 154]

We did not identify a study regarding the budget impact of a potential withdrawal of PAL from reimbursement. There is one rough estimation of the budget impact of introducing PAL plus LET (compared with LET alone) that was calculated for Switzerland.[8 154] The suggested approach is described in Chapter 10.

Legal, social and ethical issues, organisational issues

No evidence for the legal issue (Section 6.1) was obtained from the literature review and only one patient survey yielded some information on the social issue (for suggested approaches for addressing the legal and social issues, see Chapter 10). Sufficient literature was identified to address the ethical issue. A reasonable amount of literature was also found for answering the organisational issue.

Conclusion

Conducting an HTA is feasible, albeit with a considerable amount of uncertainty due to indirect evidence.

10 Outlook

Efficacy, effectiveness and safety

In sum, up to ten NMAs will have to be conducted to cover the research questions (see Chapter 9). If the construction of complete treatment networks (covering all treatments included in PICO) based on robust data is not possible for certain outcomes, analyses of incomplete networks will be conducted where a PAL treatment combination is included. If, for certain outcomes, the reported data are insufficient in terms of quantity or quality to support an NMA (complete or incomplete), a short narrative description of the available data can be provided and the evidence gap described.

For the NMA we suggest using a Bayesian approach. The whole analysis will be conducted in the R environment. We will calculate random effects models as well as a fixed effect model. The fixed effect model will be compared with the corresponding random effects model using leverage plots and the deviance information criterion. The model with the better fit will be used for further interpretation. Further, we will perform a check for inconsistency by comparing an inconsistency model with a consistency model. If the inconsistency model shows a better fit, then we assume inconsistency in the network and we will adapt our model subsequently. Due to the similarities of PFS and TTP we will combine these outcomes into a single NMA. If the final model shows signs of low transitivity, we will conduct individual NMAs for both outcomes. Another challenge in regard to PFS and TTP is that some studies exclusively reported the median time to event in combination with confidence intervals. Since pooled results of median time-to-event data tend to be biased in meta-analyses, we will exclusively use studies that report hazard ratios (HR).[189] [2]

For the NRSs on safety outcomes, we suggest conducting a brief quality assessment of the included cohort studies based on the ROBINS-I tool.[191] Further, we will provide extended evidence tables containing study results.

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[2] However, meta-analyses of HR can be prone to bias in themselves if the proportional hazards assumption is violated.[190] A violation of this assumption can be shown by non-constant HR that might lead to intersecting survival curves in extreme cases. Studies with non-proportional HRs are usually excluded in meta-analyses. An alternative is to use the fractional polynomial method that can provide unbiased results.[190] However, substantially more resources are required if this method is applied since the Kaplan-Meier curves of the individual studies would need to be extracted and analysed; to our knowledge, none of the currently available NMAs on treatments for patients with HR+/HER2- LA/MBC has used the fractional polynomial method. We therefore do not suggest using this method.

Costs, cost effectiveness and budget impact

Regarding drug costs we suggest accessing data from Tarifpool[192] with the support of the FOPH. In addition, we will consult the SL for current prices.

The cost effectiveness analysis will include direct costs (to the extent that they are available for Switzerland) and will be conducted from the perspective of the OKP. A first approach would be to adapt the existing Swiss model, as envisaged at the time of starting the scoping report.[8 154] This entails a detailed analysis of the complete model data, structure and inputs (it was agreed that they could be obtained from the study authors). However, extensive enlargements will be necessary to cover all PICO interventions and comparators and additional targeted literature searches and expert consultations for utility data, further cost data and possibly other relevant input and output parameters will have to be conducted.

For conducting the budget impact analysis, we propose to develop two or three scenarios in consultation with the FOPH and one or two clinical experts (to obtain estimates on shifts in the proportion of drugs prescribed after a withdrawal of PAL, for example a shift to another drug or shift to monotherapy). Calculations will include changes in overall drug costs.

Legal, social and ethical issues, organisational issues

We propose to interview one or two juridical experts with regard to the legal issue and to summarise the results of the interviews. With regard to the social issue, it might be desirable to conduct some patient interviews. This could shed more light on the expectations and needs of a very vulnerable patient group often confronted with end-of-life situations. For the ethical issue, we propose to provide a written summary and discussion of the results of included studies. For organisational issues, we propose to draft a concise tabular summary of recommendations from guidelines and narrative reviews regarding monitoring requirements, toxicities/drug interaction management in consultation with a clinical expert. We further suggest supplementing this with a tabular summary on related evidence from the identified real-world data.

Changes with regard to PICO and HTA key questions as a result of the expert review

Some of the reviewers pointed out that the other two CDK 4/6 inhibitors should be included as interventions (rather than as comparators only). The suggested PICO for the full HTA report was therefore

adapted. For reasons of feasibility, some other changes had to be implemented with regard to comparators as well as with regard to the HTA key and additional questions. The revised PICOs are shown in the following figures and the revised HTA key questions in the paragraphs thereafter.

Table 16: Revised PICO 1

P:	Pre/peri- (under ovarian suppression) or postmenopausal women with HR+/HER2- LA/MBC who have not relapsed or progressed during or within 12 months after adjuvant ET and have not received prior ET for advanced-stage disease
I:	- PAL + AI (ANA, LET or EXE) - RIB + AI (ANA, LET or EXE) - ABE + AI (ANA, LET or EXE)
C:	- Either of the other two CDK4/6 inhibitors + AI (ANA, LET or EXE) - AI (ANA, LET or EXE)
O:	Efficacy and effectiveness - HrQoL or other PROMs, or both (critical outcome) - OS (critical outcome) - PFS (important outcome*) Safety - Treatment-related AEs (critical outcome) - Treatment discontinuation due to AEs (critical outcome) Economics - Costs for complete treatment path including costs after stopping treatment with PAL, RIB or ABE - Costs of (severe) side effects - Budget impact - ICER, incremental/total costs, QALYs and LYG

ABE=abemaciclib; AE=adverse event; AI=aromatase inhibitor; ANA=anastrozole; ET=endocrine therapy; EXE=exemestane; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; HrQoL=health-related quality of life; ICER =incremental cost effectiveness ratio; LET=letrozole; LYG=life years gained; PAL=palbociclib; OS=overall survival; PFS=progression-free survival; PICO=population, intervention, comparator, outcome; PROM=patient-reported outcome measure; QALY=quality-adjusted life year; RIB=ribociclib
* PFS can be seen as a surrogate parameter and was therefore ranked as important (but not critical).

Table 17: Revised PICO 2

P:	Pre/peri- (under ovarian suppression) or postmenopausal women with HR+/HER2- LA/MBC who have relapsed or progressed during or within 12 months after adjuvant ET or during ET for advanced-stage disease
I:	- PAL + FUL - RIB + FUL - ABE + FUL
C:	- Either of the other two CDK4/6 inhibitors + FUL - FUL
O:	Efficacy and effectiveness - HrQoL or other PROMs, or both (critical outcome) - OS (critical outcome) - PFS (important outcome*) Safety - Treatment-related AEs (critical outcome) - Treatment discontinuation due to AEs (critical outcome) Economics - Costs for complete treatment path including costs after stopping treatment with PAL, RIB or ABE - Costs of (severe) side effects - Budget impact - ICER, incremental/total costs, QALYs and LYG

ABE=abemaciclib; AE=adverse event; ET=endocrine therapy; FUL=fulvestrant; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; HrQoL=health-related quality of life; ICER =incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PAL=palbociclib; PICO=population, intervention, comparator, outcome; PFS=progression-free survival; PROM=patient-reported outcome measure; QALY=quality-adjusted life year; RIB=ribociclib
* PFS can be seen as a surrogate parameter and was therefore ranked as important (but not critical).

Revised HTA key questions

1. What is the effectiveness/efficacy of PAL, RIB and ABE in combination with an AI (ANA, LET or EXE) in women with HR+/HER2- LA/MBC who have not received prior ET for advanced-stage disease compared with each other and with alternative treatment options*?
2. What is the effectiveness/efficacy of PAL, RIB and ABE in combination with FUL in women with HR+/HER2- LA/MBC with disease progression/recurrence during/after prior ET compared with each other and with alternative treatment options*?
3. Are PAL, RIB and ABE in combination with an AI (ANA, LET or EXE) in women with HR+/HER2- LA/MBC who have not received prior ET for advanced-stage disease safe compared with each other and with alternative treatment options*?

4. Are PAL, RIB and ABE in combination with FUL in women with HR+/HER2- LA/MBC with disease progression/recurrence during/after prior ET safe compared with each other and with alternative treatment options*?
5. What are the costs of PAL, RIB and ABE?
6. What is the budget impact of a potential change in the reimbursement status of either PAL, RIB or ABE in the two above-mentioned combinations and indications†?
7. How cost-effective is the addition of PAL, RIB or ABE to treatment with an AI (PICO 1) or to treatment with FUL (PICO 2)?
8. Are there legal, social or ethical issues related to PAL, RIB or ABE in the two above-mentioned combinations and indications‡?
9. Are there organisational issues related to PAL, RIB or ABE in the two above-mentioned combinations and indications‡?

* Due to the lack of direct comparisons of CDK4/6 inhibitors in clinical trials, these questions will be answered in an NMA. To enable the construction of meaningful treatment networks, the NMA will include as additional comparators alternative treatment options that were defined in accordance with international guidelines and in consultation with a Swiss clinical oncology expert and that are listed in the original PICOs in Chapter 5.

† The scenarios that might have to be analysed are to be defined during conduct of a full HTA based on the results of the cost effectiveness analysis.

‡ We refined and specified this question during the scoping phase in consultation with the FOPH within the additional questions in Section 6.1. For (further) suggested revision see the following paragraph. *Revised additional question(s)*

It was suggested to only include ethical and organisational issues. No change was made to the ethical issue. The following change was made to the organisational issue:

How does PAL, RIB or ABE combination therapy (either with an AI or with FUL as indicated) modify the need for other technologies and use of resources?

Revised title

To reflect the above mentioned changes accordingly, the title of the full HTA report will be changed to: Palbociclib (Ibrance®), ribociclib (Kisqali®) and abemaciclib (Verzenios®) for the treatment of hormone receptor (HR)-positive, human epidermal growth factor (HER2)-negative advanced breast cancer

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12 Appendices

12.1 Search strings for clinical effectiveness and safety (Palbociclib versus comparators)

12.1.1 MEDLINE

A search was conducted on 14 November 2019 for publications in English and German. On 24 January 2020 an additional search was conducted using identical strings except for the language restriction, which was changed to French instead of English and German.

(Including Epub Ahead of Print, In-Process and Other Non-Indexed Citations and Daily - without Revisions from 2015 to 13 November 2019)

Search strategy:

1 exp Breast Neoplasms/ (331369)

2 ((breast* or mamma*) adj3 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or sarcoma* or neoplasm* or malignan*)).mp. (464002)

3 1 or 2 (464011)

4 exp Neoplasm Metastasis/ (227947)

5 advanc*.mp. (925338)

6 metasta*.mp. (638632)

7 hormon* receptor*.mp. (38683)

8 HR*.ti,ab. (406584)

9 HR+.ti,ab. (266552)

10 exp Receptors, Estrogen/ (55110)

11 estrogen receptor*.mp. (65405)

12 oestrogen receptor*.mp. (6766)

13 ER*.ti,ab. (1431549)

14 ER+.ti,ab. (99225)

15 human epidermal growth factor* receptor*.mp. (10850)

16 HER2*.ti,ab. (31071)

17 HER 2*.ti,ab. (8534)

18 exp Receptor, ErbB-2/ (28942)

19 Erb-B2 receptor* tyrosine kinase.mp. (182)

20 ErbB2 receptor* tyrosine kinase.mp. (86)

21 Erb-B2*.ti,ab. (735)

22 Erb-B 2*.ti,ab. (188)

23 ERB?B2*.ti,ab. (7578)

24 ErbB-2*.ti,ab. (3956)

25 ERBB?2*.ti,ab. (7577)

26 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 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (3260438)

27 3 and 26 (187678)

28 exp Cyclin-Dependent Kinase Inhibitor Proteins/ (28373)

29 cyclin-dependent kinase inhibitor*.mp. (31475)

30 CDI.ti,ab. (7828)

31 CKI.ti,ab. (740)

32 CDKI.ti,ab. (359)

33 CDK*.ti,ab. (39818)

34 palbociclib.mp. (1199)

35 Ibrance.mp. (36)

36 "pd 0332991".mp. (114)

37 pd 332991.mp. (5)

38 pd0332991.mp. (109)

39 pd332991.mp. (4)

40 "pf 00080665".mp. (0)

41 "pf00080665".mp. (0)

42 exp Aromatase Inhibitors/ (9989)

43 aromatase inhibitor*.mp. (10572)

44 estrogen synthetas* inhibitor*.mp. (9)

45 oestrogen synthetas* inhibitor*.mp. (0)

46 exp Anastrozole/ (1572)

47 anastr#zole.mp. (2507)

48 arimidex.mp. (263)

49 ici d1033.mp. (7)

50 icid1033.mp. (0)

51 trozolet.mp. (0)

52 zd 1033.mp. (2)

53 zd1033.mp. (6)

54 exp Letrozole/ (2400)

55 letrozole.mp. (3804)

56 cgs 20267.mp. (52)

57 cgs20267.mp. (7)

58 femar*.mp. (144)

59 loxifan.mp. (0)

60 exemestane.mp. (1684)

61 6 methyleneandrosta 1, 4 diene 3, 17 dione.mp. (4)

62 aromasin*.mp. (33)

63 fce 24304.mp. (15)

64 fce24304.mp. (1)

65 n#kides*.mp. (0)

66 pnu 155971.mp. (2)

67 pnu155971.mp. (0)

68 exp Fulvestrant/ (2590)

69 Fulvestrant.mp. (3490)

70 faslodex.mp. (236)

71 ici 182 780.mp. (2155)

72 ici 182780.mp. (561)

73 ici182780.mp. (262)

74 zd 182780.mp. (0)

75 zd182780.mp. (0)

76 zd 9238.mp. (0)

77 zd9238.mp. (0)

78 zm 182780.mp. (18)

79 zm182780.mp. (1)

80 exp Tamoxifen/ (23002)

81 Tamoxifen.mp. (30107)

82 ebefen.mp. (0)

83 kessar.mp. (0)

84 nsc 180973.mp. (10)

85 nsc180973.mp. (0)

86 tamoplac.mp. (0)

87 tamoxasta.mp. (0)

88 tamoxifene.mp. (217)

89 Ribociclib.mp. (425)

90 kisqali.mp. (13)

91 "lee 011*".mp. (1)

92 "lee011*".mp. (77)

93 "lee 11*".mp. (1)

94 "lee11*".mp. (1)

95 Abemaciclib.mp. (291)

96 bemaciclib.mp. (0)

97 ly 2835219.mp. (1)

98 ly2835219.mp. (44)

99 verzenio*.mp. (10)

100 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 (115508)

101 27 and 100 (18920)

102 limit 101 to clinical trial, all (2218)

103 randomized controlled trial.pt. (582441)

104 controlled clinical trial.pt. (97145)

105 randomized.ab. (555245)

106 placebo.ab. (230366)

107 clinical trials as topic.sh. (204110)

108 randomly.ab. (380871)

109 trial.ti. (254101)

110 103 or 104 or 105 or 106 or 107 or 108 or 109 (1451904)

111 exp animals/ not humans.sh. (5101654)

112 110 not 111 (1329629)

113 101 and 112 (3534)

114 102 or 113 (3968)

115 limit 114 to (english or german) (3778)

116 remove duplicates from 115 (3356)

117 limit 101 to (meta analysis or "systematic review" or systematic reviews as topic) (339)

118 (((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web

of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. (554136)

119 101 and 118 (803)

120 117 or 119 (803)

121 limit 120 to (english or german) (773)

122 remove duplicates from 121 (618)

123 116 or 122 (3734)

12.1.2 EMBASE

A search was conducted on 15 November 2019 for publications in English and German. On 27 January 2020 an additional search was conducted using identical strings except for the language restriction, which was changed to French instead of English and German.

Search strategy:

No.	Query Results	Results
#114.	#109 OR #113	5’836
#113.	#103 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND ([english]/lim OR [german]/lim)	869
#112.	#111 AND 'human'/de	903
#111.	#103 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	905
#110.	#103	30’163
#109.	#108 AND ([english]/lim OR [german]/lim)	5’455
#108.	#107 AND 'human'/de	5’641
#107.	#104 OR #106	5’749
#106.	#103 AND #105	4’883

#105.	random*:ab,ti OR placebo*:de,ab,ti OR ((double 1’724’031 NEXT/1 blind*):ab,ti)	
#104.	#101 NOT #102 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	2’359
#103.	#101 NOT #102	30’163
#102.	#101 AND 'Conference Abstract'/it	6’845
#101.	#20 AND #100	37’008
#100.	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99	168’262
#99.	verzenio*:ti,ab,de,tn	24
#98.	'ly2835219':ti,ab,de,tn	74
#97.	'ly 2835219':ti,ab,de,tn	123
#96.	bemaciclib:ti,ab,de,tn	
#95.	abemaciclib:ti,ab,de,tn	817
#94.	'abemaciclib'/exp	794
#93.	'lee11':ti,ab,de,tn	
#92.	'lee 11':ti,ab,de,tn	2

#91.	'lee011*':ti,ab,de,tn	140
#90.	'lee 011*':ti,ab,de,tn	168
#89.	kisqali:ti,ab,de,tn	42
#88.	ribociclib:ti,ab,de,tn	1’024
#87.	'ribociclib'/exp	982
#86.	tamoxifene:ti,ab,de,tn	152
#85.	tamoxasta:ti,ab,de,tn	7
#84.	tamoplac:ti,ab,de,tn	1
#83.	'nsc180973':ti,ab,de,tn	
#82.	'nsc 180973':ti,ab,de,tn	16
#81.	kessar:ti,ab,de,tn	37
#80.	ebefen:ti,ab,de,tn	1
#79.	tamoxifen:ti,ab,de,tn	65’031
#78.	'tamoxifen'/exp	60’717
#77.	'zm182780':ti,ab,de,tn	
#76.	'zm 182780':ti,ab,de,tn	29
#75.	'zd9238':ti,ab,de,tn	
#74.	'zd 9238':ti,ab,de,tn	3
#73.	'zd182780':ti,ab,de,tn	
#72.	'zd 182780':ti,ab,de,tn	1
#71.	'ici182780':ti,ab,de,tn	264
#70.	'ici 182780':ti,ab,de,tn	2’179
#69.	'ici 182 780':ti,ab,de,tn	2’436
#68.	faslodex:ti,ab,de,tn	828
#67.	fulvestrant:ti,ab,de,tn	8’708
#66.	'fulvestrant'/exp	8’500
#65.	'pnu155971':ti,ab,de,tn	

#64.	'pnu 155971':ti,ab,de,tn	6
#63.	nikides*:ti,ab,de,tn	
#62.	nakides*:ti,ab,de,tn	
#61.	'fce24304':ti,ab,de,tn	3
#60.	'fce 24304':ti,ab,de,tn	49
#59.	aromasin*:ti,ab,de,tn	554
#58.	'6 methyleneandrosta 1, 4 diene 3, 17 dione':ti,ab,de,tn	3
#57.	exemestane:ti,ab,de,tn	6’157
#56.	'exemestane'/exp	5’997
#55.	loxifan:ti,ab,de,tn	1
#54.	femara:ti,ab,de,tn	1’137
#53.	femar:ti,ab,de,tn	18
#52.	femar*:ti,ab,de,tn	1’183
#51.	'cgs20267':ti,ab,de,tn	7
#50.	'cgs 20267':ti,ab,de,tn	139
#49.	letrozole:ti,ab,de,tn	11’791
#48.	'letrozole'/exp	11’546
#47.	'zd1033':ti,ab,de,tn	7
#46.	'zd 1033':ti,ab,de,tn	27
#45.	'trozolet':ti,ab,de,tn	
#44.	'icid1033':ti,ab,de,tn	
#43.	'ici d1033':ti,ab,de,tn	23
#42.	'arimidex':ti,ab,de,tn	1’719
#41.	'anastrazole':ti,ab,de,tn	299
#40.	'anastrozole':ti,ab,de,tn	9’546
#39.	'anastrozole'/exp	9’365

#38.	'estrogen synthetas* inhibitor*':ti,ab,de	15
#37.	'aromatase inhibitor*':ti,ab,de	17’446
#36.	'aromatase inhibitor'/exp	30’921
#35.	'pf00080665':ti,ab,de,tn	
#34.	'pf 00080665':ti,ab,de,tn	
#33.	pd332991:ti,ab,de,tn	9
#32.	pd0332991:ti,ab,de,tn	152
#31.	'pd 332991':ti,ab,de,tn	16
#30.	'pd 0332991':ti,ab,de,tn	636
#29.	ibrance:ti,ab,de,tn	132
#28.	palbociclib:ti,ab,de,tn	3’053
#27.	'palbociclib'/exp	2’990
#26.	cdk*:ti,ab	46’272
#25.	cdki:ti,ab	448
#24.	cki:ti,ab	840
#23.	cdi:ti,ab	9’600
#22.	'cyclin-dependent kinase inhibitor*':ti,ab,de	33’787
#21.	'cyclin dependent kinase inhibitor'/exp	40’336
#20.	#4 AND #19	258’067
#19.	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	2’763’693
#18.	'her 2*':ti,ab	232’016
#17.	her2*:ti,ab	49’583
#16.	'human epidermal growth factor* receptor*':ti,ab,de	14’978
#15.	'human epidermal growth factor receptor 2 negative breast cancer'/exp	656

#14.	'er':ti,ab	128’404
#13.	'oestrogen receptor*':ti,ab,de	7’196
#12.	'estrogen receptor*':ti,ab,de	108’064
#11.	'estrogen receptor'/exp	90’282
#10.	'hr':ti,ab	401’554
#9.	'hormon* receptor*':ti,ab,de	68’059
#8.	'hormone receptor'/exp	341’096
#7.	'advanc*':ti,ab,de	1’067’042
#6.	'metasta*':ti,ab,de	856’692
#5.	'metastasis'/exp	628’186
#4.	#2 OR #3	608’037
#3.	((breast* OR mamma*) NEAR/2 (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR 'adeno c*' OR sarcoma* OR neoplasm* OR malignan*)):ti,ab,de	603’499
#2.	'breast cancer'/exp	453’654
#1.	'metastatic breast cancer'/exp	18’035

12.1.3 The Cochrane Library

Search conducted on 17 November 2019

Search strategy:

ID	Search
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	((breast* OR mamma*) NEAR (cancer* OR tumor* OR tumour* OR neoplasm* OR malignan* OR carcinom* OR sarcoma* OR adenom* OR adeno*)):ti,ab,kw (Word variations have been searched)
#3	#1 OR #2
#4	(advanc*):ti,ab,kw (Word variations have been searched)

#5 (metasta*):ti,ab,kw (Word variations have been searched)

#6 MeSH descriptor: [Neoplasm Metastasis] explode all trees

#7 (hormon* receptor*):ti,ab,kw (Word variations have been searched)

#8 (HR*):ti,ab,kw

#9 MeSH descriptor: [Receptors, Estrogen] explode all trees

#10 (estrogen receptor*):ti,ab,kw (Word variations have been searched)

#11 (ER*):ti,ab,kw

#12 (human epidermal growth factor* receptor*):ti,ab,kw (Word variations have been searched)

#13 (HER2*):ti,ab,kw (Word variations have been searched)

#14 ("HER 2*"):ti,ab,kw (Word variations have been searched)

#15 MeSH descriptor: [Receptor, ErbB-2] explode all trees

#16 (Erb-B2 receptor* tyrosine kinase):ti,ab,kw (Word variations have been searched)

#17 (ErbB2 receptor* tyrosine kinase):ti,ab,kw (Word variations have been searched)

#18 (Erb-B2*):ti,ab,kw (Word variations have been searched)

#19 ("Erb-B 2*") (Word variations have been searched)

#20 (ERB*B2*):ti,ab,kw (Word variations have been searched)

#21 ("ErbB-2*")

#22 (ERBB*2*):ti,ab,kw (Word variations have been searched)

#23 #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 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22

#24 #3 AND #23

#25 MeSH descriptor: [Cyclin-Dependent Kinase Inhibitor Proteins] explode all trees

#26 (cyclin-dependent kinase inhibitor*):ti,ab,kw (Word variations have been searched)

#27 (CDI):ti,ab,kw

#28 (CKI):ti,ab,kw

#29 (CDK*):ti,ab,kw

#30 (palbociclib):ti,ab,kw

#31 (Ibrance):ti,ab,kw (Word variations have been searched)

#32 (pd 0332991):ti,ab,kw (Word variations have been searched)

#33 (pd 332991):ti,ab,kw (Word variations have been searched)

#34 (pd0332991):ti,ab,kw (Word variations have been searched)

#35 (pd332991) (Word variations have been searched)

#36 (pf 00080665) (Word variations have been searched)

#37 (pf00080665) (Word variations have been searched)

#38 MeSH descriptor: [Aromatase Inhibitors] explode all trees

#39 (aromatase inhibitor*):ti,ab,kw (Word variations have been searched)

#40 (estrogen synthetas* inhibitor*):ti,ab,kw (Word variations have been searched)

#41 MeSH descriptor: [Anastrozole] explode all trees

#42 (anastrozole):ti,ab,kw (Word variations have been searched)

#43 (anastrazole):ti,ab,kw (Word variations have been searched)

#44 (arimidex):ti,ab,kw (Word variations have been searched)

#45 (ici d1033) (Word variations have been searched)

#46 (icid1033) (Word variations have been searched)

#47 (trozolet) (Word variations have been searched)

#48 (zd 1033):ti,ab,kw (Word variations have been searched)

#49 (zd1033):ti,ab,kw (Word variations have been searched)

#50 MeSH descriptor: [Letrozole] explode all trees

#51 (letrozole):ti,ab,kw (Word variations have been searched)

#52 (cgs 20267):ti,ab,kw (Word variations have been searched)

#53 (cgs20267):ti,ab,kw

#54 (femar*):ti,ab,kw (Word variations have been searched)

#55 (loxifan) (Word variations have been searched)

#56 (exemestane):ti,ab,kw (Word variations have been searched)

#57 (6 methyleneandrosta 1, 4 diene 3, 17 dione) (Word variations have been searched)

#58 (aromasin*):ti,ab,kw (Word variations have been searched)

#59 (fce 24304):ti,ab,kw (Word variations have been searched)

#60 (fce24304) (Word variations have been searched)

#61 (nakides*) (Word variations have been searched)

#62 (nikides*) (Word variations have been searched)

#63 (pnu 155971) (Word variations have been searched)

#64 (pnu155971) (Word variations have been searched)

#65 MeSH descriptor: [Fulvestrant] explode all trees

#66 (Fulvestrant):ti,ab,kw (Word variations have been searched)

#67 (faslodex):ti,ab,kw (Word variations have been searched)

#68 (ici 182 780):ti,ab,kw (Word variations have been searched)

#69 (ici 182780):ti,ab,kw (Word variations have been searched)

#70 (ici182780):ti,ab,kw (Word variations have been searched)

#71 (zd 182780) (Word variations have been searched)

#72 (zd182780) (Word variations have been searched)

#73 (zd 9238) (Word variations have been searched)

#74 (zd9238):ti,ab,kw (Word variations have been searched)

#75 (zm 182780) (Word variations have been searched)

#76 (zm182780) (Word variations have been searched)

#77 MeSH descriptor: [Tamoxifen] explode all trees

#78 (Tamoxifen):ti,ab,kw (Word variations have been searched)

#79 (ebefen) (Word variations have been searched)

#80 (kessar):ti,ab,kw (Word variations have been searched)

#81 (nsc 180973):ti,ab,kw (Word variations have been searched)

#82 (nsc180973) (Word variations have been searched)

#83 (tamoplac) (Word variations have been searched)

#84 (tamoxasta) (Word variations have been searched)

#85 (tamoxifene):ti,ab,kw

#86 (Ribociclib):ti,ab,kw (Word variations have been searched)

#87 (kisqali):ti,ab,kw (Word variations have been searched)

#88 ("lee 011"):ti,ab,kw (Word variations have been searched)

#89 (lee011):ti,ab,kw (Word variations have been searched)

#90 ("lee 11"):ti,ab,kw (Word variations have been searched)

#91 (lee11) (Word variations have been searched)

#92 (Abemaciclib):ti,ab,kw (Word variations have been searched)

#93 (bemaciclib) (Word variations have been searched)

#94 (ly 2835219) (Word variations have been searched)

#95 (ly2835219):ti,ab,kw (Word variations have been searched)

#96 (verzenio*) (Word variations have been searched)

#97 #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96

#98 #24 AND #97 in Trials

#99 #24 AND #97 in Cochrane Reviews, Cochrane Protocols

#100 #98 OR #99 4’483 hits

12.1.4 CRD

Search conducted on 17 November 2019

Search strategy:

1 MeSH DESCRIPTOR Cyclin-Dependent Kinase Inhibitor Proteins EXPLODE ALL TREES

2 (cyclin-dependent kinase inhibitor*)

3 (CDI)

4 (CKI)

5 (CDK*)

6 (palbociclib)

7 (Ibrance)

8 (pd 0332991)

9 (pd0332991)

10 (pd 332991)

11 (pd332991)

12 (pf 00080665)

13 (pf00080665)

14 MeSH DESCRIPTOR Aromatase Inhibitors EXPLODE ALL TREES

15 (aromatase inhibitor*)

16 (estrogen synthetas* inhibitor*)

17 (oestrogen synthetas* inhibitor*)

18 (Anastrozole)

19 (Anastrazole)

20 (arimidex)

21 (ici d1033)

22 (icid1033)

23 (trozolet)

24 (zd 1033)

25 (zd1033)

26 (Letrozole)

27 (cgs 20267)

28 (cgs20267)

29 (femar*)

30 (loxifan)

31 (exemestane)

32 (6 methyleneandrosta 1, 4 diene 3, 17 dione)

33 (aromasin*)

34 (fce 24304)

35 (fce24304)

36 (nakides*)

37 (nikides*)

38 (pnu 155971)

39 (pnu155971)

40 (Fulvestrant)

41 (faslodex)

42 (ici 182 780)

43 (ici 182780)

44 (ici182780)

45 (zd 182780)

46 (zd182780)

47 (zd 9238)

48 (zd9238)

49 (zm 182780)

50 (zm182780)

51 MeSH DESCRIPTOR Tamoxifen EXPLODE ALL TREES

52 (Tamoxifen)

53 (ebefen)

54 (kessar)

55 (nsc 180973)

56 (nsc180973)

57 (tamoplac)

58 (tamoxasta)

59 (tamoxifene)

60 (Ribociclib)

61 (kisqali)

62 (lee 011*)

63 (lee011*)

64 (lee 11*)

65 (lee11*)

66 (Abemaciclib)

67 (bemaciclib)

68 (ly 2835219)

69 (ly2835219)

70 (verzenio*)

71 #1 OR #2 OR #3 OR #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 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70

72 MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES

73 ((breast* OR mamma*) NEAR (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adenoc* OR sarcoma* OR neoplasm* OR malignan*))

74 #72 OR #73

75 #71 AND #74

273 hits (59 in HTA, 100 in NHS EED, 114 in DARE)

12.1.5 Search results for clinical effectiveness and safety (Palbociclib versus comparators)

For MEDLINE and EMBASE, the numbers represent the total of the two searches (one for English and German, one for French publications).

Table 18: Search results for clinical effectiveness and safety (Palbociclib versus comparators)

Database	Number of hits
MEDLINE	3'783
EMBASE	5'906
The Cochrane Library	4'483
CRD	273
Total deduplicated	**9'739 (8'894 RCTs, 845 SRs)**

12.2 Search strings for safety (extended analysis), health economics as well as ethical, social, legal and organisational aspects

12.2.1 MEDLINE

A search was conducted on 4 November 2019 for publications in English and German. On 21 January 2020 an additional search was conducted using identical strings except for the language restriction, which was changed to French instead of English and German.

(Including Epub Ahead of Print, In-Process and Other Non-Indexed Citations and Daily from 2015 to 1 November 2019)

Search strategy:

1 exp Breast Neoplasms/ (384873)

2 ((breast* or mamma*) adj3 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or neoplasm*)).mp. (532'852)

3 1 or 2 (532'863)

4 palbociclib.mp. (1'248)

5 Ibrance.mp. (37)

6 "pd 0332991".mp. (119)

7 pd 332991.mp. (5)

8 pd0332991.mp. (117)

9 pd332991.mp. (4)

10 "pf 00080665".mp. (0)

11 "pf00080665".mp. (0)

12 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (1’311)

13 3 and 12 (798)

14 exp animals/ not humans.sh. (6’654’850)

15 13 not 14 (791)

16 limit 15 to (english or german) (771)

17 remove duplicates from 16 (485)

12.2.2 EMBASE

A search was conducted on 7 November 2019 for publications in English and German. On 21 January 2020 an additional search was conducted using identical strings except for the language restriction, which was changed to French instead of English and German.

Search strategy:

No.	Query Results	Results
#22.	#20 NOT #21	663
#21.	#20 AND 'Conference Abstract'/it	473
#20.	#18 AND 'human'/de AND ([english]/lim OR [german]/lim)	1’136
#19.	#18 AND 'human'/de	1’151
#18.	#7 AND #17	1’247
#17.	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	3’058
#16.	'pf00080665':ti,ab,de,tn	
#15.	'pf 00080665':ti,ab,de,tn	
#14.	pd332991:ti,ab,de,tn	9
#13.	pd0332991:ti,ab,de,tn	152
#12.	'pd 332991':ti,ab,de,tn	16
#11.	'pd 0332991':ti,ab,de,tn	635
#10.	ibrance:ti,ab,de,tn	132

#9.	palbociclib:ti,ab,de,tn	3’043
#8.	'palbociclib'/exp	2’980
#7.	#1 OR #6	151’843
#6.	#4 AND #5	149’547
#5.	advanc*:ti,ab OR metasta*:ti,ab	1’638’325
#4.	#2 OR #3	606’090
#3.	((breast* OR mamma*) NEAR/2 (cancer* OR tumor* OR tumour* OR carci nom* OR adenom* OR adenoc* OR 'adeno c*' OR neoplasm*)):ti,ab,de	601’087
#2.	'breast cancer'/exp	453’042
#1.	'metastatic breast cancer'/exp	18’001

12.2.3 The Cochrane Library

Search conducted on 7 November 2019

Search strategy:

ID Search

#1 MeSH descriptor: [Breast Neoplasms] explode all trees

#2 ((breast* OR mamma*) NEAR (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adenoc* OR neoplasm*)) (Word variations have been searched)

#3 #1 OR #2 (Word variations have been searched)

#4 (palbociclib) (Word variations have been searched)

#5 (Ibrance) (Word variations have been searched)

#6 (pd 0332991) (Word variations have been searched)

#7 (pd 332991) (Word variations have been searched)

#8 (pd0332991) (Word variations have been searched)

#9 (pd332991) (Word variations have been searched)

#10 (pf 00080665) (Word variations have been searched)

#11 (pf00080665) (Word variations have been searched)

#12#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 (Word variations have been searched)

#13#3 AND #12 (Word variations have been searched) 252 hits

12.2.4 EconLit

Search conducted on 24 January 2020.

Search strategy:

#	Query	Limiters/Expanders	Last Run Via	Results
S8	TX pf00080665	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0
S7	TX pf 00080665	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0
S6	TX pd332991	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0
S5	TX pd 332991	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0
S4	TX pd0332991	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0
S3	TX pd 0332991	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0
S2	TX Ibrance	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0
S1	TX palbo-ciclib	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0

12.2.5 CRD

Search conducted on 7 November 2019

Search strategy:

1 (palbociclib)

2 (Ibrance)

3 (pd 0332991)

4 (pd0332991)

5 (pd 332991)

6 (pd332991)

7 (pf 00080665)

8 (pf00080665)

9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

12.2.6 Scopus

A search was conducted on 8 November 2019 for publications in English and German. On 24 January 2020 an additional search was conducted using identical strings except for the language restriction, which was changed to French instead of English and German.

Search strategy:

((TITLE-ABS-KEY ((breast* OR mamma*) W/3 (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adenoc* OR neoplasm*))) AND (TITLE-ABS-KEY (advanc* OR metasta*))) AND ((TITLE-ABS-KEY (palbociclib)) OR (TITLE-ABS-KEY (ibrance)) OR (TITLE-ABS-KEY ("pd 0332991")) OR (TITLE-ABS-KEY (pd0332991)) OR (TITLE-ABS-KEY ("pd 332991")) OR (TITLE-ABS-KEY (pd332991)) OR (TITLE-ABS-KEY ("pf 00080665")) OR (TITLE-ABS-KEY (pf00080665))) AND (LIMIT-TO (EXACTKEYWORD , "Human") OR LIMIT-TO (EXACTKEYWORD , "Humans")) AND (LIMIT-TO (LANGUAGE , "English") OR LIMIT-TO (LANGUAGE , "German"))

12.2.7 TRIP database

Search conducted on 7 November 2019

Search strategy:

((breast* OR mamma*) NEAR (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adenoc* OR neoplasm*)) AND ((palbociclib OR Ibrance OR "pd 0332991" OR pd0332991 OR "pd 332991" OR pd332991 OR "pf 00080665" OR pf00080665))

12.2.8 Search results for safety (extended analysis), health economics, ethical, social, legal and organisational aspects

For MEDLINE, EMBASE and Scopus, the numbers represent the total of the two searches (one for English and German, one for French publications).

Table 19: Search results for safety (extended analysis), health economics, ethical, social, legal and organisational aspects

Database	Number of hits
MEDLINE	489
EMBASE	667
The Cochrane Library	252
EconLit	0
CRD	7
Scopus	674
TRIP-database	20
Total deduplicated	1’107

12.3 List of countries from which patients were recruited in the included RCTs

Patients were recruited from the following countries: Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Croatia, Czech Republic, Denmark, Egypt, Finland, France, Georgia, Germany, Greece, Hong Kong, Hungary, Iceland, India, Ireland, Israel, Italy, Japan, Jordan, Korea, Lebanon, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Pakistan, Peru, Philippines, Poland, Portugal, Puerto Rico, Romania, Russia, Saudi Arabia, Singapore, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, Tunisia, Turkey, Ukraine United Arab Emirates, United Kingdom, Uruguay, USA.

12.4 Preliminary quality appraisal of included RCTs

Table 20: Preliminary quality assessment of included RCTs

Trial identifier	Publication used for RoB assessment	RoB domains			
		Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
NCT01942135 PALOMA-3	Cristofanilli et al., 2016	low	low	low	low
NCT00721409 PALOMA-1	Finn et al., 2015	low	low	high/unclear	low
NCT01740427 PALOMA-2	Finn et al., 2016	low	low	low	low
NCT01958021 MONALEESA-2	Hortobagyi et al., 2016	low	low	low	low
NCT02422615 MONALEESA-3	Slamon et al., 2018	low	high/unclear	low	low
NCT02246621 MONARCH 3	Goetz et al., 2017	low	low	low	low
NCT02107703 MONARCH 2	Sledge et al., 2017	low	low	low	low
NCT02278120 MONALEESA-7	Tripathy et al., 2018	low	low	low	low
NCT01610284 BELLE-2	Baselga et al., 2017	low	low	low	low
NCT01633060 BELLE-3	Leo et al., 2018	low	low	low	low
NCT00305448 FINDER1	Ohno et al., 2010	high/unclear	high/unclear	high/unclear	high/unclear
NCT00313170 FINDER2	Pritchard et al., 2010	high/unclear	high/unclear	high/unclear	high/unclear
NCT00863655 BOLERO-2	Yardley et al., 2013	low	low	low	low
NCT00050141	Johnston et al., 2008	high/unclear	high/unclear	high/unclear	high/unclear
NCT01266213 FLAG	Kim et al., 2018	low	high/unclear	high/unclear	high/unclear
NCT00274469 FIRST	Robertson et al., 2009	low	low	high/unclear	high/unclear
NCT01602380 FALCON	Robertson et al., 2016	low	low	low	low
NCT00066378	Tryfonidis et al., 2016	high/unclear	high/unclear	high/unclear	high/unclear
NCT00073528	Johnston et al., 2009	high/unclear	high/unclear	low	low
NCT00253422 NCT00944918 SoFEA	Johnston et al., 2013	low	low	high/unclear	high/unclear
NCT00075764	Mehta et al., 2012	low	low	low	low
NCT00229697	Osborne et al., 2011	low	low	low	low
NCT00083993	Wolff et al., 2013	low	low	low	low
NCT00390455	Burstein et al., 2014	low	low	low	low
NCT00601900 CALGB 40503	Dickler et al., 2016	high/unclear	high/unclear	high/unclear	high/unclear
NCT00545077 LEA	Martin et al., 2015	low	low	high/unclear	high/unclear
NCT00626106	Robertson et al., 2013	low	low	low	low
NCT00676663	Yardley et al., 2013	low	high/unclear	low	low
NCT01142401	Adelson et al., 2016	low	high/unclear	high/unclear	high/unclear
NCT00770354	Ibrahim et al., 2011	low	high/unclear	high/unclear	high/unclear

Trial identifier	Publication used for RoB assessment	RoB domains			
		Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
NCT01151215 MINT	Johnston et al., 2016	low	low	low	high/unclear
NCT00696072	Paul et al., 2019	low	high/unclear	high/unclear	high/unclear
NCT01160718	Zaman et al., 2015	low	low	low	low
NCT01234857	Baselga et al., 2017	low	high/unclear	high/unclear	high/unclear
NCT01437566 FERGI	Krop et al., 2016	low	low	low	low
NCT01528345	Musolino et al., 2017	low	low	low	low
NCT02216786 MANTA	Schmid et al., 2019	low	low	high/unclear	high/unclear
NCT02437318	Andre et al., 2019	low	low	low	low
NA	Iwata et al., 2013	low	high/unclear	low	high/unclear
NCT02482753 ACE	Jiang et al., 2019	low	low	low	low
NCT02592746 KCSG-BR15-10	Park et al., 2019	low	low	high/unclear	high/unclear
UMIN000010087 Hi-FAIR ex	Yamamoto et al., 2013	high/unclear	high/unclear	high/unclear	high/unclear
	Bachelot et al., 2012	low	high/unclear	high/unclear	high/unclear
	Lipton et al., 2008	high/unclear	high/unclear	high/unclear	high/unclear

12.5 Quality assessment of included economic studies

Table 21: Galve-Calvo et al. 2018[151]

CHEC checklist*

	Item	Yes	No	Unclear
1.	Is the study population clearly described?		X	
2.	Are competing alternatives clearly described?	X		
3.	Is a well-defined research question posed in answerable form?	X		
4.	Is the economic study design appropriate to the stated objective?	X		
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	X		
6.	Is the actual perspective chosen appropriate?	X		
7.	Are all important and relevant costs for each alternative identified?	X		
8.	Are all costs measured appropriately in physical units?	X		
9.	Are costs valued appropriately?	X		
10.	Are all important and relevant outcomes for each alternative identified?	X		
11.	Are all outcomes measured appropriately?			X
12.	Are outcomes valued appropriately?			X
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	X		
14.	Are all future costs and outcomes discounted appropriately?	X		
15.	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?			X
16.	Do the conclusions follow from the data reported?	X		
17.	Does the study discuss the generalizability of the results to other settings and patient/client groups?		X	
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	X		
19.	Are ethical and distributional issues discussed appropriately?		X	
	Comment: ICER refers to comparator, therefore small			

* Evers S, Goossens M, De Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *International Journal of Technology Assessment in Health Care* 2005;21(2):245.

Table 22: Mamiya et al. 2017[7]

CHEC checklist*

	Item	Yes	No	Unclear
1.	Is the study population clearly described?			X
2.	Are competing alternatives clearly described?		X	
3.	Is a well-defined research question posed in answerable form?	X		
4.	Is the economic study design appropriate to the stated objective?	X		
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?			X
6.	Is the actual perspective chosen appropriate?	X		
7.	Are all important and relevant costs for each alternative identified?	X		
8.	Are all costs measured appropriately in physical units?	X		
9.	Are costs valued appropriately?			X
10.	Are all important and relevant outcomes for each alternative identified?		X	
11.	Are all outcomes measured appropriately?	X		
12.	Are outcomes valued appropriately?	X		
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	X		
14.	Are all future costs and outcomes discounted appropriately?		X	
15.	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?	X		
16.	Do the conclusions follow from the data reported?	X		
17.	Does the study discuss the generalizability of the results to other settings and patient/ client groups?		X	
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	X		
19.	Are ethical and distributional issues discussed appropriately?		X	
	Comments: societal or payer perspective is not clear, no discounting			

* Evers S, Goossens M, De Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *International Journal of Technology Assessment in Health Care* 2005;21(2):245.

Table 23: Matter-Walstra et al. 2016[8] and Matter-Walstra et al. 2017[154]

CHEC checklist*

	Item	Yes	No	Unclear
1.	Is the study population clearly described?	X		
2.	Are competing alternatives clearly described?	X		
3.	Is a well-defined research question posed in answerable form?	X		
4.	Is the economic study design appropriate to the stated objective?	X		
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	X		
6.	Is the actual perspective chosen appropriate?	X		
7.	Are all important and relevant costs for each alternative identified?		X	
8.	Are all costs measured appropriately in physical units?			X
9.	Are costs valued appropriately?			X
10.	Are all important and relevant outcomes for each alternative identified?	X		
11.	Are all outcomes measured appropriately?			X
12.	Are outcomes valued appropriately?	X		
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	X		
14.	Are all future costs and outcomes discounted appropriately?	X		
15.	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?	X		
16.	Do the conclusions follow from the data reported?	X		
17.	Does the study discuss the generalizability of the results to other settings and patient/ client groups?		X	
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	X		
19.	Are ethical and distributional issues discussed appropriately?		X	
	Comments: not all direct costs included and drug costs for PAL from US in Publication 2016, in Publication 2017 from Swiss			

* Evers S, Goossens M, De Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *International Journal of Technology Assessment in Health Care* 2005;21(2):245.

Table 24: Mistry et al. 2018[152]

CHEC checklist*

	Item	Yes	No	Unclear
1.	Is the study population clearly described?	X		
2.	Are competing alternatives clearly described?	X		
3.	Is a well-defined research question posed in answerable form?	X		
4.	Is the economic study design appropriate to the stated objective?	X		
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	X		
6.	Is the actual perspective chosen appropriate?	X		
7.	Are all important and relevant costs for each alternative identified?	X		
8.	Are all costs measured appropriately in physical units?	X		
9.	Are costs valued appropriately?			X
10.	Are all important and relevant outcomes for each alternative identified?		X	
11.	Are all outcomes measured appropriately?			X
12.	Are outcomes valued appropriately?			X
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	X		
14.	Are all future costs and outcomes discounted appropriately?	X		
15.	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?			X
16.	Do the conclusions follow from the data reported?	X		
17.	Does the study discuss the generalizability of the results to other settings and patient/ client groups?		X	
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?		X*	
19.	Are ethical and distributional issues discussed appropriately?		X	
	Comments: “Funding for this study was provided by Novartis, the manufacturer of Ribociclib, Novartis provided input on the study design and data collection, analysis and interpretation”…			

* Evers S, Goossens M, De Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *International Journal of Technology Assessment in Health Care* 2005;21(2):245.

Table 25: Raphael et al. 2017[153]

CHEC checklist*

	Item	Yes	No	Unclear
1.	Is the study population clearly described?			X
2.	Are competing alternatives clearly described?	X		
3.	Is a well-defined research question posed in answerable form?	X		
4.	Is the economic study design appropriate to the stated objective?	X		
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	X		
6.	Is the actual perspective chosen appropriate?	X		
7.	Are all important and relevant costs for each alternative identified?	X		
8.	Are all costs measured appropriately in physical units?		X	
9.	Are costs valued appropriately?			X
10.	Are all important and relevant outcomes for each alternative identified?	X		
11.	Are all outcomes measured appropriately?			X
12.	Are outcomes valued appropriately?			X
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	X		
14.	Are all future costs and outcomes discounted appropriately?	X		
15.	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?	X		
16.	Do the conclusions follow from the data reported?	X		
17.	Does the study discuss the generalizability of the results to other settings and patient/client groups?	X		
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	X		
19.	Are ethical and distributional issues discussed appropriately?		X	
	Comments: well conducted study, guidance used from Canadian Agency for Drugs and Technologies in Health (CADTH)			

* Evers S, Goossens M, De Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *International Journal of Technology Assessment in Health Care* 2005;21(2):245.

Table 26: Zhang / Long 2019[155]

CHEC checklist*

	Item	Yes	No	Unclear
1.	Is the study population clearly described?		X	
2.	Are competing alternatives clearly described?	X		
3.	Is a well-defined research question posed in answerable form?	X		
4.	Is the economic study design appropriate to the stated objective?	X		
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	X		
6.	Is the actual perspective chosen appropriate?	X		
7.	Are all important and relevant costs for each alternative identified?		X	
8.	Are all costs measured appropriately in physical units?		X	
9.	Are costs valued appropriately?	X		
10.	Are all important and relevant outcomes for each alternative identified?			X
11.	Are all outcomes measured appropriately?			X
12.	Are outcomes valued appropriately?			X
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	X		
14.	Are all future costs and outcomes discounted appropriately?	X		
15.	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?			X
16.	Do the conclusions follow from the data reported?	X		
17.	Does the study discuss the generalizability of the results to other settings and patient/client groups?		X	
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	X		
19.	Are ethical and distributional issues discussed appropriately?		X	
	Comments: Only a brief, somewhat rudimentary description of the methods, sensitivity analysis not shown in publication, cost data: only price of drugs and costs of severe neutropenia			

* Evers S, Goossens M, De Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *International Journal of Technology Assessment in Health Care* 2005;21(2):245.

Table 27: Zhang et al. 2019[156]

CHEC checklist*

	Item	Yes	No	Unclear
1.	Is the study population clearly described?	X		
2.	Are competing alternatives clearly described?	X		
3.	Is a well-defined research question posed in answerable form?	X		
4.	Is the economic study design appropriate to the stated objective?	X		
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	X		
6.	Is the actual perspective chosen appropriate?	X		
7.	Are all important and relevant costs for each alternative identified?			X
8.	Are all costs measured appropriately in physical units?			X
9.	Are costs valued appropriately?			X
10.	Are all important and relevant outcomes for each alternative identified?	X		
11.	Are all outcomes measured appropriately?			X
12.	Are outcomes valued appropriately?			X
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	X		
14.	Are all future costs and outcomes discounted appropriately?	X		
15.	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?	X		
16.	Do the conclusions follow from the data reported?	X		
17.	Does the study discuss the generalizability of the results to other settings and patient/client groups?		X	
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	X		
19.	Are ethical and distributional issues discussed appropriately?		X	
	Comments: for median OS time the authors did not use the PALOMA-3 trial (median OS time in PALOMA-3 trial not reported); instead they used OS time from the CONFIRM-3 trial (comparing FUL 250 mg with FUL 500 mg); utility values taken from the literature, which may differ from PALOMA-3			

* Evers S, Goossens M, De Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *International Journal of Technology Assessment in Health Care* 2005;21(2):245.

12.6 Ongoing studies

Table 28: Characteristics of relevant ongoing studies

Trial ID	Study design	Size (pts)*	Treatment (combination) of interest	Primary completion date†	Study completion date†
NCT04031885	RCT	300	ABE + FUL	15.04.2021	15.12.2022
NCT03939897	RCT	194	ABE + FUL	01.11.2022	01.11.2022
NCT03425838 SONIA	RCT	1050	ANA/LET + PAL/RIB/ABE FUL + PAL/RIB/ABE	30.04.2021	31.10.2022
NCT02763566 MONARCH plus	RCT	463	ABE + NSAI pbo + NSAI ABE + FUL pbo + FUL	29.03.2019	27.11.2020
NCT03966898	RCT	426	pbo + ANA/LET	01.12.2020	01.06.2022
NCT02730091 VICTORIANE	RCT	98	ANA/LET	24.02.2021	28.02.2022
NCT02072512 PROOF	RCT	180	FUL ANA	30.11.2015	31.12.2016
NCT02767661 MECCA	RCT	240	ANA/LET/EXE	31.05.2021	31.05.2023
NCT01654185	RCT	60	AI	31.07.2014	31.07.2016
UMIN000025156	RCT	130	AI	N/A (anticipated start 2017)	N/A (anticipated start 2017)
NCT02511639 EUCTR2013-004153-24-IT MAIN-A	RCT	110	ANA/LET/EXE	31.12.2019	30.06.2020
NCT03778931 EMERALD	RCT	466	FUL/ANA/LET/EXE	31.08.2021	31.08.2022
NCT02646735 FRIEND	RCT	148	FUL EXE	31.12.2019	31.12.2020
NCT03538171	RCT	327	pbo + EXE	28.02.2021	31.08.2021
NCT03291886	RCT	124	pbo + EXE	31.12.2019	30.11.2021

Trial ID	Study design	Size (pts)*	Treatment (combination) of interest	Primary completion date†	Study completion date†
NCT02115282	RCT	600	pbo + EXE	14.01.2021	N/A
NCT02007512	RCT	247	pbo + EXE	30.09.2016	31.03.2020
NCT01151046	RCT	118	pbo + EXE	30.06.2014	30.09.2014
JapicCTI-173703	RCT	124	pbo + EXE	N/A (anticipated start 2017)	N/A (anticipated start 2017)
EUCTR2010-019867-13-SE NCT01234857	RCT	400	EXE	N/A (anticipated start 2010)	N/A (anticipated start 2010)
ChiCTR-IPR-17010455	RCT	260	EXE	N/A (anticipated start 2017)	N/A (anticipated start 2017)
NCT02958852 EUCTR2016-000494-20-SE ABC-SE	RCT	126	LET	30.04.2022	30.04.2022
NCT03927456	RCT	288	pbo + FUL	01.06.2020	01.04.2021
NCT03584009	RCT	100	FUL	03.03.2022	03.03.2022
NCT03781063	RCT	100	FUL	31.07.2020	30.09.2020
NCT03280563 MORPHEUS HR+BC	RCT	126	FUL	19.02.2021	05.10.2022
NCT02756364	RCT	141	FUL	25.11.2019	25.11.2019
NCT02569801 HydranGea	RCT	71	FUL	28.03.2020	28.03.2020
NCT02374099	RCT	97	FUL	13.12.2016	21.11.2017
NCT02530411 FURVA	RCT	160	pbo + FUL	31.12.2018	31.12.2020
NCT02340221 SANDPIPER	RCT	631	pbo + FUL	15.10.2017	03.07.2021
NCT02394496 OVER	RCT	396	pbo + FUL	31.12.2016	31.01.2017
NCT01992952 FAKTION	RCT	149	pbo + FUL	31.03.2019	31.10.2020
NCT01560416	RCT	50	FUL	30.06.2016	30.06.2016
NCT01202591 GLOW	RCT	127	pbo + FUL	30.09.2014	31.10.2014

Trial ID	Study design	Size (pts)*	Treatment (combination) of interest	Primary completion date†	Study completion date†
NCT02404051 EUCTR2014-004035-38-IT FEVEX	RCT	745	FUL	31.01.2018	31.01.2019
EUCTR2014-003220-52-ES	RCT	92	FUL	N/A (anticipated start 2015)	N/A (anticipated start 2015)
NCT02344550 LEO	RCT	137	LET	31.12.2017	31.08.2018
NCT02313051 MIRACLE	RCT	200	LET	31.12.2016	31.12.2017
NCT03905343	RCT	400	RIB + ET	31.12.2026	31.12.2026
NCT03822468 PMR	RCT	350	RIB + ANA/LET	02.02.2026	02.02.2026
NCT03462251 RIBBIT	RCT	158	RIB + AI/FUL	30.06.2025	30.06.2026
NCT03671330	RCT	315	RIB + NSAI pbo + NSAI	28.10.2020	14.04.2022
NCT03555877 AMICA	RCT	150	RIB + ET ET	31.10.2019	31.01.2019
NCT01857193 EUCTR2012-005461-13-FR	RCT	132	RIB + EXE	14.03.2018	11.09.2020
NCT01872260EUCTR2013-001219-57-ES	RCT	256	RIB + LET	01.12.2020	31.12.2020
NCT03423199 PATHWAY	RCT	180	pbo + TAM	28.02.2022	28.02.2022
NCT02311933	RCT	80	TAM	01.07.2020	N/A
NCT01622361 NEST	RCT	290	TAM	29.02.2016	29.02.2016
NCT02285179 EUCTR2013-003947-51-GB Poseidon	RCT	290	pbo + TAM	31.07.2020	31.07.2022
NCT02297438 PALOMA-4	RCT	339	PAL + LET pbo + LET	31.08.2020	02.12.2022

Trial ID	Study design	Size (pts)*	Treatment (combination) of interest	Primary completion date†	Study completion date†
NCT02028507 PEARL	RCT	596	PAL + EXE/FUL	14.01.2019	31.07.2020
NCT02491983 PARSIFAL	RCT	486	PAL + LET PAL + FUL	31.12.2019	31.05.2020
NCT02384239	RCT	70	PAL + FUL/TAM	31.12.2020	31.12.2023
NCT02690480 FLIPPER	RCT	189	PAL + FUL pbo + FUL	11.01.2020	31.12.2023
NCT02917005 FATIMA	RCT	160	PAL + EXE EXE	30.11.2021	31.12.2023
NCT02913430	RCT	150	PAL + FUL PAL + TAM	31.03.2020	31.03.2020
NCT03079011 EUCTR2016-004360-18-FR PADA-1	RCT	800	PAL + ANA/LET/EXE PAL + FUL	15.04.2022	15.04.2024
NCT03322215 PASIPHAE	RCT	196	PAL + FUL	31.10.2021	31.10.2021
NCT03355157 PADMA	RCT	260	PAL + ANA/LET/EXE/FUL	31.12.2021	31.12.2021
NCT04060862 IPATunity150	RCT	370	pbo + PAL + FUL	19.05.2023	30.01.2026
NCT04047758 ChiCTR1900024998	RCT	420	PAL + LET LET	30.09.2021	30.09.2022
EUCTR2016-004191-22-DE	RCT	960	PAL + ET +/- CANKADO	N/A (anticipated start 2017)	N/A (anticipated start 2017)
UMIN000029294	Single arm	200	PAL + FUL (after FUL failure)	N/A (anticipated start 2017)	N/A (anticipated start 2017)
NCT02692755 PALINA	Single arm	35	PAL + LET/FUL	16.12.2019	30.06.2020

ABE=abemaciclib; ANA=anastrozole; ET=endocrine therapy; EXE=exemestane; FUL=fulvestrant; LET=letrozole; N/A=not applicable; NSAI=non-steroidal aromatase inhibitor; PAL=palbociclib; pbo=placebo; pts=patients; RCT=randomised controlled trial; RIB=ribociclib; TAM=tamoxifen
* Total number of patients in trial.
† When the dates in the registries were indicated only as month and year, the last day of the month concerned was used in this table.