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Federal Department of Home Affairs
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Section Health Technology Assessment

Health Technology Assessment (HTA)

HTA report

Title	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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Technology	CDK4/6 inhibitors: Palbociclib (Ibrance®), ribociclib (Kisqali®) and abemaciclib (Verzenios®)
Date	10.06.2021
Type of technology	Pharmaceuticals

Executive summary

Background: 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 (HR+/HER2- LA/MBC). Three CDK4/6 inhibitors – palbociclib (PAL), ribociclib (RIB) and abemaciclib (ABE) – are currently available in Switzerland. They are approved and reimbursed in combination with endocrine therapy (ET; aromatase inhibitors [AIs] in patients without endocrine resistance; fulvestrant [FUL] in patients with endocrine resistance) in HR+/HER2- LA/MBC patients.

This health technology assessment (HTA) report assesses 1) the efficacy, effectiveness, safety and cost-effectiveness of the three CDK4/6 inhibitors (in the respective treatment combinations) compared with each other and with endocrine monotherapies, 2) the costs and cost-effectiveness of the CDK4/6 inhibitors and the budget impact of a potential disinvestment in any one of the three CDK4/6 inhibitors, 3) related ethical and organisational issues.

Methods: We performed two separate systematic literature searches to identify (1) randomised controlled trials (RCTs) for the assessment of efficacy and safety and (2) non-randomised studies (NRSs) for the other assessment domains.

The available body of evidence from RCTs provides comparisons between any one of the CDK4/6 inhibitors with endocrine monotherapies but no direct comparisons between different CDK4/6 inhibitors. We therefore performed indirect comparisons through network meta-analysis (NMA) for the efficacy outcomes (overall survival, quality of life and progression-free survival) and safety outcomes (adverse events and treatment discontinuations). In addition, we conducted a descriptive analysis of non-randomised studies for an extended assessment of potential adverse events associated with

CDK4/6 inhibitors.

To assess cost-effectiveness, we developed a de novo economic model. Cost data and other relevant model parameters were gathered from several sources including the Swiss Specialties List, published literature and the input of Swiss clinical oncology experts. For the budget impact analysis, we considered changes in direct treatment related costs in an incident cohort and calculated several scenarios, separately assessing the consequence of disinvestment in either one of the three CDK4/6 inhibitors.

Results: The systematic literature searches identified 35 RCTs of which 24 could be included in the NMA. Of the identified NRSs, we included 56 in the descriptive analysis of adverse events.

Based on the NMA results it is likely that CDK4/6 inhibitors provide superior efficacy when compared to ET monotherapies. At the same time it is highly likely that the ET monotherapies show superior tolerability when compared to the combination therapies with CDK4/6 inhibitors. Differences between the individual CDK4/6 inhibitors are not very robust and some efficacy data on individual CDK4/6 inhibitors from primary studies are not yet available.

We performed two cost-effectiveness analyses (CEA) based on partitioned-survival models comparing four different AI-related treatment regimens (PICO 1) and four different FUL-related treatment regimens (PICO 2).

For patients without endocrine resistance, based on our results ABE+AI was most effective in terms of quality-adjusted life years gained (QALYG) compared to RIB+AI and AI monotherapy, resulting in a discounted incremental cost-effectiveness ratio (ICER) of ABE+AI vs. RIB+AI of 166,787 CHF per QALYG and a discounted ICER of RIB+AI vs. AI of 126,860 CHF per QALYG. The combination therapy PAL+AI was dominated.

For patients with endocrine resistance, based on our results RIB+FUL was most effective in terms of QALYG compared to PAL+FUL and FUL monotherapy, resulting in a discounted ICER of PAL+FUL vs. FUL of 147,808 CHF per QALYG and a discounted ICER of RIB+FUL vs. PAL+FUL of 148,342 CHF per QALYG. The combination therapy ABE+FUL was dominated.

The results were sensitive to variations in the hazard ratios for overall survival (OS) and progression-free survival (PFS) and in several other conducted sensitivity analyses.

Based on official drug prices, delisting PAL or ABE would lead to budget savings within an incident cohort, whereas delisting RIB would lead to additional costs, given that, in each scenario, patients are allocated to the other two CDK4/6 inhibitors.

The ethical issue concerning the choice of primary endpoints in clinical trials is controversially discussed in the scientific literature. The extent to which progression-free survival can be considered a patient-relevant outcome for patients with LA/MBC is currently unclear. Regarding organisational aspects of the assessed interventions, the addition of CDK4/6 inhibitors to the treatment with ET leads to additional doctor's visits and examinations for the monitoring of adverse events (AEs) and requires special considerations regarding concomitant medications.

Conclusions:

Our analyses suggest that ET+CDK4/6 inhibitor combination therapy is more efficacious but also associated with more AEs than ET monotherapy. Comparative efficacy results between individual CDK4/6 inhibitors are uncertain and inconclusive. A substantial number of currently ongoing RCTs studying CDK4/6 inhibitors in relevant patient groups might provide further insight in the future. The CEAs suggest that ABE+AI is most effective and can be considered cost-effective at a willingness-to-pay (WTP) threshold of 170,000 CHF per QALYG for patients without endocrine resistance and RIB+FUL is most effective and can be considered cost-effective at a WTP threshold of 150,000 CHF per QALYG for patients with endocrine resistance. However, the certainty of these analyses is limited because several input parameters had to be based on assumptions. Our CEAs should be updated when mature OS and quality of life (QoL) data for all CDK4/6 inhibitor combination therapies are available from clinical trials. The budget impact analysis shows a potential for reducing direct treatment costs in the assessed populations by disinvesting in either PAL or ABE.

Zusammenfassung

Hintergrund: 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 (HR+/HER2- LA/MBC). Unterdessen sind in der Schweiz drei CDK4/6-Inhibitoren verfügbar: Palbociclib (PAL), Ribociclib (RIB) und Abemaciclib (ABE). Sie sind in Kombination mit einer endokrinen Therapie (ET; Aromatasehemmer [AIs] bei Patientinnen ohne endokrine Resistenz sowie Fulvestrant [FUL] bei Patientinnen mit endokriner Resistenz) bei Patientinnen mit HR+/HER2- LA/MBC zugelassen und werden erstattet.

Mit dieser Gesundheitstechnologiebewertung (HTA) werden die folgenden Aspekte beurteilt: 1) Wirksamkeit, Effektivität, Sicherheit und Kosteneffektivität der drei CDK4/6-Inhibitoren (in den jeweiligen Therapiekombinationen) im Vergleich zu einander sowie zu endokrinen Monotherapien, 2) Kosten und Kosteneffektivität der CDK4/6-Inhibitoren und die budgetären Auswirkungen einer potenziellen

Änderung des Kostenerstattungsstatus von einem der drei CDK4/6-Inhibitoren, 3) die damit verbundenen ethischen und organisatorischen Fragen.

Methoden: Wir haben zwei separate systematische Literaturrecherchen durchgeführt, um (1) randomisierte kontrollierte Studien (RCTs) für die Beurteilung der Wirksamkeit und Sicherheit sowie (2) nicht-randomisierte Studien (NRSs) für die anderen HTA-Domains zu identifizieren.

Die verfügbaren evidenzbasierten Daten aus RCTs bieten Vergleiche der jeweiligen CDK4/6-Inhibitoren mit endokrinen Monotherapien, jedoch keine direkten Vergleiche zwischen den unterschiedlichen CDK4/6-Inhibitoren. Aus diesem Grund haben wir indirekte Vergleiche mittels Netzwerk-Metaanalysen (NMA) für die Wirksamkeitsendpunkte (Gesamtüberleben, Lebensqualität und progressionsfreies Überleben) und Sicherheitsendpunkte (unerwünschte Ereignisse und Therapieabbruch) durchgeführt. Darüber hinaus haben wir eine deskriptive Analyse nicht-randomisierter Studien durchgeführt, um eine erweiterte Beurteilung möglicher unerwünschter Ereignisse im Zusammenhang mit CDK4/6-Inhibitoren zu erhalten.

Zur Beurteilung der Kosteneffektivität haben wir ein de-novo-ökonomisches Modell entwickelt. Kostendaten und andere relevante Modellparameter wurden aus unterschiedlichen Quellen zusammengetragen, einschliesslich der Schweizer Spezialitätenliste, veröffentlichter Literatur und dem Input von Schweizer Experten für klinische Onkologie. Bei der Budget-Impact-Analyse haben wir Veränderungen der direkten behandlungsbedingten Kosten in einer Inzidenzkohorte aufgenommen und mehrere Szenarien berechnet, in denen wir die Folgen einer Änderung des Kostenerstattungsstatus von jedem einzelnen der drei CDK4/6-Inhibitoren separat bewertet haben.

Ergebnisse: In der systematischen Literaturrecherche wurden 35 RCTs, von denen 24 in die NMA eingeschlossen werden konnten, identifiziert. 56 der identifizierten NRSs haben wir in die deskriptive Analyse der unerwünschten Ereignisse einbezogen.

Ausgehend von den NMA-Ergebnissen sind CDK4/6-Inhibitoren gegenüber ET-Monotherapien hinsichtlich der Wirksamkeit wahrscheinlich überlegen. Gleichzeitig ist es überaus wahrscheinlich, dass ET-Monotherapien im Vergleich zu den Kombinationstherapien mit CDK4/6-Inhibitoren eine bessere Verträglichkeit aufweisen. Die Unterschiede zwischen den einzelnen CDK4/6-Inhibitoren sind nicht sehr robust und einige Wirksamkeitsdaten bezüglich einzelner CDK4/6-Inhibitoren aus Primärstudien liegen noch nicht vor.

Wir haben zwei Kosteneffektivitätsanalysen (CEA) durchgeführt, die auf Partitioned-Survival-Modellen basierten und in denen vier verschiedene AI-bezogene Behandlungsschemata (PICO 1) sowie vier verschiedene FUL-bezogene Behandlungsschemata (PICO 2) verglichen wurden.

Basierend auf unseren Ergebnissen zeigte ABE+AI im Vergleich zu RIB+AI und AI-Monotherapie bei

Patientinnen ohne endokrine Resistenz die höchste Wirksamkeit in Bezug auf die gewonnenen qualitätsadjustierten Lebensjahre (QALYG), was zu einem diskontierten inkrementellen Kosten-Effektivitäts-Verhältnis (ICER) von ABE+AI vs. RIB+AI von 166’787 Franken pro QALYG und einem diskontierten ICER von RIB+AI vs. AI von 126’860 Franken pro QALYG führte. Die Kombinationstherapie mit PAL+AI war unterlegen.

Bei Patientinnen mit endokriner Resistenz zeigte RIB+FUL im Vergleich zu PAL+FUL und FUL-Monotherapie basierend auf unseren Ergebnissen die höchste Wirksamkeit in Bezug auf QALYG, was zu einem diskontierten ICER von PAL+FUL vs. FUL von 147’808 Franken pro QALYG und einem diskontierten ICER von RIB+FUL vs. PAL+FUL von 148’342 Franken pro QALYG führte. Die Kombinationstherapie mit ABE+FUL war unterlegen.

Die Ergebnisse waren empfindlich gegenüber Variationen in den Hazard Ratios für das Gesamtüberleben (OS) und das progressionsfreie Überleben (PFS) sowie in mehreren anderen durchgeführten Sensitivitätsanalysen.

Ausgehend von den offiziellen Arzneimittelpreisen würde die Streichung von PAL oder ABE zu Budgeteinsparungen innerhalb einer Inzidenzkohorte führen, während die Streichung von RIB zusätzliche Kosten nach sich ziehen würde, da in jedem Szenario die Zuordnung der Patientinnen zu den anderen beiden CDK4/6-Inhibitoren erfolgt.

Die ethische Frage betreffend die Auswahl der primären Endpunkte in klinischen Studien wird in der wissenschaftlichen Literatur kontrovers diskutiert. Es ist derzeit unklar, inwiefern das progressionsfreie Überleben als patientenrelevantes Ergebnis für Patientinnen mit LA/MBC angesehen werden kann. Im Hinblick auf die organisatorischen Aspekte der beurteilten Interventionen führt die Hinzunahme von CDK4/6-Inhibitoren zur Behandlung mit ET zu zusätzlichen Arztbesuchen und Untersuchungen zur Überwachung von unerwünschten Ereignissen (AEs) und erfordert besondere Überlegungen bezüglich der Begleitmedikation.

Fazit:

Unsere Analysen deuten darauf hin, dass die ET+CDK4/6-Inhibitor-Kombinationstherapie im Vergleich zur ET-Monotherapie wirksamer ist, jedoch mit mehr AEs einhergeht. Vergleichende Wirksamkeitsergebnisse zwischen den einzelnen CDK4/6-Inhibitoren sind unsicher und nicht schlüssig. Eine erhebliche Anzahl von aktuell laufenden RCTs, bei denen CDK4/6-Inhibitoren in relevanten Patientengruppen untersucht werden, könnten in Zukunft weitere Erkenntnisse liefern. Die Kosteneffektivitätsanalysen weisen darauf hin, dass ABE+AI für Patientinnen ohne endokrine Resistenz die grösste Wirksamkeit aufweist und bei einem WTP-Grenzwert (Zahlungsbereitschaft) von 170'000 Franken pro QALYG als kosteneffektiv angesehen werden kann. Für Patientinnen mit endokriner Resistenz

weist dagegen RIB+FUL die grösste Wirksamkeit auf und kann bei einem WTP-Grenzwert (Zahlungsbereitschaft) von 150'000 Franken pro QALYG als kosteneffektiv angesehen werden. Allerdings ist die Sicherheit dieser Analysen begrenzt, da mehrere Eingabeparameter auf Annahmen beruhen mussten. Unsere Kosteneffektivitätsanalysen sollten aktualisiert werden, sofern ausgereifte Daten aus klinischen Studien zum OS und zur Lebensqualität (QoL) für alle Kombinationstherapien mit CDK4/6-Inhibitoren vorliegen. Die Budget-Impact-Analyse hat gezeigt, dass eine Änderung des Kostenerstattungsstatus von PAL oder ABE ein Potenzial zur Reduzierung der direkten Behandlungskosten in den beurteilten Populationen aufweist.

Résumé

Contexte : Les inhibiteurs des kinases 4/6 dépendantes des cyclines (CDK4/6) sont venus compléter relativement récemment les options thérapeutiques disponibles pour les patientes atteintes d'un cancer du sein localement avancé ou métastatique à récepteurs hormonaux positifs et récepteur 2 du facteur de croissance épidermique humain négatif (HR+/HER2- LA/MBC). Trois inhibiteurs de CDK4/6 – le palbociclib (PAL), le ribociclib (RIB) et l'abemaciclib (ABE) – sont actuellement disponibles en Suisse. Pour les patientes HR+/HER2- LA/MBC, ils sont autorisés et remboursés en association avec un traitement endocrinien (inhibiteurs de l'aromatase [AI] chez les patientes ne présentant pas de résistance endocrinienne et avec du fulvestrant [FUL] chez les patientes présentant une résistance endocrinienne).

Le présent rapport d'évaluation des technologies de la santé (ETS) évalue : 1) l'efficacité théorique, l'efficacité pratique, la sécurité et le rapport coût/efficacité des trois inhibiteurs de CDK4/6 (dans le cadre de leurs associations thérapeutiques respectives) en comparaison les uns des autres et en comparaison des monothérapies endocriniennes ; 2) les coûts et le rapport coût/efficacité des inhibiteurs de CDK4/6 et l'impact budgétaire d'un éventuel désinvestissement de l'un de ces trois inhibiteurs ; 3) les questions éthiques et organisationnelles y relatives.

Méthodes : Nous avons réalisé deux recherches systématiques de la littérature scientifique distinctes en vue de recenser : 1) les essais cliniques randomisés pour l'évaluation de l'efficacité théorique et de la sécurité ; 2) les études non randomisées pour les autres domaines d'évaluation.

Les données disponibles issues des essais cliniques randomisés fournissent des comparaisons entre chacun des inhibiteurs de CDK4/6 et les monothérapies endocriniennes, mais pas de comparaison directe entre les différents inhibiteurs de CDK4/6. Pour les résultats sur les plans de l'efficacité théorique (survie globale, qualité de vie et survie sans progression) et de la sécurité (événements indésirables et interruptions de traitement), nous avons donc effectué des comparaisons indirectes par l'intermédiaire d'une méta-analyse en réseau. De plus, nous avons réalisé une analyse descriptive

des études non randomisées pour procéder à une évaluation étendue des événements indésirables potentiellement associés aux inhibiteurs de CDK4/6.

Pour évaluer le rapport coût/efficacité, nous avons élaboré un modèle économique de novo. À cette fin, nous avons tiré les données relatives aux coûts et les autres paramètres pertinents de plusieurs sources, notamment la liste suisse des spécialités, la littérature publiée et des experts suisses en oncologie. S'agissant de l'analyse de l'impact budgétaire, nous avons examiné l'évolution des coûts directement liés au traitement dans le cadre d'une cohorte de cas incidents et calculé plusieurs scénarios, pour lesquels nous avons évalué séparément les conséquences d'un désinvestissement de l'un ou l'autre des trois inhibiteurs de CDK4/6.

Résultats : Les recherches systématiques de la littérature scientifique ont permis de recenser 35 essais cliniques randomisés, dont 24 ont pu être inclus dans la méta-analyse en réseau. Pour ce qui est des études non randomisées, nous en avons inclus 56 dans l'analyse descriptive des événements indésirables.

Les résultats de la méta-analyse en réseau suggèrent une probable efficacité théorique supérieure des inhibiteurs de CDK4/6 par rapport aux monothérapies endocriniennes. Parallèlement, la meilleure tolérabilité des monothérapies endocriniennes est très probable par comparaison avec les traitements combinés associant des inhibiteurs de CDK4/6. Les données suggérant des variations entre les différents inhibiteurs de CDK4/6 ne sont pas très robustes, et il manque encore certaines données provenant d'études primaires pour ce qui est de leur efficacité théorique.

Nous avons réalisé deux analyses coût/efficacité sur la base de modèles de survie partitionnée comparant quatre schémas thérapeutiques basés sur les AI (PICO 1) et quatre schémas basés sur le FUL (PICO 2).

Il ressort de nos résultats que, pour les patientes ne présentant pas de résistance endocrinienne, l'association ABE+AI est la plus efficace du point de vue du gain d'années de vie pondérées par la qualité (QALYG) comparée à l'association RIB+AI et aux AI en monothérapie. Le rapport coût/efficacité différentiel (ICER) actualisé est de 166 787 CHF par QALYG pour ABE+AI vs RIB+AI, et de 126 860 CHF par QALYG pour RIB+AI vs AI. L'association PAL+AI est dominée.

Pour les patientes présentant une résistance endocrinienne, nos résultats suggèrent que l'association RIB+FUL est la plus efficace en termes de QALYG comparée à l'association PAL+FUL et au FUL en monothérapie. Dans ce cas de figure, l'ICER actualisé est de 147 808 CHF par QALYG pour PAL+FUL vs FUL et de 148 342 CHF par QALYG pour RIB+FUL vs PAL+FUL. L'association ABE+FUL est dominée.

Les résultats étaient sensibles aux variations du rapport des risques instantanés pour la survie globale et la survie sans progression, de même que dans plusieurs autres analyses de sensibilité.

Compte tenu des prix officiels des médicaments concernés, le retrait du PAL ou de l'ABE entraînerait des économies au sein d'une cohorte de cas incidents. À l'inverse, le retrait du RIB générerait des coûts supplémentaires, puisque, dans chaque scénario, les patientes se reporteraient sur les deux autres inhibiteurs de CDK4/6.

La question éthique soulevée par le choix des indicateurs de résultat primaires dans les essais cliniques fait l'objet de débats dans la littérature scientifique. La mesure dans laquelle la survie sans progression peut être considérée comme un résultat pertinent pour les patientes LA/MBC doit être clarifiée. S'agissant des aspects organisationnels des interventions évaluées, l'ajout des inhibiteurs de CDK4/6 au traitement endocrinien donne lieu à des consultations et à des examens médicaux supplémentaires pour assurer le suivi des événements indésirables. En outre, des pesées d'intérêts particulières doivent être réalisées par rapport à l'administration concomitante de médicaments.

Conclusions :

Nos analyses suggèrent que l'association traitement endocrinien+inhibiteur de CDK4/6 est plus efficace en théorie que les monothérapies endocriniennes, mais qu'elle entraîne également plus d'événements indésirables. Les résultats issus de l'analyse comparative de l'efficacité théorique des différents inhibiteurs de CDK4/6 sont incertains et ne permettent pas de tirer de conclusions. Plusieurs des essais cliniques randomisés en cours portant sur les inhibiteurs de CDK4/6 dans des groupes pertinents de patientes pourraient fournir des résultats utiles à cet égard. Les analyses coût/efficacité suggèrent que, pour les patientes ne présentant pas de résistance endocrinienne, l'association ABE+AI est la plus efficace dans la pratique et peut être considérée comme rentable pour une disposition à payer de 170 000 CHF par QALYG. Pour les patientes présentant une résistance endocrinienne, l'association RIB+FUL est la plus efficace dans la pratique et peut être considérée comme rentable pour une disposition à payer de 150 000 CHF par QALYG. Cependant, la certitude des résultats est limitée, car plusieurs paramètres d'entrée reposent sur des hypothèses. Nous actualiserons nos analyses coûts/efficacité lorsque les essais cliniques auront livré des données matures sur la survie globale et la qualité de vie pour tous les traitements combinés associant des inhibiteurs de CDK4/6. L'analyse d'impact budgétaire montre qu'un désinvestissement du PAL ou de l'ABE recèle un potentiel de réduction des coûts directs de traitement dans les populations étudiées.

Sintesi

Premessa: gli inibitori delle chinasi ciclina-dipendenti (CDK4/6) rappresentano un'opzione di trattamento relativamente recente per pazienti con carcinoma mammario localmente avanzato o metastatico (HR+/HER2- LA/MBC) 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 (PAL), ribociclib (RIB) e abemaciclib (ABE). Nei pazienti HR+/HER2- LA/MBC, sono omologati e rimborsati in combinazione con una terapia endocrina (*endocrine therapy* ET, inibitori dell'aromatasi [AI] in pazienti senza resistenza endocrina e fulvestrant [FUL] in pazienti con resistenza endocrina).

Il presente rapporto di *Health Technology Assessment* (HTA) valuta 1) efficacia teorica, efficacia nella pratica clinica, sicurezza e rapporto costo-efficacia dei tre inibitori delle CDK4/6 (nelle rispettive combinazioni terapeutiche) confrontati l'uno con l'altro e con le monoterapie endocrine, 2) i costi e il rapporto costo-efficacia degli inibitori delle CDK4/6 e le ripercussioni sul budget di un potenziale disinvestimento in uno dei tre inibitori delle CDK4/6, 3) questioni collegate di natura etica e organizzativa.

Metodologia: abbiamo condotto due ricerche sistematiche distinte nella letteratura scientifica per identificare (1) studi controllati randomizzati (*randomised controlled trials*, RCT) per la valutazione dell'efficacia teorica e della sicurezza e (2) studi non randomizzati (*non-randomised studies*, NRS) per gli altri campi di valutazione.

Le evidenze disponibili provenienti dagli RCT forniscono confronti tra ciascuno degli inibitori delle CDK4/6 e le monoterapie endocrine ma nessun confronto diretto tra i differenti inibitori delle CDK4/6. Abbiamo quindi proceduto a confronti indiretti mediante la *network* meta-analisi (NMA) per i risultati sull'efficacia teorica (sopravvivenza globale, qualità di vita e sopravvivenza senza progressione) e per i risultati sulla sicurezza (eventi avversi e interruzioni del trattamento). Inoltre, abbiamo effettuato un'analisi descrittiva degli NRS per una valutazione estesa di potenziali eventi avversi associati agli inibitori delle CDK4/6.

Per valutare il rapporto costo-efficacia, abbiamo sviluppato un modello economico *de novo*. A tale scopo, abbiamo raccolto i dati sui costi e altri parametri rilevanti per il modello da svariate fonti, incluso l'elenco svizzero delle specialità, la letteratura pubblicata e gli input degli esperti svizzeri di oncologia clinica. Per l'analisi dell'impatto sul budget, abbiamo considerato l'evoluzione dei costi direttamente legati al trattamento nel quadro di una coorte dei casi incidenti e calcolato diversi scenari, valutando separatamente le conseguenze di un disinvestimento in ciascuno dei tre inibitori delle CDK4/6.

Risultati: dalle ricerche bibliografiche sistematiche è stato possibile identificare 35 RCT, di cui 24 sono stati inclusi nella NMA. Degli NRS reperiti, 56 sono stati inclusi nell'analisi descrittiva degli eventi avversi.

Sulla base dei risultati della NMA è probabile che gli inibitori delle CDK4/6 offrano un'efficacia teorica superiore rispetto alle monoterapie ET. Al contempo è altamente probabile che le monoterapie ET siano maggiormente tollerate rispetto alle terapie combinate con inibitori delle CDK4/6. Non sono state evidenziate differenze sostanziali tra i singoli inibitori delle CDK4/6 e non sono ancora disponibili dati di studi primari sull'efficacia teorica dei singoli inibitori delle CDK4/6.

Abbiamo svolto due analisi sul rapporto costo-efficacia basate su modelli di sopravvivenza partizionati, confrontando quattro differenti schemi terapeutici basati sull'AI (PICO 1) e quattro basati sul FUL (PICO 2).

Dai nostri risultati emerge che, per i pazienti senza resistenza endocrina, la combinazione ABE+AI è stata la più efficace nella pratica clinica in termini di anni di vita guadagnati in piena qualità di vita (*quality-adjusted life years gained*, QALYG) rispetto alla combinazione RIB+AI e alla monoterapia AI; il tasso incrementale di costo-efficacia (*incremental cost-effectiveness ratio*, ICER) ridotto è di 166,787 franchi per QALYG per la combinazione ABE+AI rispetto a RIB+AI e di 126,860 franchi per QALYG per la combinazione RIB+AI rispetto a AI. La combinazione PAL+AI ha ottenuto risultati inferiori.

Per i pazienti con resistenza endocrina, i nostri risultati suggeriscono che la combinazione RIB+FUL è stata la più efficace nella pratica clinica in termini di QALYG rispetto alla combinazione PAL+FUL e alla monoterapia FUL; l'ICER ridotto è di 147,808 franchi per QALYG per la combinazione PAL+FUL rispetto a FUL e di 148,342 franchi per QALYG per la combinazione RIB+FUL rispetto a PAL+FUL. La combinazione ABE+FUL ha ottenuto risultati inferiori.

I risultati sono stati sensibili a variazioni nei rapporti di rischio per la sopravvivenza globale e la sopravvivenza senza progressione e nelle altre numerose analisi condotte sulla sensibilità.

Sulla base dei prezzi ufficiali dei medicamenti, la cancellazione dall'elenco delle specialità di PAL o ABE comporterebbe risparmi sul budget all'interno della coorte dei casi incidenti, mentre quella di RIB genererebbe costi supplementari, poiché, in ogni scenario, i pazienti sarebbero trattati con gli altri due inibitori delle CDK4/6.

La questione etica sollevata dalla scelta di indicatori di risultato primari nelle sperimentazioni cliniche è oggetto di controversie nella letteratura scientifica. La misura in cui la sopravvivenza senza progressione può essere considerata come risultato rilevante per i pazienti con LA/MBC non è attualmente chiara. Riguardo agli aspetti organizzativi degli interventi valutati, l'inclusione degli inibitori delle CDK4/6 nel trattamento con ET comporta visite ed esami medici supplementari per il monitoraggio di eventi avversi nonché richiede considerazioni particolari in rapporto a medicamenti concomitanti.

Conclusioni: le nostre analisi suggeriscono che la combinazione ET+inibitore CDK4/6 offre la maggiore efficacia teorica ma è anche associata a maggiori eventi avversi rispetto alla monoterapia ET. I risultati dell'analisi comparativa dell'efficacia teorica tra i diversi inibitori delle CDK4/6 non sono certi né permettono di giungere a una conclusione. Un numero considerevole di RCT in corso sugli inibitori delle CDK4/6 nei gruppi di pazienti rilevanti potrebbe fornire maggiori indicazioni in futuro. L'analisi del rapporto costo-efficacia suggerisce che, per i pazienti senza resistenza endocrina, la combinazione ABE+AI è la più efficace nella pratica clinica e si può affermare che offra un buon rapporto costo-efficacia data una disponibilità a pagare nell'ordine di 170,000 franchi per QALYG, mentre, per i pazienti con resistenza endocrina, la combinazione RIB+FUL è la più efficace nella pratica clinica e si può affermare che offra un buon rapporto costo-efficacia data una disponibilità a pagare nell'ordine di 150,000 franchi per QALYG. Tuttavia, la certezza di queste analisi è limitata perché diversi parametri di input si basano su ipotesi. Provvederemo ad aggiornarle non appena le sperimentazioni cliniche forniranno dati maturi su sopravvivenza globale e qualità di vita per tutte le terapie combinate con inibitori delle CDK4/6. Le analisi dell'impatto sul budget mostrano un potenziale di riduzione dei costi diretti di trattamento nella popolazione esaminata mediante un disinvestimento in PAL o ABE.

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
CEA	Cost effectiveness analysis
CDK	Cyclin-dependent kinase
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
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
ICER	Incremental cost-effectiveness ratio
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
OFA	Ovarian function ablation
OFS	Ovarian function suppression
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)
PPS	Post-progression survival
PR	Progesterone receptor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient reported outcome
QALM	Quality-adjusted life-month
QALMG	Quality-adjusted life-month gained
QALY	Quality-adjusted life-year
QALYG	Quality-adjusted life-year gained
QoL	Quality of life
Rb	Functional retinoblastoma

RCT	Randomised controlled trial
RoB	Risk of bias
SAF	Safety (HTA assessment domain)
SL	List of specialties (Spezialitätenliste)
SR	Systematic review
SERD	Selective oestrogen receptor degrader
SERM	Selective oestrogen receptor modulator
SUCRA	Surface under the cumulative ranking
TTD	Time to deterioration
TTP	Time to progression
WTP	Willingness to pay

Short forms for interventions

ABE	Abemaciclib
ANA	Anastrozole
EXE	Exemestane
LET	Letrozole
FUL	Fulvestrant
PAL	Palbociclib
RIB	Ribociclib
TAM	Tamoxifen

Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in a HTA report include clinical effectiveness and safety, costs, cost-effectiveness and budget impact, legal, social, ethical and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1 Policy question and context

Each health technology assessment (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. This HTA report addresses the following policy question brought forward by the applicant.

CDK4/6 Inhibitors such as palbociclib, ribociclib and abemaciclib, are a novel drug class that are used in combination with endocrine therapy to treat advanced hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced (LABC) or metastatic breast cancer (MBC). Results from clinical trials suggest that some of these new compounds may cause significant side effects. There is also evidence that not all CDK4/6 inhibitors contribute equally to prolonging the survival of breast cancer patients and improving their quality of life. The aim of the HTA is therefore to evaluate the efficacy, safety, cost-effectiveness and budgetary impact of treatment with CDK4/6 inhibitors in comparison with each other and with endocrine therapy.

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, RIB or ABE 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, RIB or ABE 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.[1]

Breast cancer is the most commonly diagnosed cancer in women (in both transitioned and transitioning countries), with over 6'200 newly diagnosed cases in Switzerland every year. It is also the leading cause of cancer deaths worldwide in women. In Switzerland, around 1'400 patients die each year from the disease. (These numbers derive from an epidemiologic analysis of the years 2013 to 2017.[2])

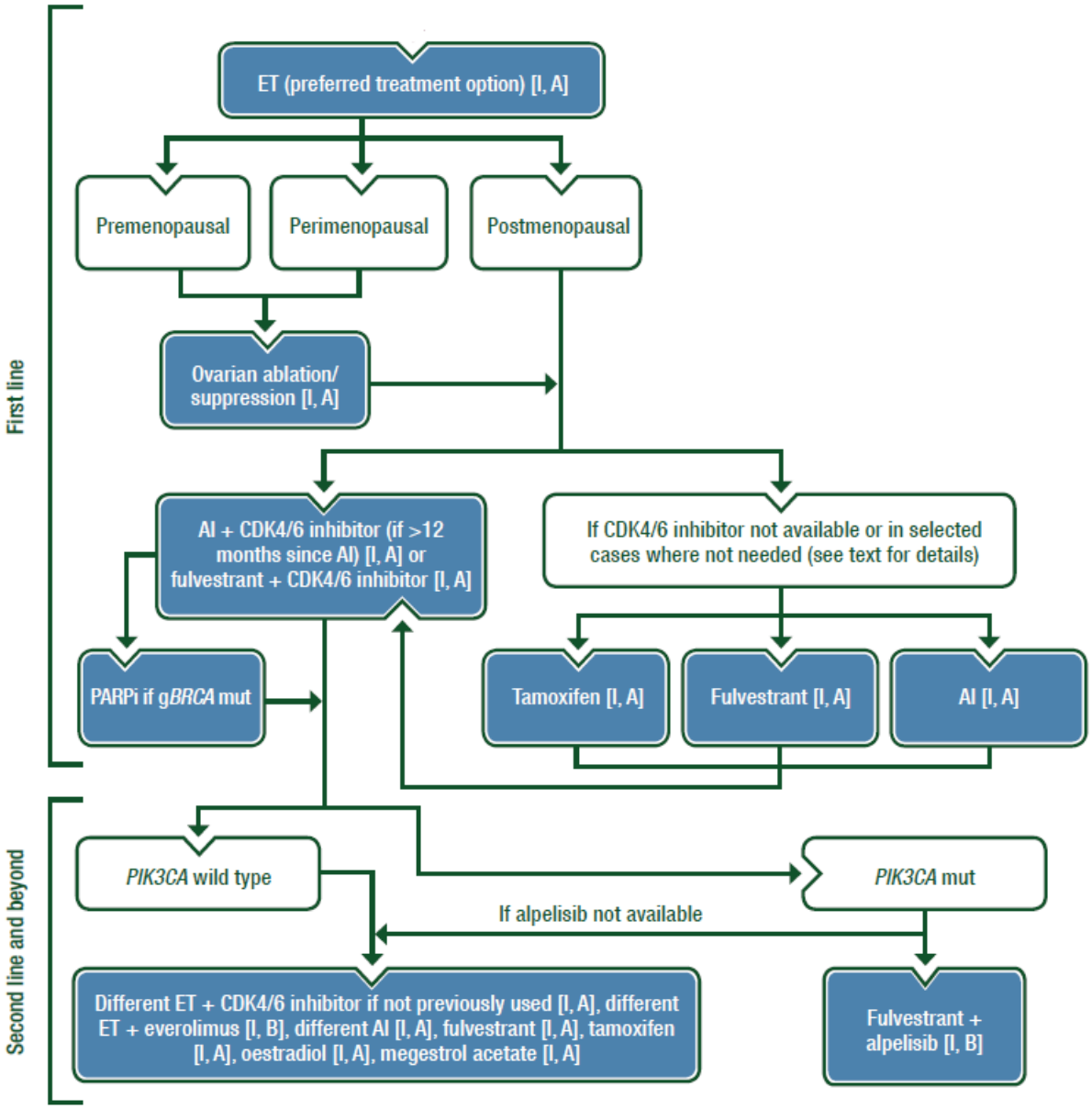
Initial signs of breast cancer may include a lump in the breast, a change in the size or shape of the breast, skin irritation and breast or nipple pain. The stage of breast cancer is determined by the cancer's characteristics, such as tumour size and receptor status. Primary invasive cancers are investigated 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.[3] Tumours expressing either ER, PR or both are termed hormone receptor HR-positive (HR+), with HR+ cancers accounting for approximately 65 per cent and 80 per cent of breast cancers in pre- and postmenopausal women, respectively.[4] HR+ and HER2- is the most common subtype, accounting for 78 per cent of all breast cancers.[7]

Advanced breast cancer (ABC) generally comprises both locally advanced breast cancer (LABC) and metastatic breast cancer (MBC). 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. Metastatic breast cancer 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.[8] Approximately 20 to 30 per cent of patients with early-stage disease will relapse with distant metastatic disease.[9] [10] As the research questions for this 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 maintaining or improving the quality of life (QoL). Treatment-associated toxicities must be outweighed by the potential benefits.[9]

Among other factors, tumour biology influences the prognosis for breast cancer patients and determines treatment options. The preferred treatment for HR+ LA/MBC is ET. This is irrespective of the patients'

menopausal status but premenopausal patients need to receive concomitant ovarian function suppression/ablation (OFS/OFA).[8] Available 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) letrozole (LET) and anastrozole (ANA).[11] In the guidelines by the German Guideline Programme in Oncology (GGPO), which were co-authored by the Swiss Society of Hematology (Onkopedia) and Gynécologie Suisse, the addition of a CDK4/6 inhibitor to ET is considered optional and the same statement was made in the fourth version of the ESO-ESMO guidelines.[12-14] The most recent version of the ESO-ESMO guidelines revoked this statement based on clinical trial data and now considers ET+CDK4/6 inhibitor combination therapy to be the standard of care for patients with HR+/HER2- LA/MBC (see Figure 1).[8] The GGPO recently prepared an amendment to the guidelines that also defines ET+CDK4/6 inhibitor combination therapy as the standard of care. This amendment is currently under review.[15] There is no clear evidence on the optimal sequence of different ET agents nor whether CDK4/6 inhibitors should be used in first- or second-line therapy. After treatment failure with ET+CDK4/6 inhibitors, patients can be treated with ET agents they have not yet received, some of which can be combined with other targeted therapies. Patients with visceral crisis or without further ET options can be treated with different single-agent or combination cytotoxic chemotherapy regimens.[8 13 14]

Figure 1: Treatment of HR+/HER2- LA/MBC (ESO-ESMO, ABC 5)



AI=aromatase inhibitor; CDK=cyclin-dependent kinase; ET=endocrine therapy; gBRCA mut=genomic mutation in BRCA1 or BRCA2 genes; PARPi=poly-adenosine diphosphate ribose polymerase inhibitor; PIK3CA=phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha;

Source: Minimally modified from Cardoso et al. 2020

4 Technology

4.1 Technology description

In recent years, a novel class of drugs that prevent cell cycle progression has been introduced 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.[16] Highly selective oral CDK4/6 inhibitors can inhibit the proliferation of Rb-positive tumour cells and show dose-dependent growth inhibition in animal models of HR+ breast cancer.[17 18]

PAL (Ibrance®) is available as capsules and RIB (Kisqali®) and ABE (Verzenios®) are available as film-coated tablets. RIB is available in the concentration of 200 mg per tablet while PAL and ABE are available in several concentrations each: 75 mg, 100 mg and 125 mg for PAL and 50 mg, 100mg, 150 mg and 200 mg for ABE. The recommended dose for PAL is 125 mg once a day for 21 consecutive days, followed by a 7-day break to complete a 28-day treatment cycle.[19] The recommended dose for RIB is 600 mg per day, adhering to the same schedule as for PAL (28-day cycle) while the recommended dose for ABE is 300 mg (150 mg twice a day) continuously.[20 21] In the case of AEs, the daily dose of CDK4/6 inhibitors can be reduced to 100 mg or 75 mg for PAL, 400 mg or 200 mg for RIB and 200 mg or 100 mg for ABE.

The three CDK4/6 inhibitors have similar safety profiles but some of their side effects differ.[22 23] A high incidence of abnormal blood counts, especially neutropenia, has been reported for PAL and RIB but to a lesser extent for ABE. RIB has a potential for QT interval prolongation. ABE is associated with less haematological toxicity but more gastrointestinal symptoms and a higher rate of fatigue.[22]

PAL, RIB and ABE are primarily metabolised by Cytochrome P450 3A4 (CYP3A4).[24] Concomitant treatment with strong inhibitors of CYP3A4 may lead to increased toxicity and their use during treatment with a CDK4/6 inhibitor should be avoided. If co-administration with a strong CYP3A4 inhibitor is unavoidable, a dose reduction of the CDK4/6 inhibitor is required. Co-administration of CYP3A4 inducers may lead to decreased plasma levels of the CDK4/6 inhibitor and consequently to a risk of inefficacy. Therefore, concomitant use of strong CYP3A4 inducers should also be avoided.[19-21]

4.2 Alternative technologies

The main treatment alternatives for HR+/HER2- LA/MBC patients eligible for ET+CDK4/6 inhibitor combination therapy are monotherapies with ET agents. 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.

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 while 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.

The SERD FUL achieves oestrogen receptor degradation and is administered by intramuscular injection. In the first month of treatment, the injections are given two 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.[25]

The oral SERM TAM acts as an oestrogen receptor antagonist in breast tissue. It is the only available ET for premenopausal LA/MBC patients who refuse OFS/OFA but due to its inferior efficacy compared with other ET agents, it is not the treatment of choice.[8] Commonly reported side effects of TAM include hot flashes, nausea, vaginal dryness and vaginal discharge. The recommended dose for the patient population studied in this report is 20 mg to 40 mg orally per day.

Further therapeutic options for HR+/HER2- LA/MBC patients include the mammalian target of rapamycin (mTOR) inhibitor everolimus (EVE) in combination with ET or cytotoxic chemotherapy. However, due to their high toxicity, these treatments are only recommended for later treatment lines.

4.3 Regulatory status/provider

The CDK4/6 inhibitors are approved by Swissmedic and indicated for the treatment of HR+/HER2- LA/MBC in combination with an AI in patients without endocrine resistance or in combination with FUL in patients with endocrine resistance. In pre- or perimenopausal women, ET should be combined with an LHRH agonist.[19-21] ABE is also indicated for patients with endocrine resistance who have received one or two regimens of cytotoxic chemotherapy and are not eligible for further treatment with cytotoxic chemotherapy and RIB is also indicated in combination with FUL in patients without endocrine re-

sistance. However, these indications are not being assessed in this report. Treatment with CDK4/6 inhibitors is continued as long as there is a clinical benefit and AEs are tolerable. If treatment-associated AEs occur, treatment may need to be interrupted or stopped or the dose may need to be reduced.

Currently, all three CDK4/6 inhibitors are reimbursed by the mandatory health insurance (obligatorische Krankenpflegeversicherung; OKP) with limitations corresponding to the indications determined by Swissmedic. Reimbursement does not cover patients who have suffered disease progression during previous treatment with a CDK4/6 inhibitor. The reimbursement regulations are temporary and in force until 31 October 2021 (PAL), 31 May 2021 (RIB) and 30 September 2021 (ABE), respectively.[26]

Treatment with a CDK4/6 inhibitor should be started and supervised by a doctor experienced in the use of cancer medication.

Table 1 shows the different CDK4/6 inhibitors and ET combination partners that are approved in Switzerland and their reimbursement status. Table 2 provides an overview of national coverage policy for CDK4/6 inhibitors in selected European countries. The countries included are those named in Art. 34a KLV (Krankenpflege-Leistungsverordnung, Healthcare Benefits Ordinance) with whom an external reference price (ERP) is determined during the triennial review of all pharmaceuticals included in the Spezialitätenliste (SL) carried out by the Federal Office of Public Health (FOPH).

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

Substance class	ATC Code	Substance	Preparation	Authorisation holder	Reimbursed 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
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
* 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 for 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.

Table 2: National coverage policy in selected European countries

Country	PAL (Ibrance®)	RIB (Kisqali®)	ABE (Verzenios®)
Belgium	Reimbursed (authorisation required)*	Reimbursed (authorisation required)*	Reimbursed (authorisation required)*
Denmark	Only available through hospitals	Only available through hospitals	Only available through hospitals
Finland	Reimbursed†	Reimbursed†	Partially reimbursed‡
France	Reimbursed	Reimbursed	Reimbursed
Germany	Reimbursed	Reimbursed	Reimbursed
Netherlands	Reimbursed	Reimbursed	Only available through hospitals
Sweden	Reimbursed	Reimbursed	Reimbursed
UK	Reimbursed	Reimbursed	Reimbursed

* Authorisation for reimbursement can only be issued by the health insurance after a formal request is made.
† 100% of the cost of the product, minus a co-payment of EUR 4.50 for each product purchased. Eligibility for reimbursement is granted on the basis of a doctor's statement only.
‡ 40% of the cost of the product. Eligibility for reimbursement is granted on the basis of a doctor's statement only.

5 PICO

Table 3: 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.e. patients without endocrine resistance)
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 (critical outcome) - OS (critical outcome) - PFS (important outcome*) Safety - 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; LA=locally advanced; LET=letrozole; LYG=life years gained; PAL=palbociclib; MBC=metastatic breast cancer; 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 4: 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.e. patients with endocrine resistance)
I:	- PAL+FUL - RIB+FUL - ABE+FUL
C:	- Either of the other two CDK4/6 inhibitors + FUL - FUL
O:	Efficacy and effectiveness - HrQoL (critical outcome) - OS (critical outcome) - PFS (important outcome*) Safety - 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).

6 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. Is the addition of PAL, RIB or ABE to treatment with an AI (PICO 1) or to treatment with FUL (PICO 2) cost effective?
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 a network metaanalysis (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.

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

6.1 Additional question(s)

6.1.1 Ethical issues

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

6.1.2 Organisational issues

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?*

6.1.3 Social issues

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?*

6.1.4 Legal issues

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)?[27]

* In consultation with the FOPH, we identified this question from the EUnetHTA Core Model® ontology as being relevant for the ETH and ORG assessment domains.[28] The original question was rephrased according to the context of this assessment.

7 Effectiveness, efficacy and safety

7.1 Methodology effectiveness, efficacy and safety

7.1.1 Databases and search strategy

7.1.1.1 Literature search for RCTs (NMAs for efficacy and safety)

7.1.1.1.1 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'. Since the purpose of this search was to inform the planned NMA, studies were searched that included either one of the CDK4/6 inhibitors in combination with an AI or FUL, either one of the AIs, FUL or TAM monotherapy (see also HTA key questions in Chapter 6 and selection criteria in Table 5). The search was restricted to randomised controlled trials (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 15.7.

7.1.1.1.2 Update of included RCTs for the NMAs in the EFF and SAF domains

During the scoping phase, an extensive literature search was performed to identify both completed and ongoing RCTs that are relevant for the specified research question. To identify articles reporting new data from those RCTs that were published between the systematic literature searches in November 2019 and the start of the HTA phase in April 2020, we manually searched in MEDLINE, EMBASE, The Cochrane Library and CRD as well as in the clinical trial registries using the clinical trial identifiers and acronyms of the identified relevant completed or ongoing RCTs. In addition, we updated the list of relevant ongoing RCTs by searching the clinical trial registries (ClinicalTrials.gov and ICTRP, which contains entries from EUCTR and ISRCTN) using their search interfaces and the defined inclusion and exclusion criteria.

7.1.1.1.3 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[29] 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 5 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 (and did not report data from a trial that investigated a CDK4/6 inhibitor) or have been 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 5). 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 would 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 7.1.1.1.1) were checked for relevance to the research questions of this HTA.

7.1.1.1.4 Inclusion and exclusion criteria

Table 5 lists the inclusion and exclusion criteria for selecting the studies to be included in a potential NMA for the assessment of efficacy and safety.

Table 5: Selection criteria for the systematic review of efficacy 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
* PICOs were refined after the review of the scoping report. TAM was originally defined as a treatment of interest but then removed because it is not considered an equivalent alternative to other ET agents. It is still listed in Table 5 because it was used as an inclusion criterion in the literature selection, which was not redone after the changes in the PICOs. However, no clinical trial investigating TAM has been included in the assessment, see evidence tables in Subchapter 7.2.3.1.

7.1.1.2 Literature search for non-randomised studies (extended safety assessment, economic, ethical, social, legal and organisational issues)

7.1.1.2.1 Systematic literature search

To include all available evidence on the CDK4/6 inhibitors regarding safety (non-randomised studies such as cohort studies and case reports) as well as to cover the other five assessment domains, we conducted additional literature searches. During the scoping phase we conducted a search where 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. A supplementary search in the EconLit database yielded no hits. The search

strings for the databases are included in Appendix 15.8. 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.

7.1.1.2.1.1 Update search for extended SAF assessment

In order to identify new literature relevant for the SAF assessment of PAL at the start of the full HTA production, we repeated the systematic literature search described above with a limitation to publications in the period between November 2019 and April 2020. In addition, because the focus of the assessment had been extended to all three CDK4/6 inhibitors, the same search (without limiting the date of publication) was modified to contain the keywords “ribociclib” and “abemaciclib” (and synonyms) instead of “palbociclib”. The literatue selection at the start of the full HTA production was focused exclusively on medical literature relevant for the SAF assessment and therefore covered the databases MEDLINE, EMBASE and The Cochrane Library but not EconLit and Scopus. The search strings for the databases are included in Appendices 15.9 and 15.10. We applied the selection procedure and inclusion and exclusion criteria described in the following paragraphs but only publications that are relevant for the SAF domain were selected.

7.1.1.2.2 Selection procedure for extended safety assessment

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), on PAL, RIB or ABE and on AEs. The initial selection of abstracts was then cross-checked by a second reviewer. The second reviewer also integrated publications from the literature search for RCTs described in Subsection 7.1.1.1 that were tagged as being relevant for the extended SAF assessment (after checking for duplicates). Full-text screening was then performed by two reviewers.

7.1.1.2.3 Selection procedure for economic, ethical, social, organisational and legal domains

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 Subsection 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 for RCTs described in Subsection 7.1.1.1 that were tagged as being relevant for the other domains (after checking 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.

7.1.1.2.4 Inclusion and exclusion criteria for extended SAF assessment

The inclusion and exclusion criteria regarding the extended SAF assessment are laid out in Table 6. As the extended SAF assessment serves the purpose of identifying additional, potentially rare AEs that had not been reported in RCTs, we applied less strict inclusion criteria. We included studies irrespective of the receptor status and studies on patients who received a CDK4/6 inhibitor as monotherapy or in combination with TAM.

Table 6: Selection criteria for the extended safety assessment of PAL, RIB and ABE

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	LA/MBC	**Other study population** e.g. other cancer, males
Study intervention	- PAL, RIB or ABE in combination with ET (LET, ANA, EXE, FUL or TAM) - PAL, RIB, ABE monotherapy	**Other intervention**
Study outcomes	- Treatment-related AEs	**None of the defined study outcomes included**

AE=adverse event; AI=aromatase inhibitor; ANA=anastrozole; EXE=exemestane; FUL=fulvestrant; HR=hormone receptor; LA=locally advanced; LET=letrozole; MBC=metastatic breast cancer; PAL=palbociclib; TAM=tamoxifen
* RCTs were tagged for inclusion in the clinical effectiveness and safety search (see Subsection 7.1.1.1) while SRs and MAs were tagged to be used as background information and for reference list screening.

7.1.1.2.5 Inclusion and exclusion criteria for economic, ethical, social, organisational and legal aspects

The inclusion and exclusion criteria regarding economic studies are laid out in Table 7. 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 Subsection 6.1 of the scoping report were included in the full-text review.

Table 7: 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 Other sources

The following additional sources were searched for relevant publications during the scoping phase:

- 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

7.1.3 Assessment of quality of evidence

7.1.3.1 Risk of bias assessment of RCTs

We assessed the risk of bias (RoB) for individual outcomes in those RCTs that were included in the NMAs for that particular outcome. If available, we also used the clinical trial protocols in addition to the research articles for the assessment. We used the Cochrane RoB tool v2.0 and did not change the assessments computed by the underlying algorithm.[30] In general, all signalling questions were answered

with strict adherence to the guidance provided with the tool with two exceptions concerning signalling question 2.6: in the RoB assessment for the outcome AEs, analysis of an “as treated” population was considered appropriate; in the RoB assessment of the efficacy outcomes, an analysis population excluding patients who withdrew their consent prior to treatment initiation was considered appropriate.

7.1.3.2 Risk of bias assessment of NRSs

Since all of the included cohort studies and single-arm trials were uncontrolled studies, we applied the three criteria that are provided by the German Cochrane Group for the RoB assessment of this study type[31]:

i) Prospective planning with a protocol defining inclusion criteria, interventions and endpoints of interest

ii) Consecutive patient inclusion

iii) Transparent, non-selective reporting with regard to patient characteristics, intervention and outcome

For (i), retrospective studies were rated “no” and prospective studies were rated “yes” if they stated adherence to a protocol defining inclusion criteria, interventions and endpoints of interest.

For (ii), studies were rated as “yes” if there was transparent reporting on the start and end of data inclusion and there was no indication that some patients may have been selectively excluded.

For (iii), studies were rated “yes” if they reported patient characteristics and frequencies of AEs for all included patients. Studies were also rated “yes” if only certain types of AEs (e.g. haematological) were defined as outcomes of interest and subsequently reported on. Studies were rated “no” if only a selective subset of AEs was reported on without prespecification or AEs were reported only if the frequency of their occurrence was above a certain threshold.

The studies were assessed with respect to the reported AEs only. Other outcomes reported in these studies are not analysed in this report and were not considered in the RoB assessment.

7.1.4 Methodology data analyses efficacy, effectiveness and safety

7.1.4.1 Data extraction

Two reviewers independently extracted the data from the included RCTs. In case of missing data, we screened the study supplements for additional information. If data did not match between study supplements and the published paper, we used the data that seemed more likely to be correct. If the data extracted by the two reviewers did not match, they were checked for errors. Any disagreement was solved by discussion. We extracted HRs and CIs for PFS, OS and TTD of QoL, numbers of treatment

discontinuations, numbers of patients who experienced AEs (of any kind) and numbers of patients who experienced AEs (of any kind) grade 3 or worse. Additional extracted variables included age and menopausal status. A detailed description of the extracted variables from RCTs can be found in the Appendix, Table 33. Data from the included NRSs were extracted by one reviewer and cross-checked by another. We extracted information on study design, patient characteristics (receptor status and disease stage), number of included patients (the number of patients who received CDK4/6 inhibitors and for whom AEs were reported; this was smaller than the total number of patients in some studies), received interventions, types (and grades if available) of reported AEs, incidence (for cohort and single-arm studies) of reported AEs (percentage of participants with the event), study sponsors and COIs with either one of the CDK4/6 inhibitor manufacturers (Pfizer, Novartis, Lilly) as well as the countries in which the studies were conducted. Many of the case studies included a full list of all the co-medications of the described patient. We did not extract the complete lists of medications but instead only extracted those medications that were administered to treat the patient's BC as well as those for which the authors reported adverse interactions. Extraction of the numbers and types of prior treatments was not feasible because the reporting was highly heterogeneous.

7.1.4.2 Network meta-analysis

Due to the lack of direct comparisons between the treatments of interest, we conducted an NMA including the different treatments that had been studied in the patient populations defined in the PICOs. An NMA usually consists of a decision set including the focal treatments of the analysis (i.e. interventions and comparators defined in the PICOs). The decision set is accompanied by a supplementary set. The supplementary set provides information on treatments that are not of practical interest but can establish connections between the focal treatments and provide additional evidence. The principal inclusion criteria for this supplementary set are whether the treatments could be used for the considered population and whether they could be compared in a single trial (i.e. "jointly randomisable").[32]

Heterogeneity, transitivity and coherence belong to the main concepts of network meta-analysis. These concepts are related to each other.[i] There is currently no consensus on how to investigate heterogeneity

[i] In brief, heterogeneity - or the opposite – homogeneity refers to the similarity of studies. The literature usually differs between clinical (e.g. differences in patients, interventions or outcomes), methodological (differences in study designs) and statistical heterogeneity. Statistical heterogeneity is present, if the study results differ more than we would expect by random error alone. However, even if there is high clinical and methodological heterogeneity it does not necessarily lead to statistical heterogeneity. In specific, a set of entirely different studies could have very similar results, even if the studies were too different to compare them in a meta-analysis. On the other hand, statistical heterogeneity does not necessarily mean that the studies were different. Consequently, negative statistical tests for heterogeneity do not allow the conclusion that there is no heterogeneity present, leading to a false sense of security. The transitivity assumption is fulfilled when indirect comparisons between treatments are justified. This requires that the included studies are sufficiently similar in regard to potential effect modifiers. Transitivity cannot be assumed in case there is large heterogeneity between the individual treatments and their trials. If treatments are not jointly randomisable (for instance comparison between treatments for HR positive patients with treatments for HR negative patients), transitivity cannot be

in systematic reviews and authors use a wide range of methods.[37] This issue is especially relevant for network meta-analysis since heterogeneity negatively affects transitivity and consistency. A requirement for the assessment of coherence is the availability of direct as well as indirect evidence, represented as closed loops in the network architecture. Since our treatment network did not meet this requirement, we assessed heterogeneity graphically and by a critical appraisal of study characteristics. We created interactive networks using the R package "visNetwork".[i] The colours of the links (i.e. studies) between the individual nodes (i.e. treatments) indicate whether HRs were proportional and the line type (dashed or solid) indicates whether the definition of endocrine resistant patients applied in the study concerned was consistent with the definition applied in this assessment. The networks were comprehensively discussed by the research team with respect to the comparability and heterogeneity of the included studies (variables that might influence the results, for example). In an iterative process we optimised network connectivity by aggregating several individual treatments into single treatment nodes. Specifically, we aggregated: 1) treatments that were identical except for the presence or absence of a placebo (e.g. LET and placebo+LET);2) FUL 500 mg (continuous) and FUL 500 mg loading dose followed by FUL 250 mg as these two dosing schemes have been shown to be equally efficacious.[38 39]

We conducted NMAs for the outcomes PFS, OS, QoL, discontinuations and AEs grade 3 or worse (AE3+). The frequencies of AEs of any grade were also extracted but could not be used for a meaningful analysis as this frequency was close to 100% in all included study arms.

Table 34 (Appendix) shows which nodes the individual treatments were assigned to and explains the abbreviations of substance names that are used in the graphs and tables. The three AIs (ANA, LET, EXE) have been shown to be equally efficacious and safe and the consulted clinical experts confirmed that they are used interchangeably in Switzerland.[40-42] Thus, we built treatment networks where we aggregated the AIs into one treatment (or one combination partner in a combination treatment) as well as networks where we treated the different AIs separately and conducted analyses in both networks. Since aggregating AIs resulted in improved network connectivity, allowing for more indirect comparisons between the three CDK4/6 inhibitors, we decided to focus the reporting of results on these networks.

Strict inclusion criteria minimised the heterogeneity between the included studies, thereby reducing the risk of inconsistency. Statistical analysis of inconsistency by a node-splitting approach was not possible due to the lack of closed loops. The robustness of our results was assessed by sensitivity analyses.

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assumed. Consistency (or coherence) is the statistical manifestation of transitivity. The results are coherent, if the direct and indirect evidence lead to similar effect estimates. [33-36]

[i] visNetwork: Network Visualization using 'vis.js' Library; available at: https://visjs.org/

We excluded trials from the NMA that focused entirely on premenopausal women. The participants in these studies were not comparable to those of the other studies included as they differed considerably with regard to median patient age and treatments (concomitant treatment with ovarian function suppressing therapies). Creating an artificial connection to the treatment network by ignoring these differences could have biased the overall results of the NMAs. While the majority of the remaining trials included exclusively postmenopausal women, some studied a mixed cohort of pre- and postmenopausal patients. Since the cohorts in these trials have a reduced mean or median age, we used age as a covariate in the network meta-regression. In addition, we analysed how the results differed between the fixed and random effects models and between the networks where AIs were considered as individual treatments or one aggregated treatment node.

To make the extracted data suitable for the NMAs, we condensed the results from individual articles to one record per trial. If multiple articles reported the same outcome for a specific trial, we included the most recent results. If studies reported only p-values instead of confidence intervals (CIs) we calculated an approximate CI.[43] While some studies reported only either general numbers of AEs and discontinuations or numbers of treatment-related AEs and discontinuations, several studies reported both. In these cases, we prioritised the general numbers over the treatment-related numbers. We created a study-specific age variable by calculating a weighted average age using the sample size of the intervention and control groups as the weights. The study-specific age variable was used for sensitivity analyses.

We transferred the HR of PFS, OS and QoL to log HR before pooling the results. Multi-arm trials were treated as previously described.[44] The summary measures for the report at hand were reconverted to HR after the results were pooled. The pooled results of AE3+ and discontinuations are reported as risk ratios.

The NMAs were conducted using Bayesian methods. Analyses were conducted in the gemtc package[i] and rjags[ii]. We used the standard uninformative priors from gemtc for our analyses[iii]. The results are presented as surface under the cumulative ranking curves (SUCRA), forest plots and heat maps. Graphs were created using the tidyverse package[45], igraph[46], ggraph[iv], ggrepel[v] and cowplot[vi].

Model fit was assessed by trace plots, density plots of the posterior effect size estimates and Gelman-Rubin-Brooks plots. Additionally, we assessed whether the potential scale reduction factor (PSRF)

[i] gemtc: network meta-analysis using Bayesian methods; available at: https://CRAN.R-project.org/package=gemtc
[ii] rjags: Bayesian graphical models using MCMC; available at: https://rdrr.io/cran/rjags/
[iii] The heterogeneity settings were as follows: "std.dev", "dunif", 0, "om.scale" The model settings and the description are available at: https://cran.r-project.org/web/packages/gemtc/gemtc.pdf
[iv] ggraph: an implementation of Grammar of Graphics for graphs and networks; available at: https://ggraph.data-imaginist.com/
[v] ggrepel: automatically position non-overlapping text labels with 'ggplot2'; available at: https://rdrr.io/cran/ggrepel/
[vi] cowplot: streamlined plot theme and plot annotations for 'ggplot2'; available at: https://wilkelab.org/cowplot/

reached a value below 1.05. Our calculations used 50,000 adaptions and 1,000,000 iterations with a thinning factor of 100.

We followed the PRISMA guidelines for executing and reporting the NMAs. The PRISMA checklist can be found in the supplement.

7.2 Results effectiveness, efficacy and safety

7.2.1 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 hospitalization or cause prolongation of existing hospitalization (serious adverse events) and those that occur repetitively and the most frequent (highest rate).

Overall, we extracted data from 62 articles for the NMAs. During this process, an additional 21 articles had to be excluded from the analysis. The excluded articles, with exclusion reasons, are listed in Table **27** in the Appendix. The most common exclusion reasons were premenopausal populations (n=6) and separate data on relevant subgroups (e.g. HER2- and no endocrine resistance) not being available (n=5). We also excluded studies on special populations based on specific biomarkers as results from these studies cannot be transferred to the general population defined by our PICOs. The exclusion of these trials did not affect the connectivity between treatments in the decision set. Two trials (BELLE-2 and FALCON) included one HER2+ patient each due to errors in the recruitment process but we did not exclude these trials from the analyses.[47 48] We did not calculate a separate set of NMAs in a network of trials focusing entirely on premenopausal women because this would not have generated any connections between different CDK4/6 inhibitors. The only trial in which an ET+CDK4/6 inhibitor combination was compared with ET monotherapy in an exclusively premenopausal cohort was MONALEESA-7, which is discussed separately in Subsection 7.2.7.

If a study reported results for subgroups that fit either PICO 1 or PICO 2, we included the results from these subgroups. However, such subgroup-specific data were usually only available for selected outcomes (e.g. PFS, OS), with the effect that other data (e.g. age, discontinuations, adverse events) from these studies are missing.

We extracted data from 56 NRSs, encompassing 25 cohort studies and 31 case studies.

The characteristics extracted from the relevant ongoing trials are presented in Table **26** in Appendix 15.3. Sixty-seven ongoing trials were identified that might provide additional data in the future on any of the treatments compared in the present assessment of clinical effectiveness and safety; twenty-four of these include a CDK4/6 inhibitor in one or more treatment arms.

7.2.2 PRISMA flow diagrams

Table 57 in Appendix 15.7.5 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 removing duplicates in Endnote, 8’894 hits remained. Figure 2 shows the PRISMA flow chart for RCTs in the NMAs for efficacy and safety.

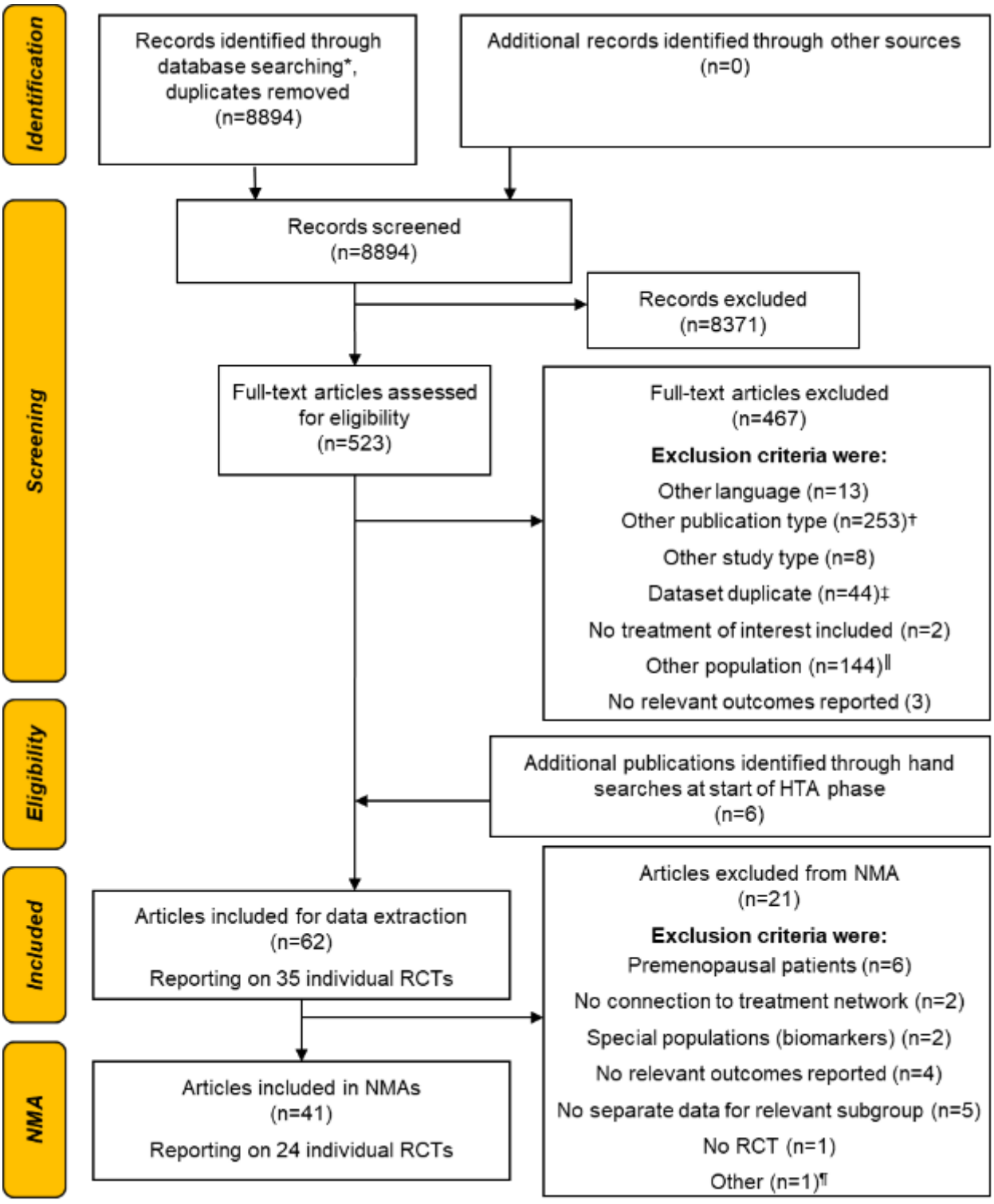


Figure 2: PRISMA flow diagram for RCTs analysed in the NMAs

* literature search for RCTs
† publications other than complete primary articles, for example: conference abstracts (except for conference abstracts reporting on included PALOMA, MONALEESA and MONARCH 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
‖ includes 14 publications (reporting on 11 RCTs with cohorts with mixed HER2 status) that were included in the scoping report on the condition that supplementary data could be obtained from the study authors during the HTA report and where additional data could not be obtained

¶ Beck et al. 2019 report on three different RCTs; their publication was excluded for various reasons (see Table 27 in Appendix 15.3).

Table 58, Table 59 and Table 60 in Appendices 15.8.8, 15.9.4 and 15.10.4 respectively show the number of hits retrieved through the systematic searches described in Subsections 7.1.1.1 and 7.1.1.2. in MEDLINE, EMBASE, The Cochrane Library, TRIP database, CRD and Scopus. After removing duplicates in Endnote, 2'040 hits remained. Figure 3 shows the PRISMA flow chart for NRSs for the extended safety assessment of PAL, RIB and ABE.

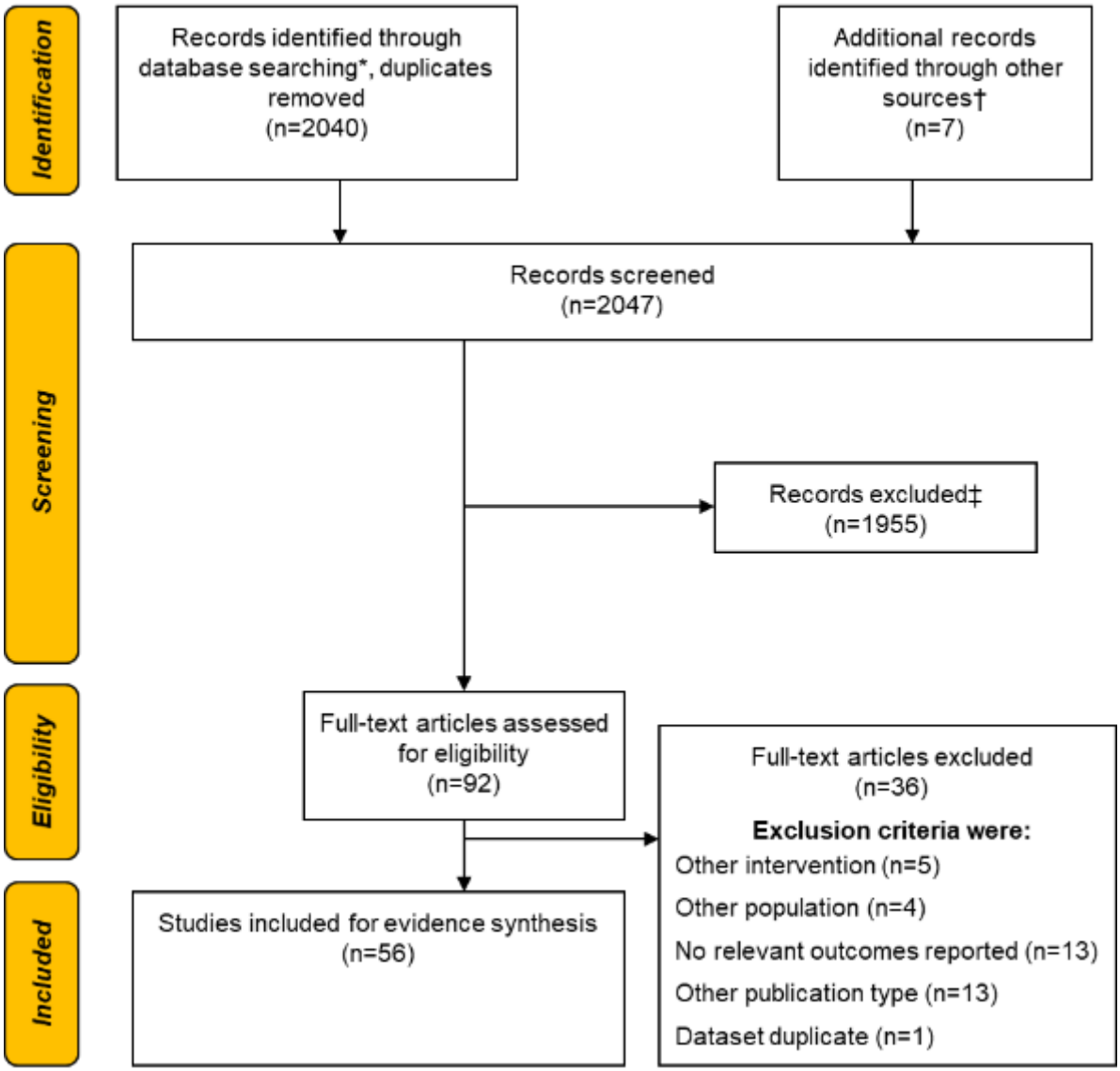


Figure 3: PRISMA flow diagram for NRSs analysed in the extended SAF assessment

* literature searches for NRSs
† literature search for RCTs
‡ either excluded overall or selected for other domains

7.2.3 Evidence tables

7.2.3.1 RCTs

Table 8 and **Table 9** depict the main characteristics of the included RCTs.

Table 8: RCTs included in the NMAs for PICO 1

Trial	Author, Year	Treatment*	n (pts.)†	Outcomes (statistics)	Sponsor	MP status	Endocrine resistance‡
NCT00721409 PALOMA-1	Finn et al. 2015[49] Finn et al. 2017[50]	LET	32	OS (Cox proportional hazards) PFS (Cox proportional hazards) Disc	Pfizer	post	matched
		PAL + LET	34				
NCT01740427 PALOMA-2	Finn et al. 2016[51] Rugo et al. 2018[52] Rugo et al. 2019[53] Dieras et al. 2019[54]	pbo + LET	222	QoL (FACT-B total) PFS (Cox proportional hazards) AE3+ Disc	Pfizer	post	matched
		PAL + LET	444				
NCT01958021 MONALEESA-2	Hortobagyi et al. 2016[55] Verma et al. 2017[56] Hortobagyi et al. 2018[57] Verma et al. 2018[58] Janni et al. 2018[59] Beck et al. 2019[60]	pbo + LET	334	OS (Cox proportional hazards) QoL (EORTC QLQ-C30 - global, linear effect model) PFS (Cox proportional hazards) AE3+ Disc	Novartis	post	matched
		RIB + LET	334				
NCT02422615 MONALEESA-3	Slamon et al. 2018[61] Slamon et al. 2019[62] Beck et al. 2019[60]	pbo + FUL	128	OS (Cox proportional hazards) PFS (Cox proportional hazards) Disc	Novartis	post	deviation
		RIB + FUL	237				
NCT01602380 FALCON	Roberston et al. 2016[48] Roberston et al. 2018[63]	pbo + FUL	230	QoL (FACT-B total, Kaplan-Meier) PFS (Kaplan-Meier) AE3+ Disc	AstraZeneca	post	matched
		pbo + ANA	232				
Johnston 2009	Johnston et al. 2009[64]	pbo + LET	unclear§	PFS (Kaplan-Meier)		post	deviation

		LAP + LET	unclear§		GSK NHS		
NCT00696072	Paul et al. 2019[65]	LET	63	PFS (Kaplan-Meier) Disc	BMS	post	matched
		DAS + LET	57				
NCT00770354	Ibrahim et al. 2011[66]	LET	54	PFS (Cox proportional hazards) AE3+ Disc	Antisoma	post	matched
		AS1402 + LET	56				
NCT01151215 MINT	Johnston et al. 2016[67]	pbo + ANA	121	PFS (unclear) AE3+	Astra-Zeneca	post	matched
		AZD8931 20 mg + ANA	118				
		AZD8931 40 mg + ANA	120				
NCT02763566 MONARCHplus	Jiang et al. 2019[68]	pbo + ANA/LET	99	PFS (unclear) AE3+	Eli Lilly	post	deviation
		ABE + ANA/LET	207				
NCT02246621 MONARCH 3	Johnston et al. 2019[69]	pbo + ANA/LET	165	PFS (Cox proportional hazards) AE3+ Disc	Eli Lilly	post	matched
		ABE + ANA/LET	328				

ABE=abemaciclib; AEs=adverse events; ANA=anastrozole; BMS=Bristol-Myers Squibb; DAS=dasatinib; Disc.=discontinuations; EORTC=European Organisation for Research and Treatment of Cancer; FACT-B=Functional Assessment of Cancer Therapy - Breast Cancer; FUL=fulvestrant; GSK=GlaxoSmithKline; LAP=lapatinib; LET=letrozole; MP=menopause; NHS=national health service (UK); OS=overall survival; PAL=palbociclib; pbo=placebo; PFS=progression-free survival; QoL=quality of life; RIB=ribociclib

* If not otherwise indicated, the medications were dosed according to the label.
† Patient numbers refer to the individual subgroups that were used in the analysis (e.g. HER2- or endocrine resistance).
‡ "matched" if definition of endocrine resistance is identical to definition in PICO, "deviation" if, for instance, a different timespan since last ET was used.
§ Patient number in subgroup not reported.

Table 9: RCTs included in the NMAs for PICO 2

Trial	Author, Year	Treatment*	n (pts.)†	Outcomes (statistics)	Sponsor	MP status	Endocrine resistance‡
NCT01942135 PALOMA-3	Cristofanilli et al. 2016[70] Verma et al. 2016[71] Harbeck et al. 2016[72] Cristofanilli et al. 2018[73] Turner et al. 2018[74]	pbo + FUL	174	OS (Cox proportional hazards) EORTC (QLQ-C30 - global) PFS (Cox proportional hazards) AE3+ Disc	Pfizer	mixed	matched
		PAL + FUL	347				
NCT02422615 MONALEESA-3	Slamon et al. 2018[61] Slamon et al. 2019[62] Beck et al. 2019[60]	pbo + FUL	109	OS (Cox proportional hazards) PFS (Cox proportional hazards)	Novartis	post	deviation
		RIB + FUL	237				

NCT02107703 MONARCH 2	Sledge et al. 2017[75] Sledge et al. 2019[76] Kaufmann et al. 2019[77]	pbo + FUL	223	OS (Cox proportional hazards) QoL (EORTC QLQ-C30 - global, Cox proportional hazards) PFS (Cox proportional hazards) AE3+ Disc	Eli Lilly	mixed	matched
		ABE + FUL	446				
NCT00863655 BOLERO-2	Burris et al. 2013[78] Yardley et al. 2013[79] Piccart et al. 2014[80]	pbo + EXE	239	OS (Cox proportional hazards) QoL (EORTC QLQ-C30 - global, Cox proportional hazards) PFS (unclear) AE3+ Disc	Novartis	post	matched
		EVE + EXE	485				
NCT01610284 BELLE-2	Baselga et al. 2017[81] Campone et al. 2018[47]	pbo + FUL	571	OS (Cox proportional hazards) PFS (Cox proportional hazards) AE3+ Disc	Novartis	post	matched
		BUP + FUL	576				
NCT01633060 BELLE-3	Di Leo et al. 2018[82]	pbo + FUL	143	PFS (Cox proportional hazards) AE3+ Disc	Novartis	post	deviation
		BUP + FUL	289				
NCT01234857	Baselga et al. 2017[83]	EXE	33	OS (Cox proportional hazards) PFS (Cox proportional hazards) AE3+ Disc	Merck	post	deviation
		RID + DAL	29				
Johnston 2009	Johnston et al. 2009[64]	pbo + LET	unclear	PFS (Kaplan-Meier)	GSK NHS	post	deviation
		LAP + LET	unclear				
NCT00944918 NCT00253422 SoFEA	Johnston et al. 2013[84]	pbo + FUL 500/250 mg[§]	141	OS (Cox proportional hazards) PFS (Cox proportional hazards)	Astra-Zeneca NHS ICR	post	matched
		ANA + FUL 500/250 mg[§]	122				
		EXE	142				
NCT01142401	Adelson et al. 2016[85]	FUL	59	PFS (Kaplan-Meier; Greenwood's formulae) Disc	NCI	post	deviation
		BOR + FUL	59				

NCT01437566 FERGI	Krop et al. 2016[86]	pbo + FUL	79	PFS (Cox proportional hazards) AE3+ Disc	Roche	post	deviation
		PIC + FUL	89				
NCT01528345 Musolino 2017	Musolino et al. 2017[87]	pbo + FUL	50	OS (Kaplan-Meier) PFS (Cox proportional hazards) AE3+ Disc	Novartis	post	matched
		DOV + FUL	47				
NCT02216786 MANTA	Schmid et al. 2019[88]	FUL	67	OS (Cox proportional hazards) PFS (Cox proportional hazards) Disc	Astra-Zeneca NIHR CRUK	post	matched
		VIS 50 mg daily + FUL	103				
		VIS 125 mg intermittent + FUL	98				
		EVE + FUL	65				
NCT02482753	Jiang et al. 2019[68]	pbo + EXE	121	PFS (Cox proportional hazards) AE3+ Disc	Chipscreen	post	deviation
		TUC + EXE	244				
NCT01992952 FAKTION	Jones et al. 2020[89]	pbo + FUL	71	OS (Cox proportional hazards) PFS (Cox proportional hazards) AE3+ Disc	Astra-Zeneca NCRN	post	matched
		CAP + FUL	69				
NCT02763566 MONARCHplus	Jiang et al. 2019[68]	pbo + FUL 500/250 mg§	53	PFS (unclear)	Eli Lilly	post	deviation
		ABE + FUL 500/250 mg§	104				

ABE=abemaciclib; AEs=adverse events; ANA=anastrozole; BOR=bortesimib; BUP=buparlisib; CAP=Capivasertib; CRUK=Cancer Research UK; DAL=dalotuzumab; Disc.=discontinuations; DOV=dovitinib; EORTC=European Organisation for Research and Treatment of Cancer; EVE=everolimus; EXE=exemestane; FACT-B=Functional Assessment of Cancer Therapy - Breast Cancer; FUL=fulvestrant; GSK=GlaxoSmithKline; LAP=lapatinib; MP=menopause; NCI=national cancer institute (US); NCRN=National Cancer Research Network (UK); NIHR=National Institute for Health Research (UK); NHS=national health service (UK); OS=overall survival; PAL=palbociclib; pbo=placebo; PIC=pictilisib; PFS=progression-free survival; QoL=quality of life; RIB=ribociclib; RID=ridaforolimus; TUC=tucinostat; VIS=vistusertib

* If not otherwise indicated, the medications were dosed according to the label.
† Patient numbers refer to the individual subgroups that were used in the analysis (e.g. HER2- or endocrine resistance).
‡ "matched" if definition of endocrine resistance is identical to definition in PICO, "deviation" if, for instance, a different timespan since last ET was used.
§ 500 mg loading dose, then 250 mg each cycle.

7.2.3.2 NRSs

Table 10 and Table 11 depict the main characteristics of the included studies.

Table 10: Cohort studies included in the extended SAF assessment

						COI with†			
Author Year	**Study design**	**n (pts.)‖**	**Intervention(s)**	**Relevant outcomes**	**Sponsor***	**Pfizer**	**Novartis**	**Lilly**	**Country**
Ban et al. 2018[90]	retr. cohort	24	PAL +/- AI	various AEs	Pfizer (drug)‡	no	no	no	HR
Battisti et al. 2019[91]	retr. cohort	118	PAL + ET	various AEs	Pfizer (drug)‡	yes	yes	yes	GB
Bui et al. 2019[92]	retr. cohort	46	PAL + ET	various AEs	none	no	no	no	NL
Clifton et al. 2019[93]	retr. cohort	605	PAL + ET	haematological AEs	none	yes	yes	no	US
Demir et al. 2020[94]	retr. cohort	43	PAL + ET	various AEs	none	no	no	no	TR
du Rusquec et al. 2018[95]	prosp. cohort	60	PAL + FUL	various AEs	none	yes	no	no	FR
Herrscher et al. 2019[96]	retr. cohort	77	PAL + FUL	various AEs	n.disc.	yes	no	no	FR
Iwamoto et al. 2018[97]	retr. cohort	26	PAL + ET	various AEs	n.disc.	n.disc.	n.disc.	n.disc.	JP
Kikuchi et al. 2019[98]	retr. cohort	35	PAL + ET	various AEs	none	no	no	no	JP
Kish et al. 2018[99]	retr. cohort	299	PAL + LET	neutropenia	Pfizer	yes	no	no	US

Masuda et al. 2018[100]	retr. cohort	42	PAL + LET	various AEs	Pfizer	yes	yes	yes	JP
Maurer et al. 2018[101]	retr. cohort	34	PAL + ET	various AEs	Pfizer (drug)‡	yes	no	no	BE
Mendes et al. 2020[102]	prosp. cohort	4	PAL + ET	neutropenia	none	no	no	no	PT
Nigro et al. 2020[103]	retr. cohort	22	PAL + AI	various AEs	n.disc.	no	no	no	IT
Pizzuti et al. 2019[104]	retr. cohort	423	PAL + ET	various AEs	n.disc.	no	no	no	IT
Schickli et al. 2019[105]	retr. cohort	53	PAL + LET	haematological AEs	none	yes	yes	no	US
Stearns et al. 2018[106]	retr. cohort	334	PAL + LET	various AEs	Pfizer	yes	yes	yes	US/CA
Tamura et al. 2016[107]	retr. cohort	6	PAL + LET	various AEs	Pfizer	yes	yes	yes	JP
Varella et al. 2019[108]	retr. cohort	411	PAL + ET	various AEs	n.disc.	no	yes	no	US
Watson et al. 2019[109]	retr. cohort	64	PAL + ET	various AEs	n.disc.	no	no	no	IE
Wilkie et al. 2019[110]	retr. cohort	70	PAL + AI	neutropenia	n.disc.	yes	yes	no	US
Xi et al. 2019[111]	retr. cohort	200	PAL + ET	various AEs	n.disc.	yes	yes	yes	US
Dickler et al. 2017[112]	single arm	132§	ABE	various AEs	Lilly	yes	yes	yes	BE/FR/ES/US
Patnaik et al. 2016[113]	single arm	19	ABE + FUL	various AEs	Lilly	yes	no	yes	n.decl.
Gervaso et al. 2020[114]	retr. cohort	424 PAL: 390 RIB: 4 ABE:3 mixed: 27	PAL/RIB/ABE + ET	various AEs	n.disc.	no	no	no	US

ABE=abemaciclib; AEs=adverse events; AI=aromatase inhibitor; COI=conflict of interest; ET=endocrine therapy; FUL=fulvestrant; LET=letrozole; n.decl.=not declared; n.disc.=not disclosed; PAL=palbociclib; prosp.=prospective; retr.=retrospective; RIB=ribociclib

* 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, when receiving consultation fees or serving on advisory boards. As the publications listed in this table pertain to safety data on PAL, we extracted declared COIs 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 a COI was provided in the publication.
‡ CDK4/6 inhibitor was provided free of charge.
§ for laboratory abnormalities n=130; for thrombocyte count n=128.
‖ Refers to the number of MBC patients treated with a CDK4/6 inhibitor for whom AEs were reported. The total number of patients in the actual study may be larger.

Table 11: Case studies included in the extended SAF assessment

Author Year	Design	n (pts.)	Intervention(s)	Reported AEs	Sponsor*	COI with†			Country
						Pfizer	Novartis	Lilly	
Bromberg et al. 2016[115]	CS	2	PAL + LET	hyperuricemia	n.disc.	n.disc.	n.disc.	n.disc.	US
Dhanushkodi et al. 2019[116]	CR	1	PAL + TAM	refractory bone marrow involvement, cytopenia	none	no	no	no	IN
Felip et al. 2019[117]	CR	1	PAL + LET + ZOL	pneumonitis	none	yes	yes	yes	ES
Gao et al. 2015[118]	CR	1	PAL + LET	G3 febrile neutropenia, shortness of breath	Pfizer (drug)‡	yes	no	no	US
Gowarty et al. 2019[119]	CR	1	PAL + LET + VER	adverse drug interaction: increased PAL levels due to VER febrile neutropenia periorbital oedema G3 stomatitis G3 AST elevation G2 ALT elevation	none	no	no	no	US
Guillaume et al. 2020[120]	CR	1	PAL + EXE	severe cellular immunodeficiency, reactivation of multiple latent viruses, pneumocystis pneumonia	n.disc.	no	no	no	FR
Guillemois et al. 2018[121]	CR	1	PAL + FUL	cutaneous and gastrointestinal leukocytoclastic vasculitis	n.disc.	no	no	no	FR
Harrold et al. 2019[122]	CR	1	PAL + FUL	posterior reversible encephalopathy syndrome	n.disc.	no	no	no	IE
Jazieh et al. 2019[123]	CR	1	PAL + FUL	drug-induced pneumonitis	none	no	no	no	US

Karagounis et al. 2018[124]	CR	1	PAL + FUL	Stevens-Johnson syndrome	none	no	no	no	US
Kawamoto et al. 2019[125]	CR	1	PAL + RT	radiosensitising effect: acute radiation-induced enterocolitis	n.disc.	no	no	no	JP
Messer et al. 2019[126]	CR	1	PAL + RT	radiosensitising effect: radiation-induced dermatitis and esophagitis	none	no	no	no	US
Momper et al. 2019[127]	CR	1	PAL + LET + CYC	adverse drug interaction: increased CYC levels due to PAL	none	no	no	no	US
Nelson et al. 2017[128]	CR	1	PAL + FUL + ATO	adverse drug interaction: increased plasma levels of ATO due to PAL necrotising rhabdomyolsis	none	no	no	no	US
Nersesjan et al. 2019[129]	CR	1	PAL + FUL + SIM	adverse drug interaction: increased plasma levels of SIM due to PAL severe rhabdomyolisis	none	no	no	no	DK
Nwabudike et al. 2018[130]	CR	1	PAL + FUL	aplastic anaemia	n.disc.	no	no	no	US
Orlandi et al. 2019[131]	CS	4	PAL (150/100 mg) + FUL	myelotoxicity	n.disc.	no	no	no	IT
Palleschi et al. 2020[132]	CR	1	PAL + LET	burning tongue, glossodynia	n.disc.	no	yes	yes	IT
Park et al. 2020[133]	CR	1	PAL (150 mg) + LET	acute lymphoblastic leukaemia	n.disc.	no	no	no	KR
Pinard et al. 2018[134]	CR	1	PAL + FUL	subacute cutaneous lupus erythematosus	none	yes	yes	yes	US
Raiss et al. 2018[135]	CR	1	PAL + FUL	thrombotic microangiopathy	none	no	no	no	MA
Roberts et al. 2018[136]	CR	1	PAL + FUL	elevated LFTs	n.disc.	no	no	no	US
Stoffaës et al. 2020[137]	CR	1	PAL + ANA + DEN	sarcoidosis-like reaction	n.disc.	n.disc.	n.disc.	n.disc.	FR
Vuppalanchi et al. 2017[138]	CS	2	PAL + LET	hepatic failure and liver-related death, pseudocirrhosis and non-cirrhotic portal hypertension	n.disc.	yes	no	no	US
Awidi et al. 2019[139]	CS	4	RIB + LET	Glanzmann thrombasthaenia-like picture	Novartis (drug)‡	no	no	no	JO

Bozkaya et al. 2020[140]	CR	1	RIB + LET + ZOL	toxic epidermal necrolysis	n.disc.	n.disc.	n.disc.	n.disc.	TR
Farhat et al. 2020[141]	CR	1	RIB + LET + ZOL	G3/G4 elevated LFTs	n.disc.	no	no	no	n.decl.
Meattini et al. 2018[142]	CS	5	RIB + LET	neutropenia, diarrhoea, vomiting	n.disc.	no	no	no	IT
Rudlowsk et al. 2019[143]	CR	1	RIB + LET	severe neutropenia, mild persistent arthralgia and myalgia	none	no	yes	no	DE
Widmer et al. 2018[144]	CR	1	RIB	Stevens-Johnson Syndrome	n.disc.	n.disc.	n.disc.	n.disc.	US
Wilson et al. 2019[145]	CS	32 (1 male)	RIB + AI	elevated creatinine levels	none	no	no	no	AU

ABE=abemaciclib; AEs=adverse events; AI=aromatase inhibitor; ALT=alanine transaminase; ANA=anastrozole; AST=aspartate transaminase; ATO=atorvastatin; COI=conflict of interest; CR=case report; CS=case series; CYC=cyclosporine; DEN=denosumab; EXE=exemestane; FUL=fulvestrant; G2=grade 2; G3=grade 3; LET=letrozole; mg=milligram; LFTs=liver function tests; n.decl.=not declared; n.disc.=not disclosed; PAL=palbociclib; prosp.=prospective; RT=radiotherapy; retr.=retrospective; RIB=ribociclib; SIM=simvastatin; VER=verapamil; ZOL=zolendronic acid

* 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, when receiving consultation fees or serving on advisory boards. As the publications listed in this table pertain to safety data on PAL, we extracted declared COIs 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 a COI was provided in the publication.
‡ CDK4/6 inhibitor was provided free of charge.

7.2.3.3 Risk of bias assessment

Table 28 to Table 31 in Appendix 15.3 show the detailed RoB assessment for the included RCTs.

For PFS and OS, the trials investigating CDK4/6 inhibitors have a low RoB. For PALOMA-1 we could not assess whether the data was analysed in accordance with a prespecified protocol since no trial protocol is available, resulting in a “some concerns” rating. For the same reason more than half of the other trials were also rated as having “some concerns”. Three trials have a high RoB due to issues with the randomisation process or deviations from intended interventions.

For AEs, almost all of the trials, including the trials investigating CDK4/6 inhibitors (with the exception of MONALEESA-7) were rated as having “some concerns” because they only reported AEs with an incidence above a certain threshold, which was not prespecified in the trial protocols.

For QoL, PALOMA-2 is the only trial with a low RoB. PALOMA-3 and MONARCH 2 were rated as having “some concerns” because they did not analyse the intention-to-treat population, MONALEESA-2 was rated as having “some concerns” because there is no information on whether data was available for all or almost all of the patients and MONALEESA-7 was rated with a high RoB because data were not available for all or almost all of the patients.

Table 32 in Appendix 15.3 shows the detailed RoB assessment for the included observational studies. Out of the 25 studies we assessed, 7 fulfilled quality criterion (i), 18 fulfilled quality criterion (ii) and 24 fulfilled quality criterion (iii). Only five of the studies fulfilled all three quality criteria.

7.2.4 Findings efficacy

The published clinical trials report an OS benefit for ABE in PICO 2 and for RIB in PICO 1 (in an exclusively premenopausal patient cohort, see Subchapter 7.2.7), while OS results for the other CDK4/6 inhibitors (or other PICO, respectively) are either not yet available or did not reach the pre-defined statistical significancy threshold. Similarly, for QoL, a benefit above the pre-defined statistical significance threshold has so far been reported only for PAL in PICO 2 and RIB in PICO 1 (in an exclusively premenopausal patient cohort, see Subchapter 7.2.7). All three CDK4/6 inhibitors showed a statistically significant PFS benefit in both PICOs.

In the following, we present findings from our NMAs concerning the two critical outcomes OS and QoL. The NMA findings concerning PFS are presented in Appendix 15.1.

7.2.4.1 NMAs PICO 1

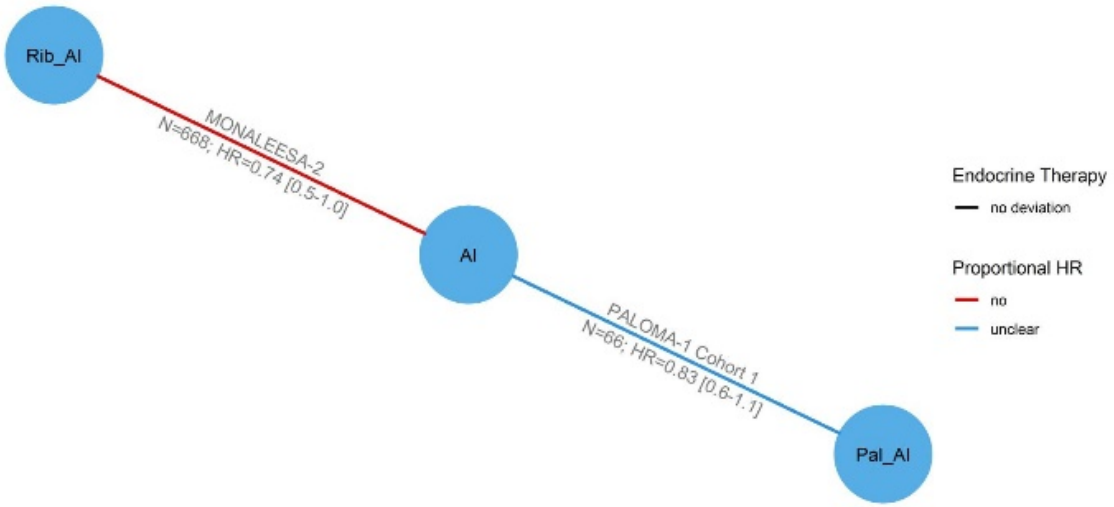
7.2.4.1.1 Overall survival (OS)

Network characteristics:

The network on OS led to two connected trials that matched our inclusion criteria (Figure 4). Both trials used AI as a comparator. The mean or median age per study arm ranged from 62 to 64 years. The most recent articles on these trials were published in 2017 and 2019, respectively.

The Kaplan-Meier plot for MONALEESA-2 showed a tendency for non-proportional hazards. No Kaplan-Meier plot was available for PALOMA-1. The definition of endocrine resistance matched our criteria in both studies. Not aggregating the individual AIs did not change the treatment network since both treatments were compared with LET.

Figure 4: PICO 1 treatment network for OS



Comparative efficacy:

The SUCRA and forest plots show a tendency for improved OS for with either PAL+AI or RIB+AI compared with AI monotherapy. The respective probabilities for each treatment to rank highest are indicated in Figure 5, Table 35 (Appendix) shows the probabilities for each rank for each treatment. The detailed results of the comparisons between all treatments are provided in the heat map (Figure 6).

The random effects model shows comparable results with larger credibility intervals for the individual treatments (Appendix, Figure 52). The results remained stable in the other sensitivity analyses (Appendix, Figure 53 and Figure 54).

Figure 5: PICO 1 SUCRA and forest plots for OS; fixed effect model

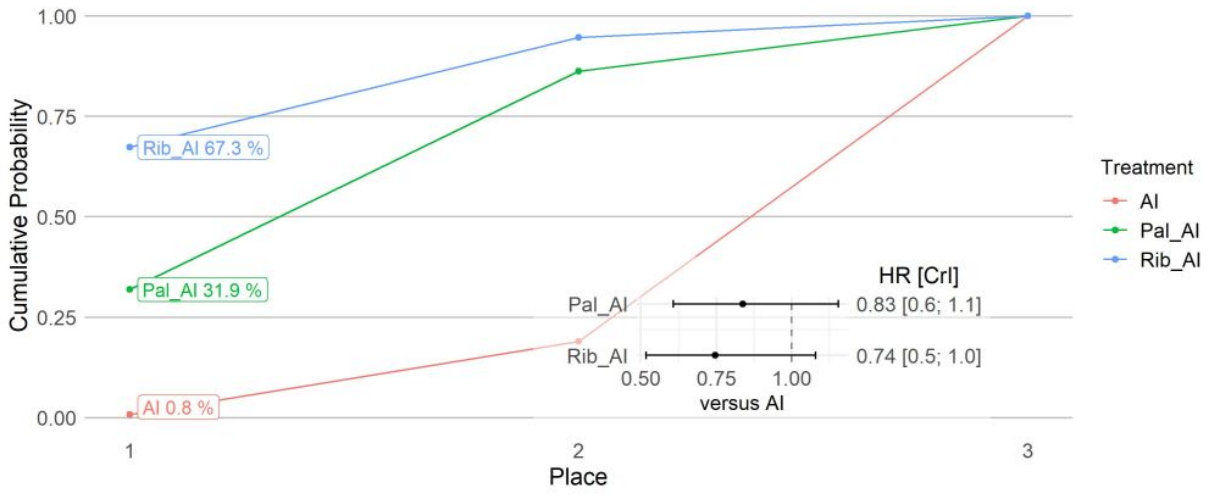
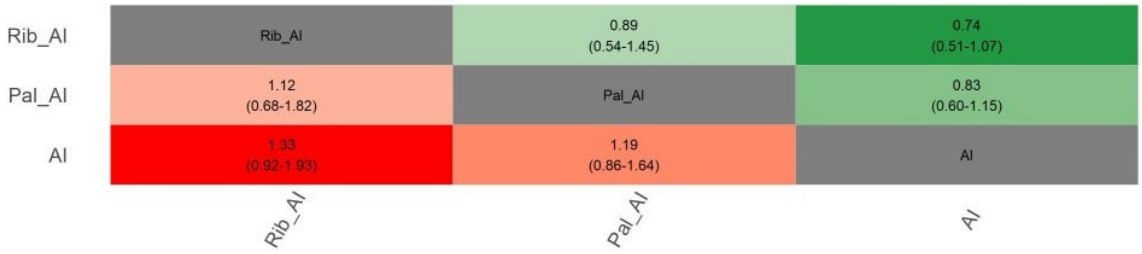


Figure 6: PICO 1 heat map for OS; fixed effect model



Hazard ratios are indicated for treatments on Y-axis versus treatments on X-axis. Green fields indicate superiority of treatments on Y-axis, red fields inferiority of treatments on Y-axis.

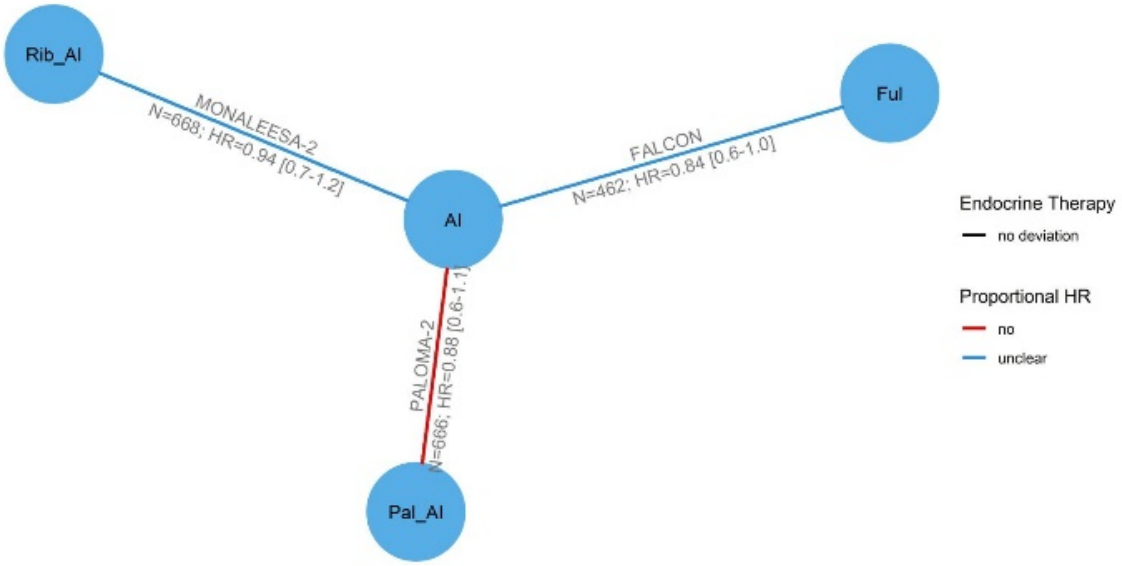
7.2.4.1.2 Quality of life (QoL)

Network characteristics:

Three trials reported results on QoL, leading to four individual treatments in our network (Figure 7). All treatments were compared with AI. For each comparison only one trial was available. The mean or median age per study arm ranged from 61 to 64 years. The most recent results were published in 2018 and 2019.

PALOMA-2 showed a tendency for non-proportional HRs while Kaplan-Meier curves were not available for MONALEESA-2 and FALCON. Two studies used a different definition of endocrine resistance or did not provide enough data to assess whether their definition matched ours. Not aggregating the individual AIs led to a smaller network with three treatments and two trials (Appendix, Figure 56). FUL dropped out of the network.

Figure 7: PICO 1 treatment network for QoL



Comparative efficacy:

The SUCRA and forest plots show a tendency for improved QoL with either PAL+AI or RIB+AI compared with AI. The respective probabilities for each treatment to rank highest are indicated in Figure 8, Table **35** (Appendix) shows the probabilities for each rank for each treatment. The detailed results of the comparisons between all treatments are provided in the heat map (Figure 9).

In the network with the individual AIs, the results remained stable with a tendency for a better efficacy for the CDK4/6 inhibitors (Appendix, Figure 55).

The random effects model shows comparable results with larger credibility intervals for the individual treatments (Appendix, Figure 57). The inclusion of age as a predictor in the network meta-regression led to similar results (Appendix, Figure 58 and Figure 59).

Figure 8: PICO 1 SUCRA and forest plots for QoL; fixed effect model

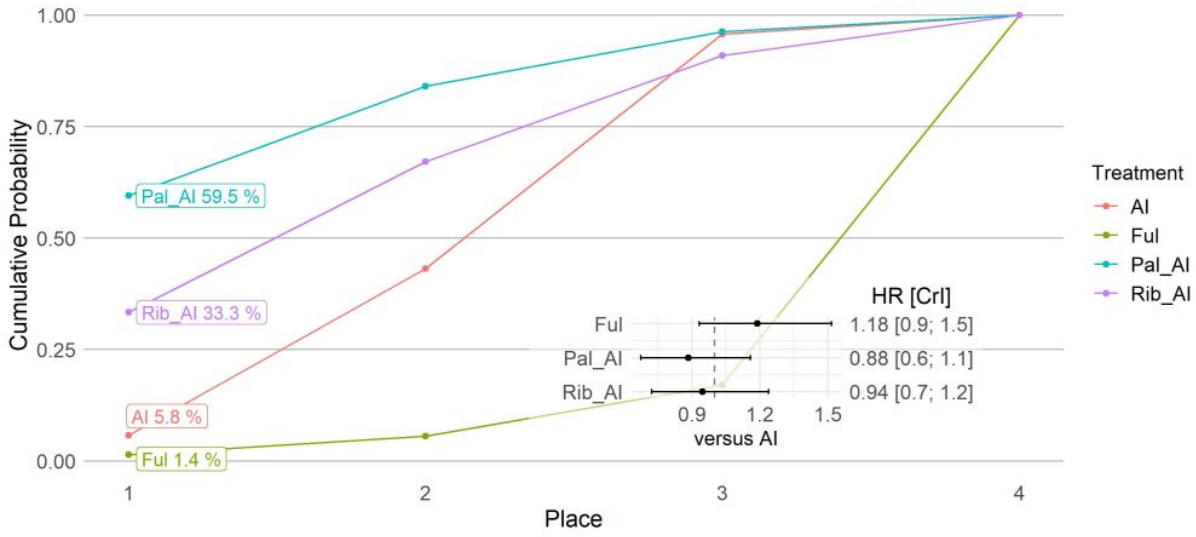
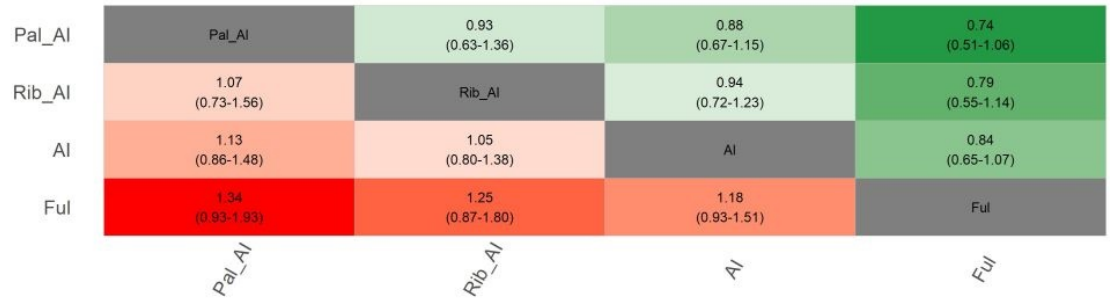


Figure 9: PICO 1 heat map for QoL; fixed effect model



Hazard ratios are indicated for treatments on Y-axis versus treatments on X-axis. Green fields indicate superiority of treatments on Y-axis, red fields inferiority of treatments on Y-axis.

7.2.4.2 NMAs PICO 2

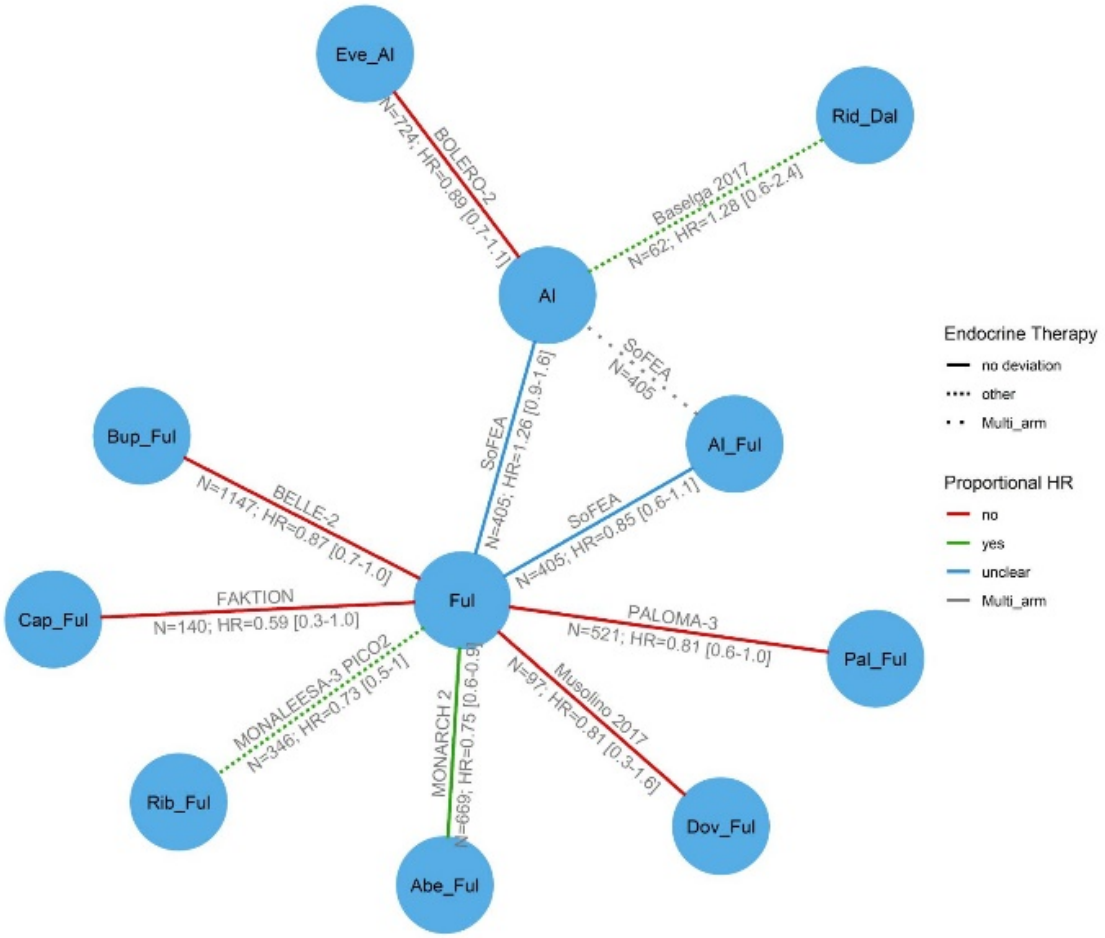
7.2.4.2.1 Overall survival (OS)

Network characteristics:

The OS treatment network for PICO 2 led to 9 connected trials comparing 11 treatments. All treatments were compared with FUL apart from EVE+AI and RID+DAL, which were compared with AI. The mean or median age per study arm ranged from 62 to 64 years. The most recent results from these trials were published between 2013 and 2020 (Figure 10).

Five Kaplan-Meier curves showed signs of non-proportional HRs. Three Kaplan-Meier curves were proportional. Two trials used a different definition of endocrine resistance than we did. Not aggregating the individual AIs did not change the treatment network.

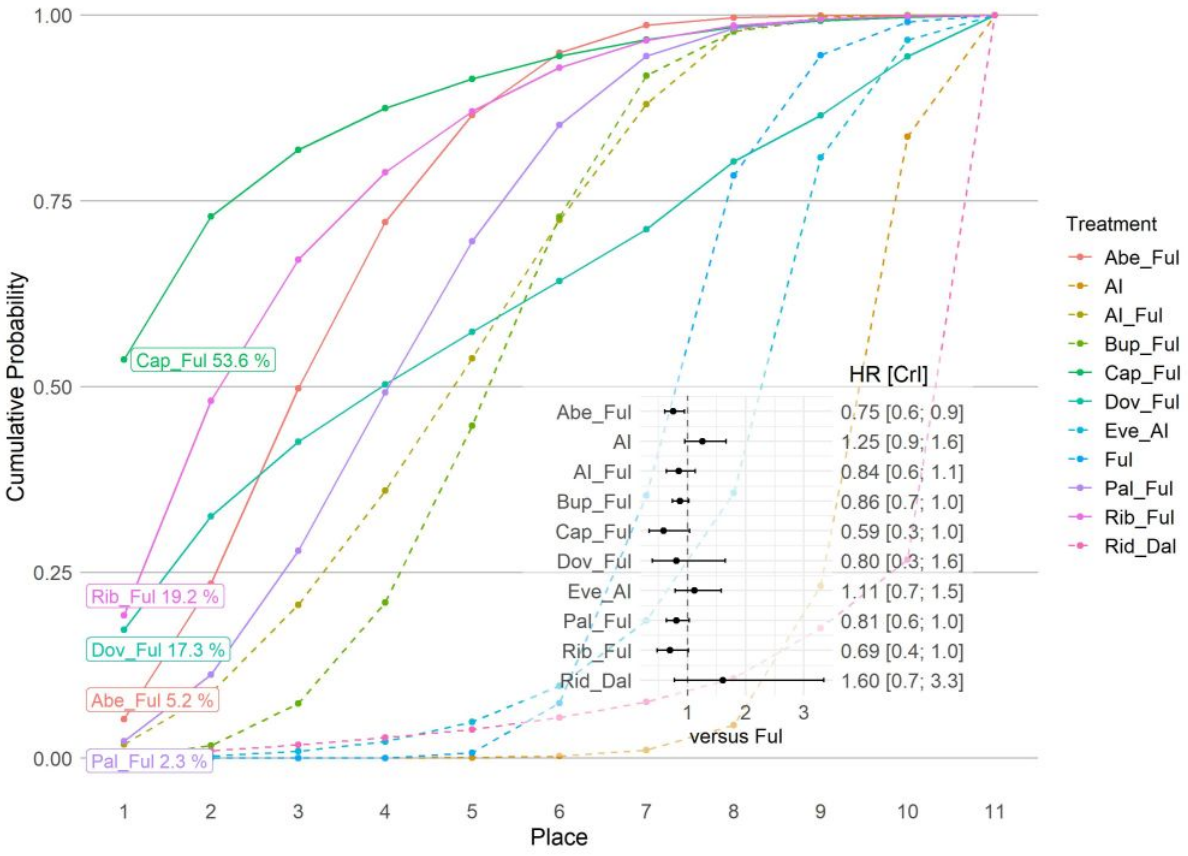
Figure 10: PICO 2 treatment network for OS



Comparative efficacy:

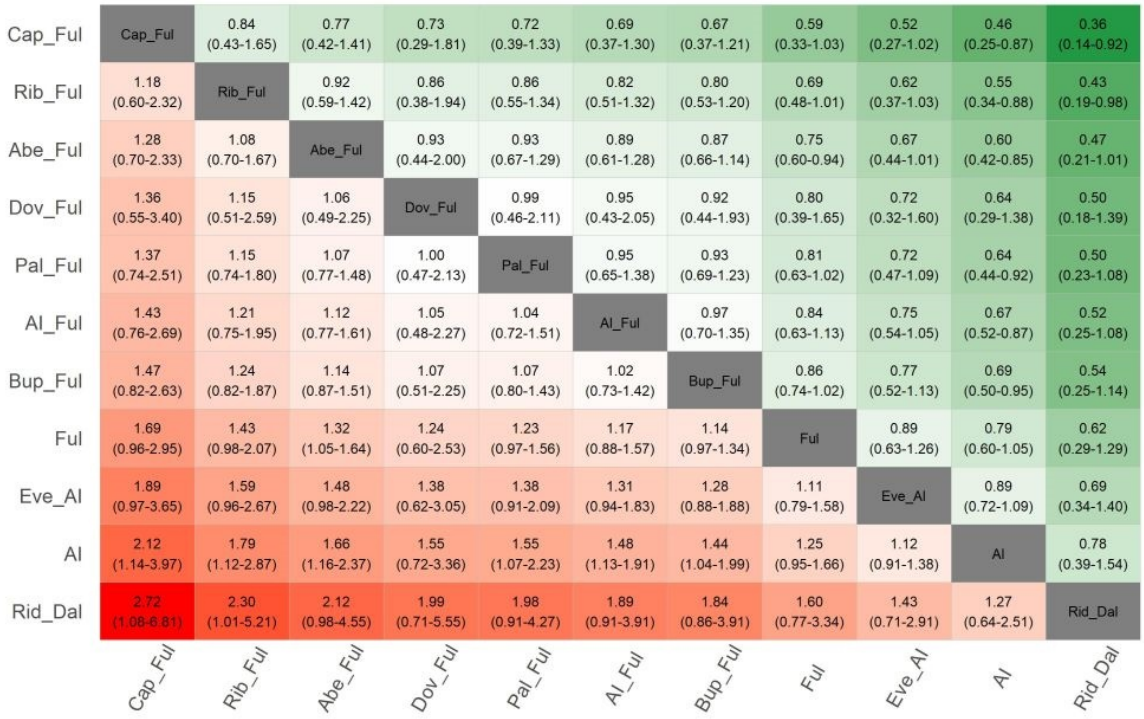
The SUCRA and forest plots show a tendency for improved OS with either one of the CDK4/6 inhibitors combined with FUL compared with FUL monotherapy. For the CDK4/6 inhibitors, the probability of ranking place five or better out of the eleven compared treatments ranged from 70% (PAL) to 87% (RIB and ABE) (Figure 11) compared to 1% for FUL monotherapy. Table 36 (Appendix) shows the probabilities for each rank for each treatment. The detailed results of the comparisons between all treatments are provided in the heat map (Figure 12).

Figure 11: PICO 2 SUCRA and forest plots for OS; fixed effect model



The random effects model again resulted in reduced certainty and larger credibility intervals for the individual treatments. The curves for most treatments were similar apart from FUL, EVE+AI, RID+DAL and AI, which showed the worst results (Appendix, Figure 76). The network meta-regressions led to comparable results (Appendix, Figure 75 and Figure 77).

Figure 12: PICO 2 heat map for OS; fixed effect model



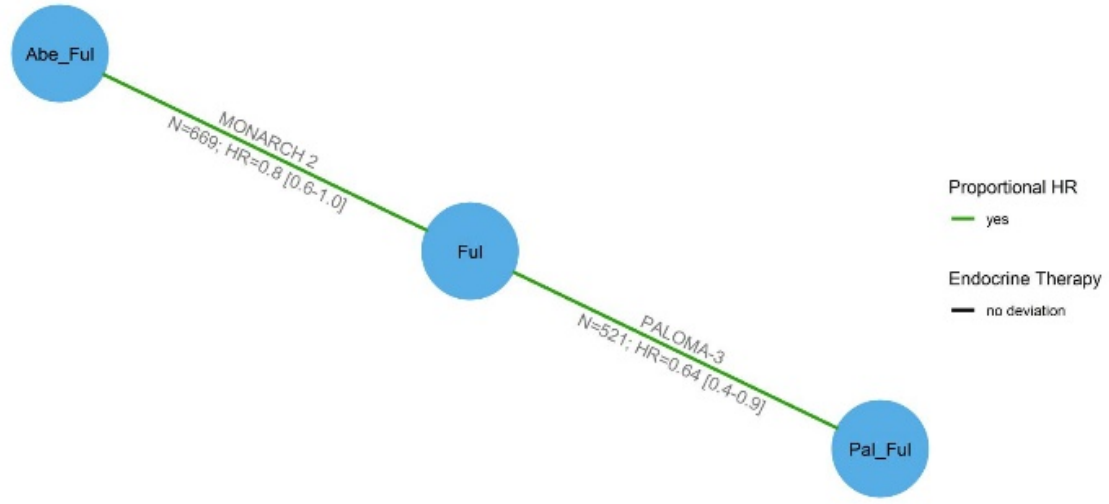
Hazard ratios are indicated for treatments on Y-axis versus treatments on X-axis. Green fields indicate superiority of treatments on Y-axis, red fields inferiority of treatments on Y-axis.

7.2.4.2.2 Quality of life (QoL)

Network characteristics:

Two trials (MONARCH 2 and PALOMA-3) reported results on QoL, leading to three individual treatments in our network (Figure 13). All treatments were compared with FUL. For each comparison only one trial

Figure 13: PICO 2 treatment network for QoL



was available. The median age per study arm ranged from 56 years in PALOMA-2 to 62 years in MONARCH 2. The most recent trial results were published in 2018 and 2019, respectively. Both trials had proportional HRs and used the same criteria for defining endocrine resistance as we did.

Comparative efficacy:

The SUCRA and forest plots show a tendency for improved QoL with PAL+FUL or ABE+FUL compared with FUL monotherapy. The respective probabilities for each treatment to rank highest are indicated in Figure 14, Table 36 (Appendix) shows the probabilities for each rank for each treatment. The detailed results of the comparisons between all treatments are provided in the heat map (Figure 15).

The random effects model shows comparable results with larger credibility intervals for the individual treatments (Appendix, Figure 78). The inclusion of age as a predictor in the network meta-regression led to similar results (Appendix, Figure 80 and Figure 79).

Figure 14: PICO 2 SUCRA and forest plots for QoL; fixed effect model

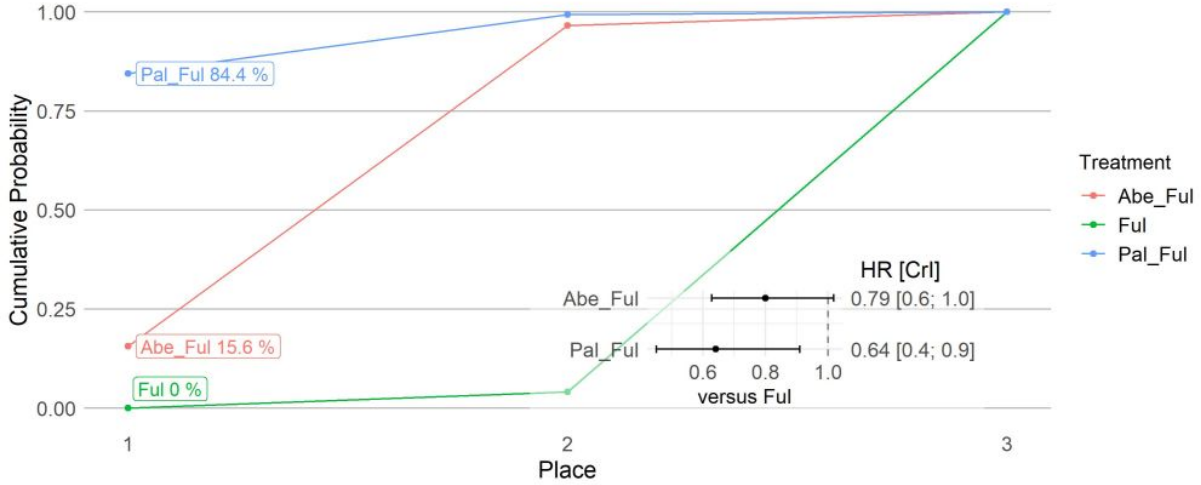
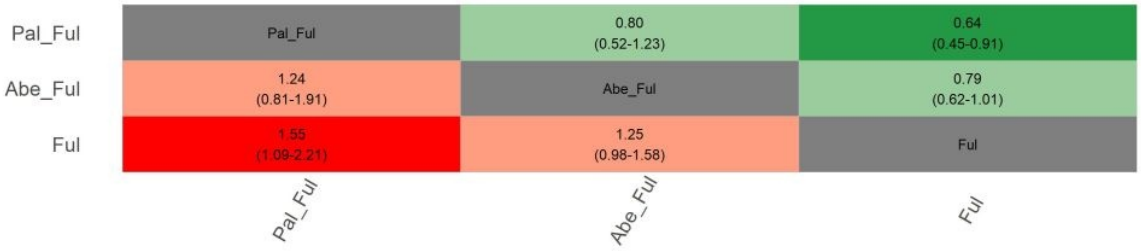


Figure 15: PICO 2 heat map for QoL; fixed effect model



Hazard ratios are indicated for treatments on Y-axis versus treatments on X-axis. Green fields indicate superiority of treatments on Y-axis, red fields inferiority of treatments on Y-axis.

7.2.5 Findings effectiveness

The included RCTs are mostly explanatory in design. The study settings do not seem to differ seriously from common Swiss settings; however, none of the included RCTs investigating CDK4/6 inhibitors recruited patients in Switzerland. Observational studies were only included for the safety results.

7.2.6 Findings safety

7.2.6.1 NMAs PICO 1

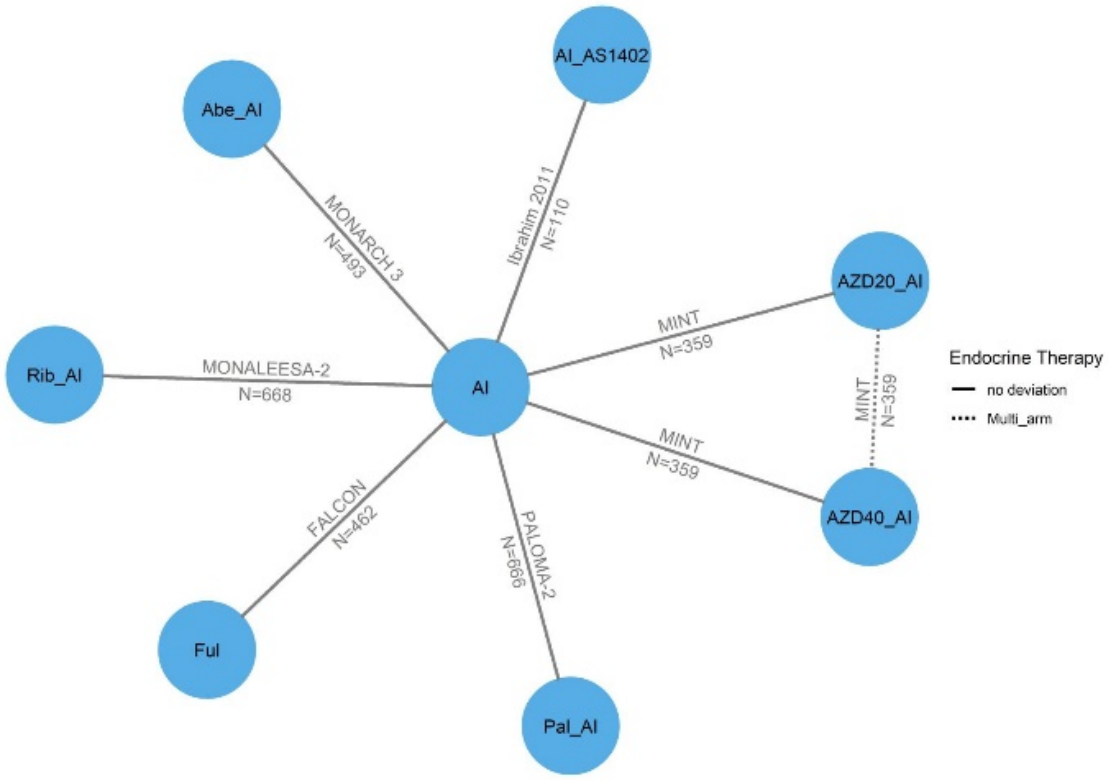
7.2.6.1.1 Adverse events grade 3 or worse (AE3+)

Network characteristics:

Six trials reported results on AE3+, leading to eight individual treatments in our network (Figure 16). All treatments were compared with AI. For each comparison only one trial was available. The mean or median age per study arm ranged from 60 to 64 years. Apart from NCT00770354[66], the most recent trial results were published between 2016 and 2019.

Not aggregating the individual AIs led to a smaller network with four treatments and three trials and LET as the central comparator (Appendix, Figure 61). FUL, ABE+AI, AZD20+AI and AZD40+AI dropped out of the network.

Figure 16: PICO 1 treatment network for AE3+



Comparative results:

The SUCRA and forest plots show a tendency for AI and AS1402+AI having the lowest risk for AE3+. The respective probabilities for each treatment to rank highest are indicated in Figure 17, Table **35** (Appendix) shows the probabilities for each rank for each treatment. In all models the CDK4/6 inhibitors showed the worst results with regard to AE3+.The detailed results of the comparisons between all treatments are provided in the heat map (Figure 18).

In the network with the individual AIs, the results remained stable with the lowest risk for AE3+ for AS1402+LET, followed by LET (Appendix, Figure 60).

The random effects model again ranks AS1402+AI best and the curves for FUL, AZD20+AI and AI are similar (Appendix, Figure 62). The network meta-regression with age as a predictor had insufficient model fit with AIPSRF above 1.05 and should be assessed with caution (Appendix, Figure **63** and Figure 65).

Figure 17: PICO 1 SUCRA and forest plots for AE3+; fixed effect model

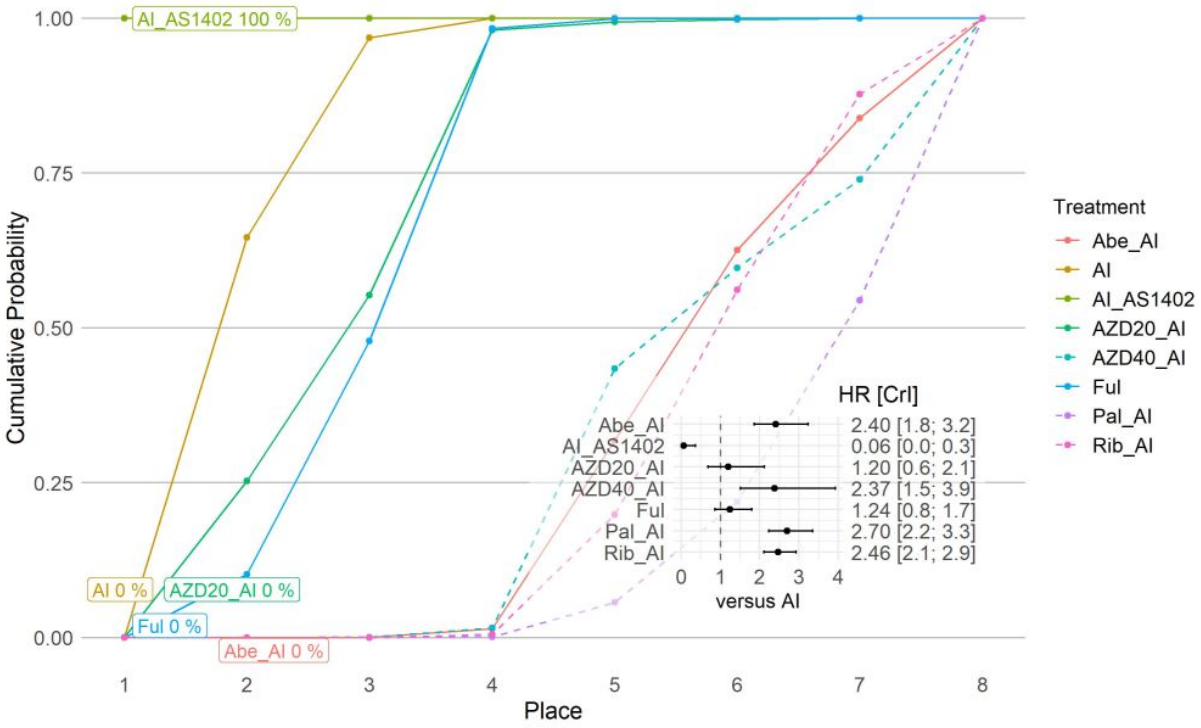
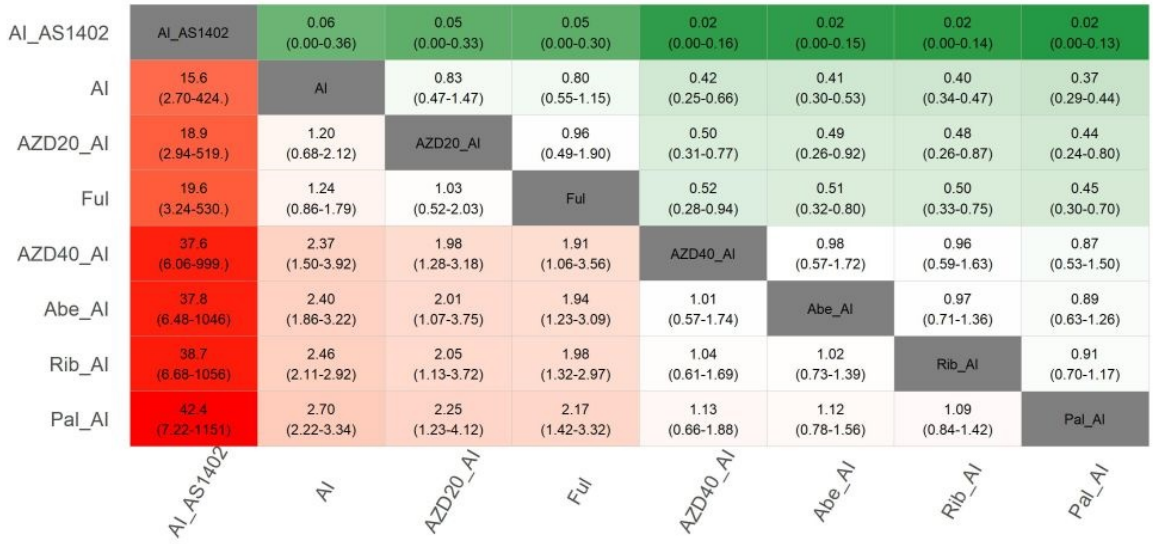


Figure 18: PICO 1 heat map for AE3+; fixed effect model



Hazard ratios are indicated for treatments on Y-axis versus treatments on X-axis. Green fields indicate superiority of treatments on Y-axis, red fields inferiority of treatments on Y-axis.

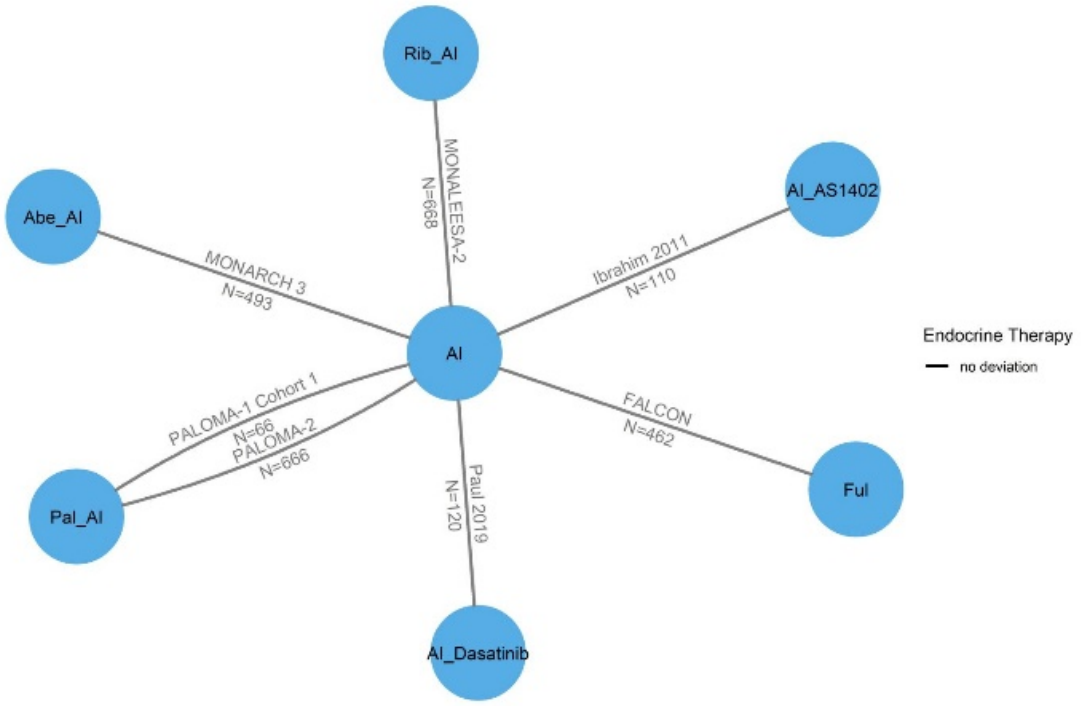
7.2.6.1.2 Discontinuations

Network characteristics:

Seven trials reported results on discontinuations, leading to seven individual treatments in our network (Figure 19). All treatments were compared with AI. Two trials compared PAL+AI with AI. For all other comparisons only one trial was available. The mean or median age per study arm ranged from 61 to 66 years. Apart from NCT00770354[66], the most recent trial results were published between 2017 and 2019.

Not aggregating the individual AIs led to a smaller network with five treatments and five trials and LET as the central comparator (Appendix, Figure 64). FUL and ABE+AI dropped out of the network.

Figure 19: PICO 1 treatment network for discontinuations



Comparative results:

The SUCRA and forest plots show a tendency for AI and DAS+AI having the lowest risk for discontinuations, while the highest risk was observed for ABE+AI. The respective probabilities for each treatment to rank highest are indicated in Figure 21, Table 35 (Appendix) shows the probabilities for each rank for each treatment. The detailed results of the comparisons between all treatments are provided in the heat map (Figure 20).

In the network with the individual AIs, the results remained stable with fewer discontinuations in the DAS+LET group (Appendix, Figure 67).

The random effects model shows comparable results with larger credibility intervals for the individual treatments and less certainty with regard to treatment rankings (Appendix, Figure 66). The inclusion of age as a predictor in the network meta-regression led to similar results (Appendix, Figure 68 and Figure 69).

Figure 21: PICO 1 SUCRA and forest plots for discontinuations; fixed effect model

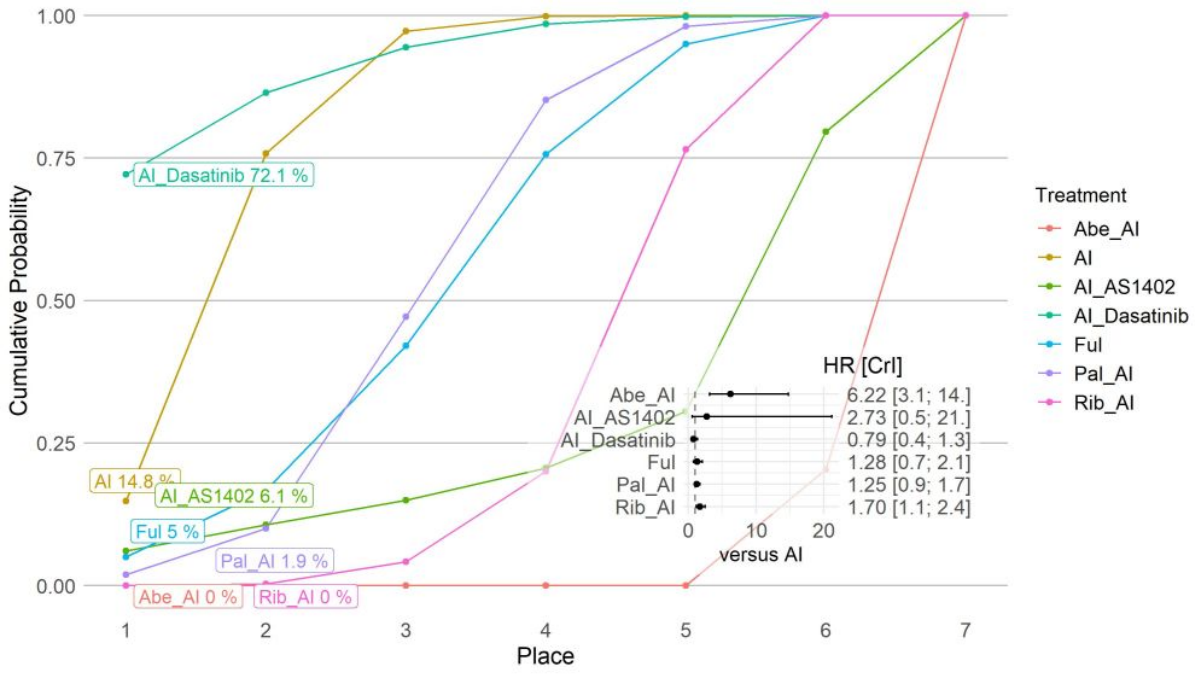
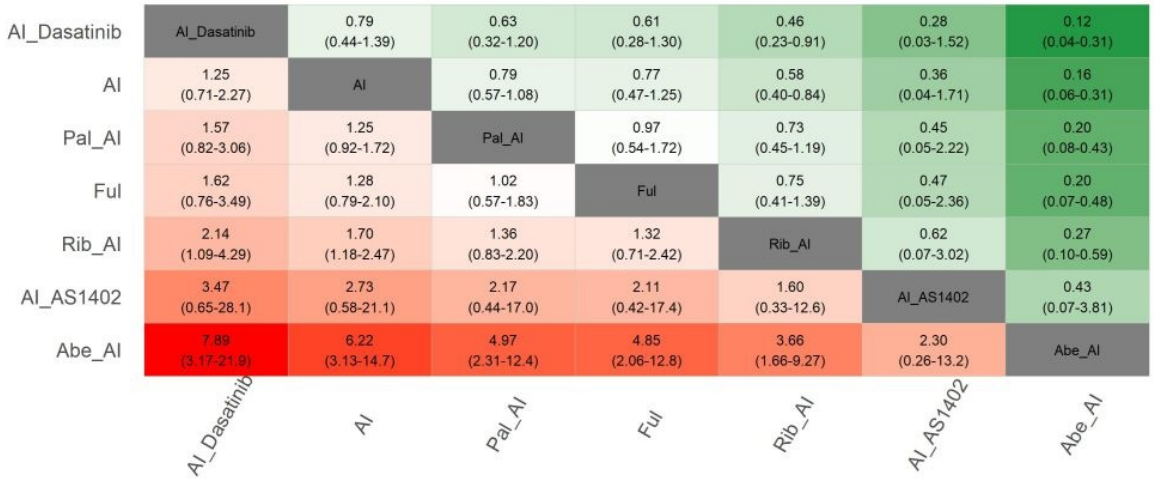


Figure 20: PICO 1 heat map for discontinuations; fixed effect model



Hazard ratios are indicated for treatments on Y-axis versus treatments on X-axis. Green fields indicate superiority of treatments on Y-axis, red fields inferiority of treatments on Y-axis.

7.2.6.2 NMAs PICO 2

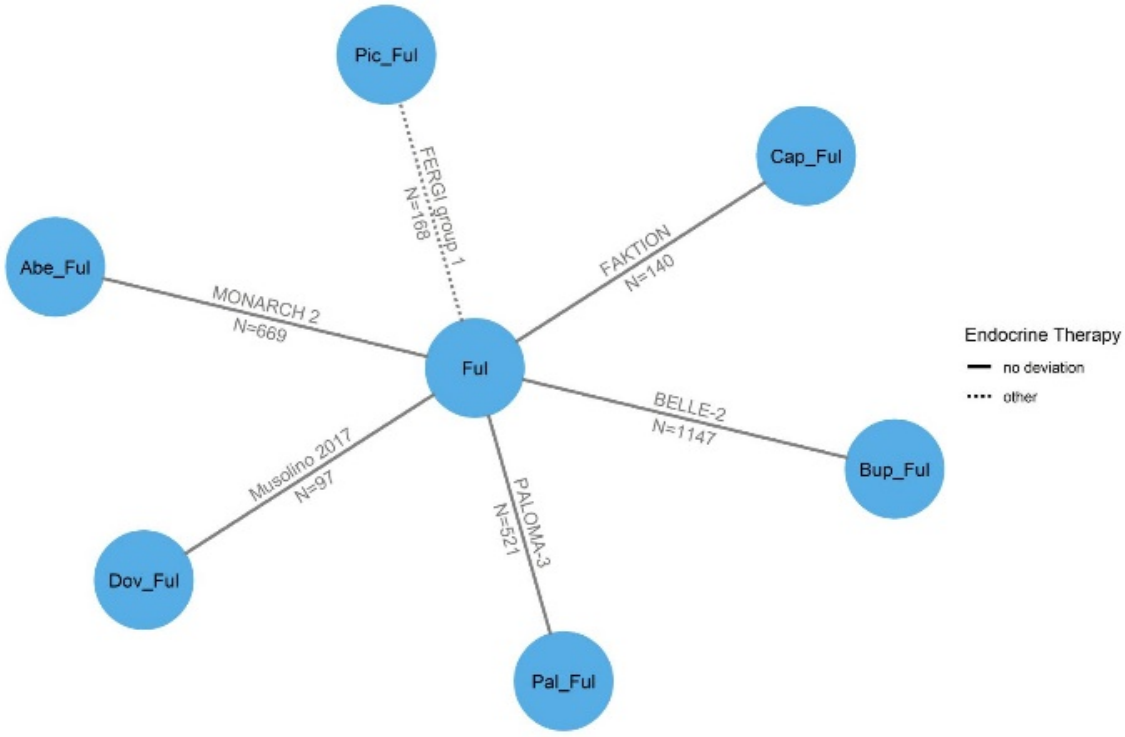
7.2.6.2.1 Adverse events grade 3 or worse (AE3+)

Network characteristics:

Six trials reported results on AE3+, leading to eight individual treatments in our network (Figure 22). All treatments were compared with FUL. For each comparison only one trial was available. The mean or

median age per study arm ranged from 56 to 63 years. The most recent trial results were published between 2016 and 2020. Not aggregating the individual AIs did not change the network.

Figure 22: PICO 2 treatment network for AE3+



Comparative results:

The SUCRA and forest plots show a tendency for FUL having the lowest risk of AE3+. The respective probabilities for each treatment to rank highest are indicated in Figure 24, Table 36 (Appendix) shows the probabilities for each rank for each treatment. The treatment least likely to have the lowest risk of AE3+ is PAL+FUL. The detailed results of the comparisons between all treatments are provided in the heat map (Figure 23).

The random effects model shows the same rank order with considerably larger credibility intervals (Appendix, Figure 82). The network meta-regression with age as a predictor increased the credibility intervals even more to the extent that there were no meaningful differences between the treatments (Appendix, Figure 81 and Figure 84).

Figure 24: PICO 2 SUCRA and forest plots for AE3+; fixed effect model

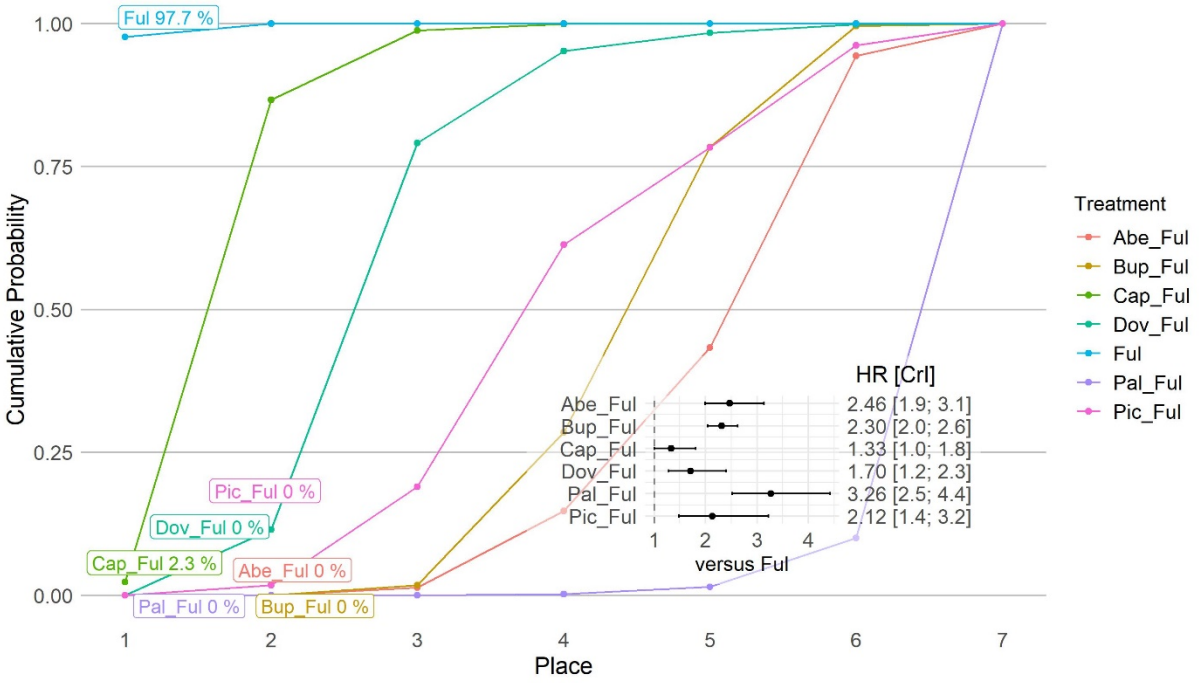
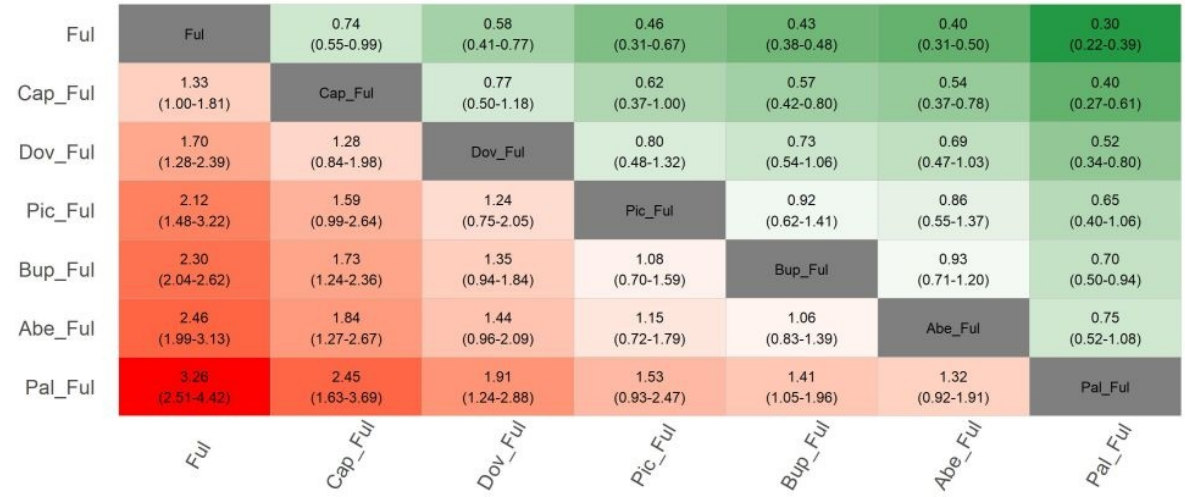


Figure 23: PICO 2 heat map for AE3+; fixed effect model



Hazard ratios are indicated for treatments on Y-axis versus treatments on X-axis. Green fields indicate superiority of treatments on Y-axis, red fields inferiority of treatments on Y-axis.

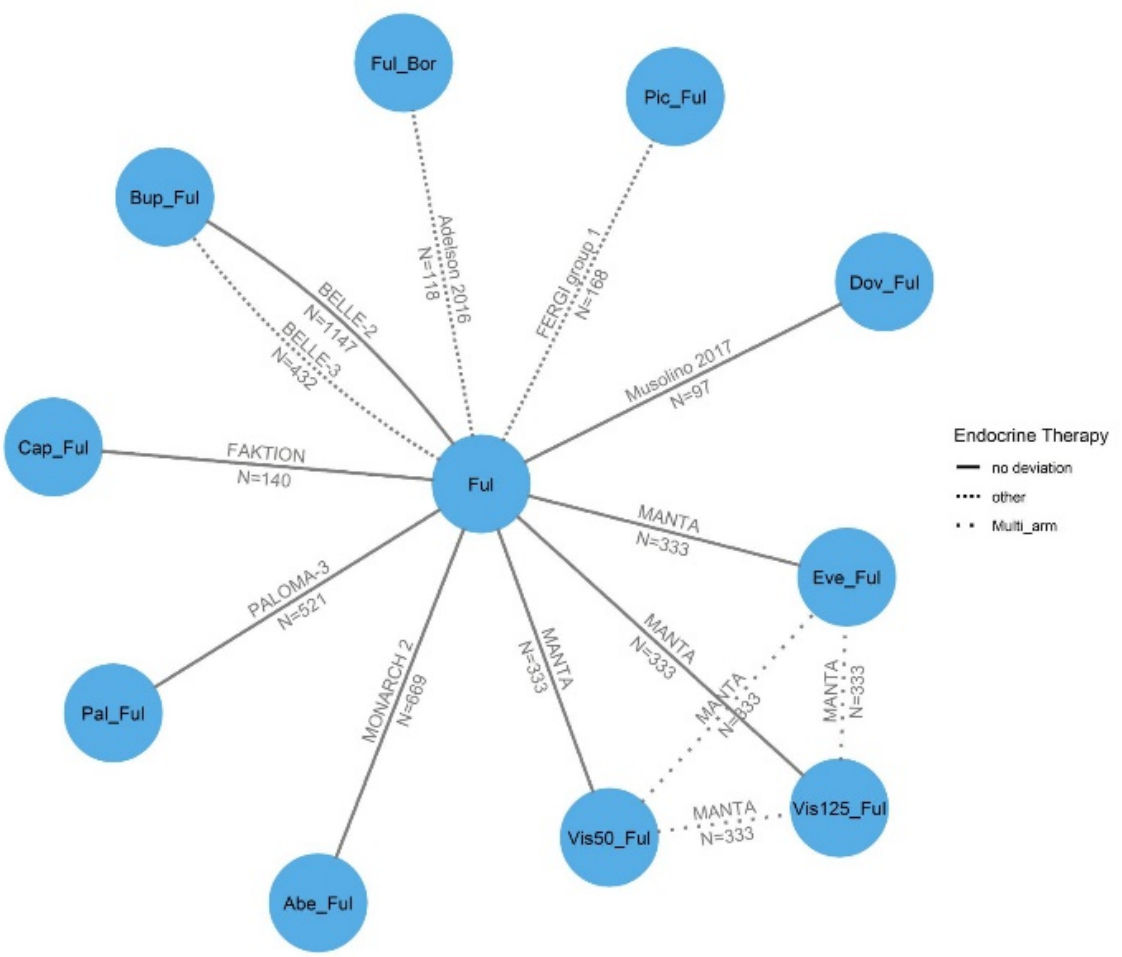
7.2.6.2.2 Discontinuations

Network characteristics:

Nine trials reported results on discontinuations, leading to eleven individual treatments in our network. All treatments were compared with FUL. Two trials compared BUP+FUL with FUL. For all other comparisons only one trial was available. The mean or median age per study arm ranged from 56 to 64

years. Three trials used a different definition of endocrine resistance than we did (Figure 25). The most recent trial results were published between 2016 and 2020. Not aggregating the individual AIs did not

Figure 25: PICO 2 treatment network for discontinuations



change the network.

Comparative results:

The SUCRA and forest plots show a tendency for FUL and PAL+FUL having the lowest risk of discontinuations, while the highest risk was observed for EVE+FUL, VIS50+FUL and CAP+FUL. The respective probabilities for each treatment to rank highest are indicated in Figure 26, Table 36 (Appendix) shows the probabilities for each rank for each treatment. The detailed results of the comparisons between all treatments are provided in the heat map (Figure 27).

The random effects model shows comparable results with larger credibility intervals resulting in less certainty with regard to treatment rankings (Appendix, Figure 83). The inclusion of age as a predictor in the network meta-regression widened the credibility interval of PAL+FUL vs. FUL from 0.6;1.8 to 0.0;18

in the fixed effect model, leading to a flat curve reflecting the high uncertainty in the ranking of this treatment (Appendix, Figure 85 and Figure 86).

Figure 26: PICO 2 SUCRA and forest plots for discontinuations; fixed effect model

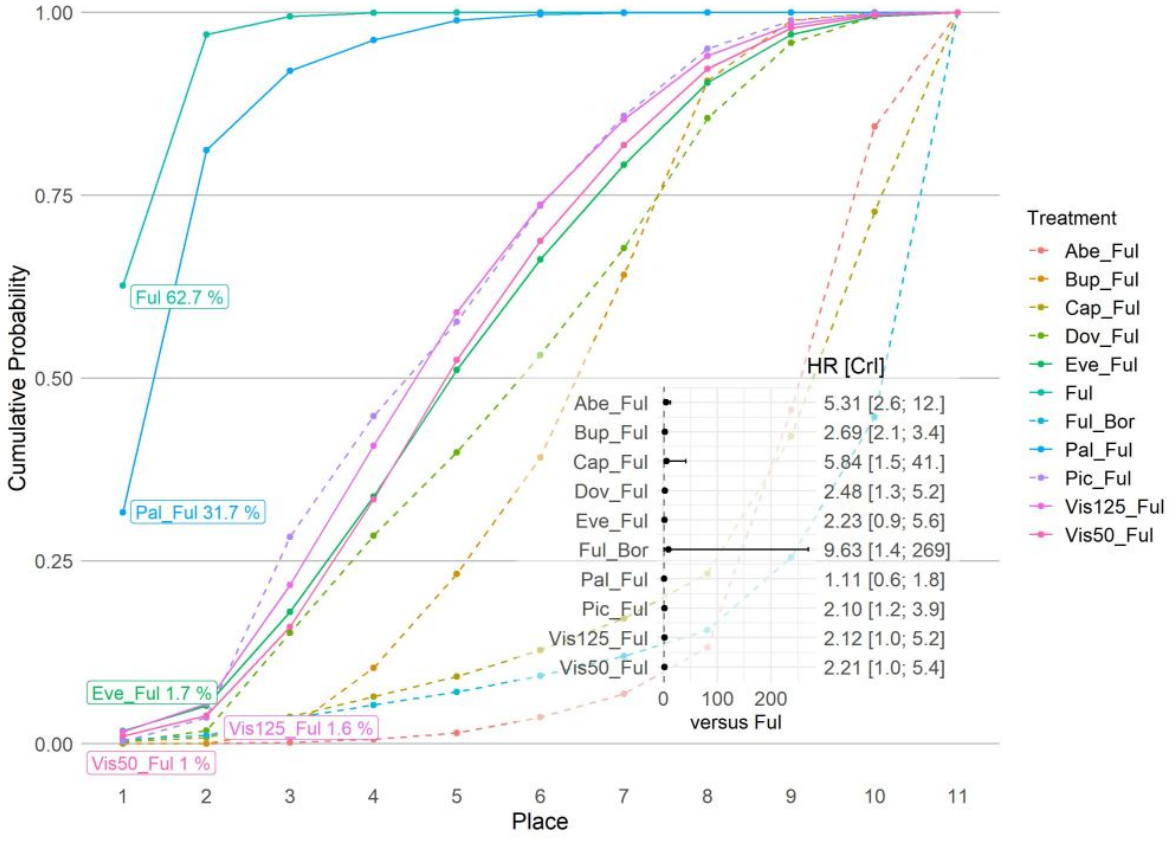
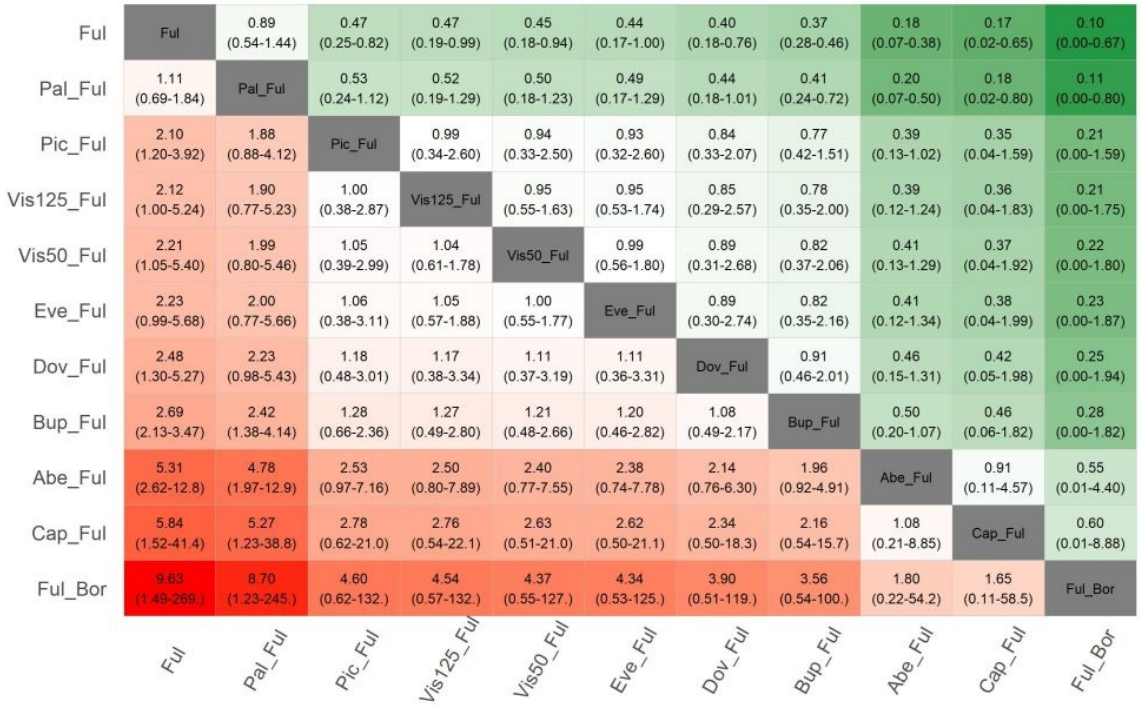


Figure 27: PICO 2 heat map for discontinuations; fixed effect model



Hazard ratios are indicated for treatments on Y-axis versus treatments on X-axis. Green fields indicate superiority of treatments on Y-axis, red fields inferiority of treatments on Y-axis.

7.2.6.3 Extended safety analysis from non-randomised studies (NRSs)

Most of the included NRSs covered patients whose basic disease characteristics match those of the patients included in the RCTs: 48 studies reported on HR+ patients with 1 study on patients with mixed HR status and 8 studies which did not declare the patients' HR status. Further 38 studies reported on HER2- patients, with 1 study on HER2+ patients, 3 studies on patients with mixed HER2 status and 15 studies did not declare the patients' HER2 status. Finally, 55 studies reported on patients with LA/MBC or "inoperable BC" and 2 studies did not declare the stage of the patients' BC. The number and type of previously received antineoplastic treatments varied substantially. However, the reporting on these parameters is very heterogeneous and does not allow any comparisons between studies. The vast majority of NRSs (22 cohort studies and 24 case studies) reported on patients who received PAL while only 2 cohort studies reported on patients who received ABE and 7 case studies covered patients who received RIB. One cohort study reported on patients who received one of the three CDK4/6 inhibitors and did not provide separate analyses of the incidence of AEs.[114]

We summarised the AEs (of any grade) that were reported in at least two studies on patients who received PAL in Table 12, listing the lowest and highest reported incidence as well as the mean and median across all studies. A more detailed summary including the different grades of AEs and a list of AEs that were reported in only one NRS is given in the Appendix, Table 37 and Table 38, respectively. Overall, the safety profile reported in the cohort studies is quite similar to what was reported in the RCTs, with the most frequent AEs being abnormal blood counts, nausea, fatigue, infections, elevated LFTs

and stomatitis. Table 13 shows the AEs (any grade) that were reported in the two cohort studies on patients who received ABE. Table 39 in the Appendix lists the AEs reported for ABE including different grades. As with PAL, AEs reported in NRSs on patients who received ABE are similar to what was reported in the RCTs; however, due to the low number of studies, the significance of this observation is limited. Similar tables for AEs associated with RIB could not be generated becaused no cohort studies investigating patients who were treated with RIB were available.

The AEs reported in the case studies are listed in Table 11. Notably, the related severe dermatological conditions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) were reported more than once with one case of SJS in a patient treated with PAL, one in a patient treated with RIB and one case of TEN in a patient treated with RIB.[124 140 144] Another recurring complication is adverse interactions in patients treated with PAL: two patients experienced a radio-sensitising effect when receiving radiation therapy and PAL[125 126], two patients suffered from severe rhabdomyolysis (fatal in one case), which the authors attributed to increased plasma levels of their statin medications[128 129] and one patient experienced increased plasma levels of her cyclosporine medication[127]. The authors of the reports concerned attributed these complications to co-medication with PAL. In addition, one patient suffered from severe adverse events, which the authors attributed to increased plasma levels of PAL due to co-medication with verapamil.[119]

Table 12: Incidence of AEs in patients receiving PAL reported in two or more NRSs

		Reported incidence			
Adverse event	**N (studies)**	**lowest**	**highest**	**median**	**mean**
ALT increased[90 92]	2	13.0%	19.0%	16.0%	16.0%
Alopecia[95 96 100 104 109]	5	1.6%	16.7%	5.0%	7.2%
Anaemia[90-92 95-98 100 101 104 106 109]	12	5.9%	66.9%	41.5%	38.4%
Arthralgia[92 104 106]	3	1.4%	12.3%	2.0%	5.2%
AST increased[90 92]	2	16.7%	28.0%	22.4%	22.4%
Constipation[96 100 104 106]	4	3.9%	21.4%	8.9%	10.8%
Cutaneous toxicity[96 104]	2	2.6%	15.6%	9.1%	9.1%
Decreased appetite[92 106 109]	3	3.1%	37.0%	11.1%	17.1%
Diarrhoea[91 96 104 106 107 111]	6	1.5%	17.4%	6.3%	8.5%
Dizziness[92 96]	2	2.6%	26.0%	14.3%	14.3%
Emergency room encounters/hospitalisation[93 109]	2	10.4%	18.8%	14.6%	14.6%
Fatigue[90-92 95 97 98 101 104 106 107 109 111]	12	3.5%	59.0%	35.7%	34.3%
Febrile neutropenia[91 93-98 100 101 104 109]	11	1.3%	5.1%	3.0%	3.0%
Headache[96 100 104 106]	4	0.7%	14.3%	8.4%	7.9%
Hypertransaminasaemia[94 95 100 104 111]	5	1.5%	58.1%	2.4%	14.7%
Infections[91-93 100 106 109]	6	19.3%	35.0%	24.4%	25.4%
Leukopenia[92 98 100 104 106 107]	6	1.9%	100.0%	70.2%	58.5%
LFTs elevated[91 109]	2	4.7%	32.2%	18.4%	18.4%
Lymphopenia[92 105 110]	3	17.0%	30.0%	23.0%	23.3%
Malaise[90 92]	2	15.0%	16.7%	15.9%	15.9%
Mucositis[103 104 111]	3	4.0%	7.1%	5.6%	5.6%
Nausea[90-92 96-98 106]	7	5.2%	69.7%	19.5%	25.1%
Nausea/Vomiting[95 104 111]	3	2.0%	14.2%	3.3%	6.5%
Neutropenia[90-111]	22	2.1%	100.0%	84.0%	76.3%
Renal failure[95 97]	2	1.7%	3.8%	2.8%	2.8%

(Skin) rash[91 95 97 100 111]	5	1.5%	19.0%	3.4%	5.9%
Stomatitis[90 91 95 97 100 106]	6	3.3%	73.8%	16.4%	23.5%
Thrombocytopenia[90-92 95-98 100 101 104 106 107 109]	13	10.9%	55.0%	42.3%	36.4%

ALT=alanine transaminase; AST=aspartate transaminase; LFTs=liver function tests

Table 13: Incidence of AEs in patients receiving ABE reported in NRSs

Adverse event	**Dickler et al. 2017[112] (n=132)***	**Patnaik et al. 2016[113] (n=19)**
Anaemia	68.5%	11.0%
Anorexia	N/A	32.0%
Constipation	N/A	11.0%
Cramps in lower limbs	98.5%	N/A
Creatinine levels increased	46.9%	11.0%
Decreased appetite	45.5%	N/A
Dehydration	N/A	16.0%
Diarrhoea	90.2%	79.0%
Dyspepsia	N/A	11.0%
Fatigue	65.2%	68.0%
Headache	20.5%	N/A
Hypokaliaemia	26.2%	16.0%
Hyponatriaemia	20.8%	N/A
Increased ALT	30.0%	N/A
Infections	31.1%	N/A
Leukopenia	90.8%	32.0%
Nausea	64.4%	63.0%
Neutropenia	87.7%	42.0%
Pain, abdominal	38.6%	21.0%
Thrombocytopenia	41.4%	11.0%
Vomiting	34.8%	42.0%
Watering eye	N/A	16.0%

ALT=alanine transaminase; N/A=not reported
* for laboratory abnormalities n=130; for thrombocyte count n=128

7.2.7 Additional findings: MONALEESA-7

The clinical trial MONALEESA-7 investigated the efficacy and safety of RIB+NSAI/TAM compared with placebo+NSAI/TAM in a cohort of exclusively premenopausal women with HR+/HER2- LA/MBC without endocrine resistance, all of whom received concomitant OFS with gosereline. Since the focus on premenopausal patients results in a considerably lower median age for the cohort, MONALEESA-7 could not be included in the NMAs. The reported HRs for OS, TTD of QoL (measured with EORTC QLQ-C30 global) and PFS in the NSAI group are 0.70 (95% CI, 0.50 to 0.98), 0.69 (95% CI, 0.52 to 0.91) and 0.57 (95% CI, 0.44 to 0.74), respectively.[146-148] Thus, the efficacy of RIB+NSAI (for QoL) in the premenopausal patient cohort appears to be similar to or better than in the postmenopausal (older) patient cohort studied in MONALEESA-2 (HR OS: 0.75 [95% CI, 0.52 to 1.08]; HR TTD QoL: 0.94 [95% CI, 0.72 to 1.24]; HR PFS: 0.57 [95% CI, 0.46 to 0.70]).[57 58] The incidence of AE3+ in MONALEESA-7 was 80% in the RIB group and 30% in the placebo group and thus very similar to the incidence in MON-

ALEESA-2 (81% in the RIB group and 32% in the placebo group). However, the AE data from MON-ALEESA-7 includes patients treated with TAM (26% in the RIB group and 27% in the placebo group); separate data for patients treated with NSAI are not available.[55 146]

Summary statement efficacy, effectiveness and safety

Based on the available evidence, it is likely that CDK4/6 inhibitors provide superior efficacy when compared with ET monotherapies. The probabilities that either one of the CDK4/6 inhibitors in combination with ET ranks best among the compared treatments are 99% and 91%, respectively for OS and QoL in PICO 1 and 98% for QoL in PICO 2. For OS in PICO 2, the CDK4/6 inhibitors are among several treatments with higher probability for top ranking. The probabilities of ranking place five or better out of eleven compared treatments are 87% for both RIB+FUL and ABE+FUL and 70% for PAL+FUL but only 1% for FUL monotherapy.

At the same time, it is highly likely that the ET monotherapies show superior tolerability when compared with the combination therapies with CDK4/6 inhibitors. When the treatments are ranked according to the lowest RR for AE3+, AI monotherapy has a 65% probability of ranking place two or better out of eight compared treatments in PICO 1, while these probabilities are 0% for either of the CDK4/6 inhibitors combined with AI. The probability that FUL monotherapy ranks best for AE3+ in PICO 2 is 98%.

Differences between the individual CDK4/6 inhibitors are not very robust. Moreover, the available data do not allow the comparison of all three CDK4/6 inhibitors in each network. ABE+AI is missing in the networks for OS and QoL in PICO 1 and RIB+FUL is missing in the network for QoL in PICO 2.

While the AEs reported in cohort studies on patients treated with CDK4/6 inhibitors are similar to those reported in the equivalent RCTs (PAL, ABE), additional AEs were reported in case studies, some recurring (PAL, RIB).

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8 Costs, cost-effectiveness and budget impact

8.1 Methodology costs, cost-effectiveness and budget impact

8.1.1 Databases and search strategy

The systematic literature search and the selection procedure for relevant economic studies are described in Subchapter 7.1.1.2.

8.1.2 Other sources

Additional literature sources are described in Subchapter 7.1.2. Furthermore we conducted an orienting literature and internet research to identify data or information on breast cancer prevalence and incidence, including the relevant subgroups for this assessment (LABC, MBC). We performed manual searches, for example within the reference lists of identified economic evaluations, for retrieving additional information (sources) on several cost parameters (monitoring, adverse events, follow-up costs after progression). We also consulted a group of up to three clinical experts in Switzerland.

8.1.3 Assessment of quality of evidence

The quality of the included economic studies was assessed using the Consensus Health Economic Criteria (CHEC) list (see Subsection 15.2) .[149]

8.1.4 Methodology health economic analyses

As the evaluated treatments are expected to have clinical and economic effects beyond the follow-up of the clinical trials, we used decision-analytic modelling to estimate benefits, costs and cost-effectiveness based on published evidence.[150] [151] We developed two evidence-based decision-analytic partitioned-survival models[152] to inform the HTA on long-term comparative cost-effectiveness of the breast cancer treatment regimens according to both research questions: 1) AI, 2) PAL+AI, 3) RIB+AI, 4) ABE+AI for PICO 1; 1) FUL, 2) PAL+FUL, 3) RIB+FUL, 4) ABE+FUL for PICO 2. As interaction between patients was not relevant for treatment effects, we performed a cohort simulation.[153] For result reporting we followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[154]

In the modelling study, we followed the ISPOR-SMDM international guidelines on modelling and guidelines for economic evaluations.[154-160]

8.1.4.1 Model design and assumptions

We chose a partitioned-survival model approach, because state occupancy (i.e., dwelling time in the health states) can be estimated directly from trial-based estimates of OS and PFS.[161] [162] We programmed and validated the decision-analytic model using the decision-analytic software package TreeAge Pro 2020 (TreeAge Software Inc., Williamstown, MA, USA).

Figure 87 and Figure **88** (Appendix) display the structures of the models for PICO 1 and PICO 2. In each model we considered three mutually exclusive health states, that is, PFS, progressive disease (PD) and death in each treatment arm. We estimated the proportions of patients in each health state over time assuming time to progression and time to death are exponentially distributed. The hypothetical cohort was followed for an analytic-time horizon of 20 years. This time horizon was sufficiently long, as survival was minimal (<1%) after 20 years.

8.1.4.2 Clinical data

In each treatment arm, for the time to progression, we applied the mean time to progression of 15.794 months (standard error of the mean [SEM] = 3.293) for AI (PICO 1) and 5.877 months (SEM = 1.875) for FUL (PICO 2), respectively, based on primary data from the clinical trials that were analysed in the NMAs of this report. In each treatment arm, we applied the mean time to death of 33.3 months (SEM = 6.993) for AI (PICO 1) and 28.892 months (SEM = 6.095) for FUL (PICO 2), respectively based on primary data from the clinical trials that were analysed in the NMAs of this report. The effectiveness of the CDK4/6 inhibitors with respect to prolongation of time to progression and overall survival was modelled based on hazard ratios derived from the NMAs of this report (Appendix: Table 41, Figure 89, Figure 90, Figure 91, Figure 92, Figure 93, Figure 94, Figure 95, Figure 96).

8.1.4.3 Utilities

For PICO 1 quality-adjusted progression-free survival time and time post progression were calculated according to utilities published by Rugo et al. (EQ-5D index scores, PALOMA-2 trial, see Table 42), assuming that the reported utilities for the health state PFS for patients treated with LET apply also to the treatment with the other AIs (i.e., utility depends only on the health state and not on the specific administered AI).[52] We applied the reported PAL+LET utilities for individuals in PFS under CDK4/6 inhibitor treatment. For PICO 2 we used utilities published by Loibl et al. (EQ-5D index scores, PALOMA-3 et al., see Table 43), assuming that the reported utilities for the treatment with FUL apply to the FUL arm in PICO 2 for the health state PFS and that the reported utilities for PAL+FUL apply for individuals in PFS under CDK4/6 inhibitor treatment in PICO 2.[163] We applied utilities for individuals in the post progression state from Xie et al. for PICO 1 and PICO 2.[164]

8.1.4.4 Resource use and costs

We included direct costs (to the extent they were available for Switzerland) from the payer perspective. We derived drug costs from the Swiss Specialties List (as of 1st October 2020).[26] In case of LET, ANA, EXE and FUL, for which several medicinal products are on the Swiss market, we calculated a weighted average for each of the substances based on utilisation data received from FOPH (Tarifpool ©SASIS AG, data processing: ©COGE GmbH[165]). Moreover, in analogy to the approach in the NMA, the AIs LET, ANA and EXE were aggregated based on their presumed market shares, which were estimated

by our clinical experts (see Table 40 in the Appendix). Daily dose, frequency and AE monitoring requirements were set according to the Swissmedic medicinal product information[19-21 166-170]. We assumed that administration of FUL needs a doctor's visit in half of the cases. Otherwise we assumed that a doctor is visited (including a blood test) every third cycle (1 cycle = 28 days) with AI and FUL. We estimated costs for AE monitoring with the help of the clinical experts from different sources (see Table 15, Section 8.2.3. Proportions of patients with dose reductions in CDK 4/6 inhibitors were derived from clinical trial data – with the exception of ABE plus FUL, for which they had to be estimated based on PAL and RIB data. Only one trial[71] reported time until dose reduction (with median times between the second and fourth cycle) and only some of the trials reported detailed information on single vs. repeat dose reductions. The latter, however, was only relevant for RIB, as with PAL and ABE different doses have the equal prices. Based on RIB trial data we assumed that one fifth of patients required two dose reductions. We further assumed that all CDK 4/6 reductions occurred in the third cycle. Based on the availability of doses and package sizes on the Swiss market and the dosing and frequency recommendations in the medicinal product information, we assumed an average waste of half a package with PAL dose reductions and an average waste of half a package in 50% of the patients with ABE dose reductions. All assumptions were accorded within the authoring team and with FOPH.

Disease monitoring requirements were derived from expert opinion together with treatment guidelines and other literature sources. Regarding the use of positron emission tomography-computed tomography (PET-CT) estimates of the two involved Swiss experts varied significantly (5% vs. 80%). None of the identified economic studies (as far as described)[171-179] included PET-CT. To acknowledge the role of this imaging technique we assumed a proportion of 10% in the base-case analyses. We estimated the costs for imaging techniques based on data from a reference hospital and according to expert opinions. We extracted type and frequency of AEs from included clinical studies and discussed treatment requirements and costs arising from individual AEs with two clinical experts. Costs for treatment of febrile neutropenia were taken from the literature.[173] In consultation with the clinical experts we decided to assume that 10% of patients, who develop febrile neutropenia would be treated for it. This is in agreement with reommendations from the literature and the Swissmedic medicinal product information, stating that CDK4/6 inhibitor-induced neutropenia is reversible by dose reduction/interruption and does generally not require treatment.[19-21 23 180 181] Determination of costs of other individual AEs was not deemed feasible, due to: 1) a lack of available data on their duration; 2) a lack of standardized recommendations as to whether and how they should be treated, rendering this choice highly dependent on the preferences of patients and physicians. In addition, the majority of the AEs that were observed in clinical trials in patients threated with ET+CDK4/6 inhibitor also occurred – less frequently – in the ET monotherapy trial arms. We therefore assumed an average (lump sum) monthly cost for AE treatment, based on the esti-

mate of a clinical expert. It was assumed to be twice as high for patients treated with ET+CDK4/6 inhibitor than for patients treated with ET monotherapy. Follow-up costs for the treatment of patients after disease progression were estimated from literature[173] and expert input.

8.1.4.5 Outcomes, analyses and model validation

In the partitioned-survival analysis, we evaluated the hypothetical cohort continuously over 20 years. Predicted clinical outcomes included quality-adjusted life-months gained (QALMG). Economic outcomes included long-term costs and discounted incremental cost-effectiveness ratios (ICER) expressed in additional costs (in CHF) per quality-adjusted life expectancy (in quality-adjusted life years gained; QALYG). The ICER is calculated by dividing the discounted incremental costs when comparing two alternatives by the discounted incremental health effects of these alternatives. Following European guidelines of health-economic evaluation, an annual discount rate of 3% was applied to both effects and costs in the cost-effectiveness analysis.[159] Strategies are considered (strongly) dominated if they provide less health benefit at higher costs when compared to any other strategy. Therefore, dominated strategies should not be considered by decision makers and no ICER is calculated. Furthermore, extended (weakly) dominance has been used to eliminate strategies, for which costs and benefits are dominated by any mix of any two other alternatives. A dominant strategy provides better health effects at lower cost compared to other strategies. The model was validated internally and externally on several levels: (1) face validity, (2) internal validation (e.g., debugging, consistency and plausibility checks). For validation, we followed the ISPOR-SMDM guideline on validation.[155]

We performed several deterministic one-way sensitivity analyses and probabilistic multi-way sensitivity analyses, as well as deterministic scenario analyses on crucial input parameters and on relevant assumptions to evaluate the robustness of the results and to identify future research priorities.

8.1.4.5.1 Deterministic and probabilistic sensitivity analyses

In the one-way sensitivity analyses, we varied the mean PFS and OS, utilities, follow-up costs, and dose reductions. Table 42 and Table 43 in the appendix provide an overview on parameter ranges and distributions used in the probabilistic sensitivity analyses (with 1000 runs). As OS inherently depends on PFS, these two parameters were varied simultaneously. We multiplied the HRs for PFS and OS by the same factor, derived from the confidence intervals for the hazard ratios for OS with AI (respectively FUL) alone compared to OS with AI+CDK4/6 inhibitor (respectively FUL+CDK4/6 inhibitor) from the NMA. We varied the other parameters according to reported confidence intervals if available or according to plausible ranges otherwise.

8.1.4.5.2 Deterministic scenario analyses

In addition, we performed six deterministic scenario analyses. We considered: (1) a discount rate of 6%; (2) a range of discount rates from 0-10%; (3) a price reduction for CDK4/6 inhibitors ranging from 10% to 90%; (4) a variation of costs for doctors' visits from 123.2 CHF to 343.2 CHF; (5) a variation of the percentage of patients examined with CT (50% to 100%) and a variation of the percentage of patients examined with PET-CT (0% to 20%); (6) a scenario analysis assuming weighted HRs for OS of 1.326 and PFS of 1.912 for AI alone vs. AI+CDK4/6 inhibitors (PICO 1) and weighted HRs for OS of 1.316 and PFS of 1.947 for FUL alone vs. FUL+CDK4/6 inhibitors (PICO 2). In the scenario analysis with weighted HRs for OS and PFS it was assumed that the efficacy of the three CDK4/6 inhibitors may be the same and differences in the study results are only due to differences in the populations (e.g. number of prior therapies). Hazard ratios were weighted according to the number of included patient populations in the underlying studies.

8.1.4.6 Budget impact analysis

The most recent version of the ESO-ESMO guidelines considers ET+CDK4/6 inhibitor combination therapy the standard of care for patients with HR+/HER2- LA/MBC (see Chapter 3).[8] We therefore assumed that – in case of disinvestment – PAL, RIB or ABE combination therapy would be substituted by combination therapies with the other two CDK4/6 inhibitors. Based on this assumption we estimated the likely effects of a potential disinvestment decision on the Swiss healthcare budget by including all cost parameters described in Section 8.1.4.4 and by including the yearly costs for an incident cohort of patients, that is a cohort of patients newly starting with treatment in this indication. We used undiscounted monthly costs per treatment regime from the cost effectiveness analysis, cumulated over the first, second and so forth year. Thereby we ensured capturing the cost effects of transitions from the progression-free state to post-progression or to death.

The Swiss federal statistical office publishes data on breast cancer mortality and incidence. The National Institute for Cancer Epidemiology and Registration (NICER) published a 2020 prognosis on 10-year prevalence of breast cancer in Switzerland.[182] We identified published Swiss data regarding the proportion of women with HR+/HER2-BC[7], but did not identify published data on the incidence or prevalence of (HR+/HER2-) LA/MBC in Switzerland. Incidence rates moreover only include de novo cases with LA/MBC (that is without a previous BC diagnosis).[183] We therefore estimated the incidence of HR+/HER2- LA/MBC partly from US and Dutch data[183-185 7] as well as expert input. We further estimated the proportions of the PICO 1 and PICO 2 populations from expert input. The two involved Swiss experts also helped in estimating the proportions of patients treated with ET+CDK4/6 inhibitor combination, ET monotherapy or other therapies in this population, as well as the proportions of PAL, RIB and ABE use within the cohort treated with CDK4/6 inhibitors. We also compared the latter estimations with utilisation data received from FOPH (Tarifpool ©SASIS AG, data processing: ©COGE GmbH[165]) for plausibility.

We used incidence data for estimating the budget impact and used prevalence data only for plausibility checks. Detailed data and sources are shown in Table **52** in the Appendix. We performed univariate sensitivity analyses by varying three parameters – estimated HR+/HER2- LA/MBC incidence (+/- 20%), the proportions of ET+CDK4/6 combination, ET monotherapy or other therapies (estimate of expert 1 vs. estimate of expert 2) and a price reduction for CDK4/6 inhibitors ranging from 10% to 90%. We did not vary the proportions of patients eligible for CDK4/6 inhibitor combination therapy receiving PAL, RIB or ABE, respectively, because the estimates differed only minimally between the two experts.

8.2 Results costs, cost-effectiveness and budget impact

8.2.1 PRISMA flow diagram

Table 58 in Appendix 15.8.8 shows the number of hits retrieved through the systematic search described in Subsection 7.1.1.2.1 in MEDLINE, EMBASE, The Cochrane Library, TRIP database, CRD and Scopus. After removal of duplicates in Endnote, 1’107 hits remained. Figure 28 shows the PRISMA flow chart for economic studies.

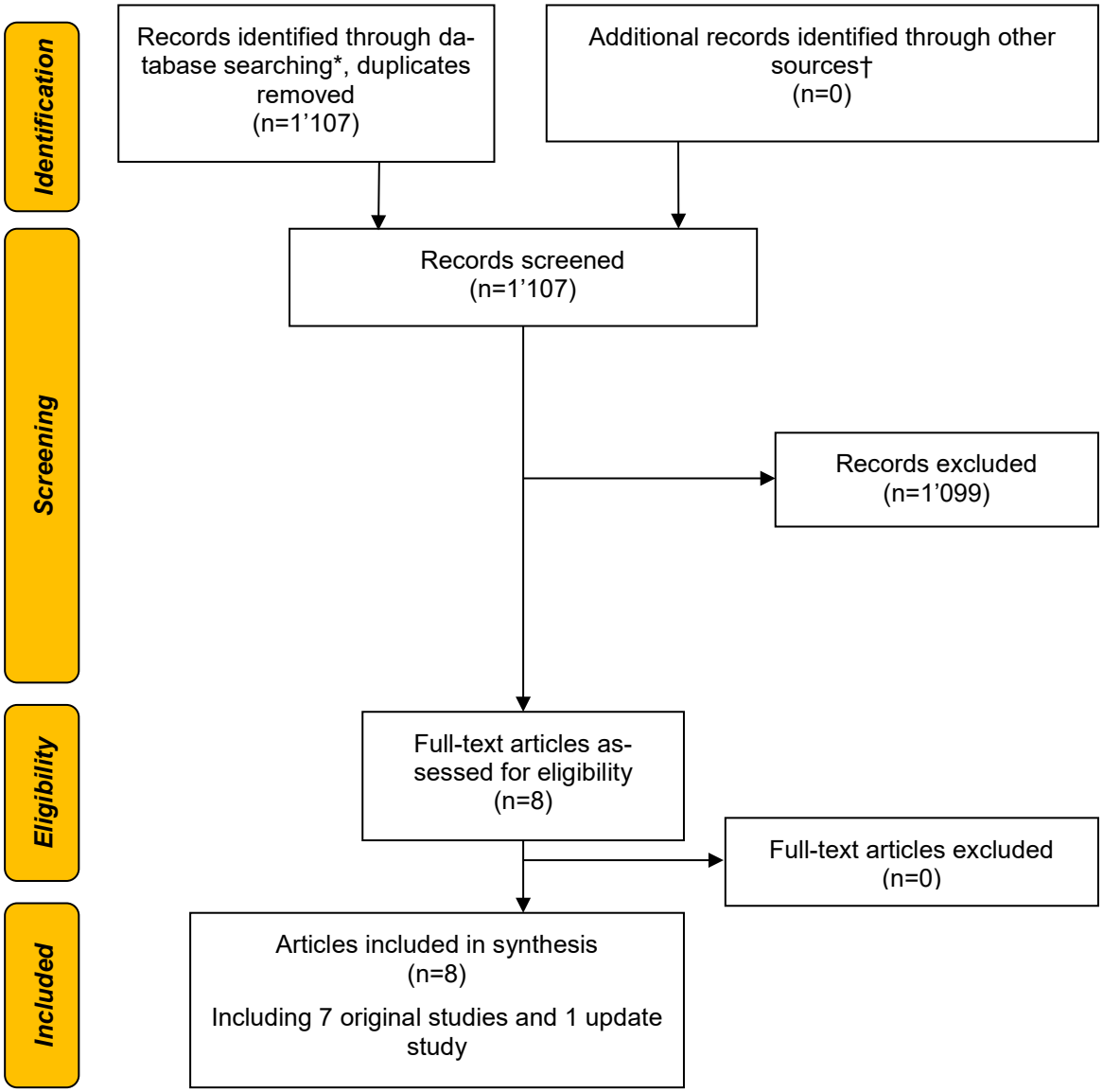


Figure 28: PRISMA flow chart for economic studies

* Literature search described in Subchapter 7.1.1.2.1.

† Refers to the literature search described in Subchapter 7.1.1.1.1 as well as other sources described in Section 8.1.2.

8.2.2 Evidence table

Table 14: Evidence table for economic studies

Study (author/year)	**Galve-Calvo et al. (2018)[171]**	**Mamiya et al. (2017)[172]**	**Mistry et al. (2018)[175]**	**Raphael et al. (2017)[176]**	**Matter-Walstra et al. (2016)[173]**	**Matter-Walstra et al. (2017) – update[174]**	**Zhang B.; Long, E.F. (2019)[177]**	**Zhang et al. (2019)[178]**
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 14: 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 14: 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.

The results of the identified CEAs are described in Appendix 15.2.

8.2.3 Findings costs

Table 15 to Table 17 detail included costs and resource consumption.

Table 15. Costs and resource consumption

		(Unit) costs		Resource consumption		
Substance name		*Costs per day with recommended dose, CHF*	*Source*	*Doses per day*	*Days per cycle*	*Source*
LET		2.59	[26]	2.5 mg	28	[167]
ANA		2.89	[26]	1 mg	28	[170]
EXE		3.24	[26]	25 mg	28	[169]
PAL		163.69	[26]	125 mg	21	[19]
RIB		165.81	[26]	600 mg	21	[21]
ABE		128.19	[26]	2x150 mg	28	[20]
FUL		688.10	[26]	500 mg	2 (1st cycle), 1 (after 1st cycle)	[168]
Substance name	*% patients with one or more dose reductions when taking CDK4/6 inhibitors in combination with AI / with FUL*	*Costs per day with reduced dose / waste, CHF*	*Source*	*Reduced dose per day*	*Days per cycle*	*Source*
PAL	40.0%[61] / 34.0%[49 70] starting in 3rd cycle	163.69* / 1,718.78***	[26]	100 mg / 75 mg	21	[19]
RIB	10.8%[110] / 7.6%[55 61] starting in 3rd cycle#	55.27 / 0	[26]	200 mg	21	[21]
	43.1%[110] / 30.3%[55 61] starting in 3rd cycle#	110.54 / 0	[26]	400 mg	21	[21]
ABE	46.5%[69] / 36.1%# starting in 3rd cycle#	128.19* / 1,794.63† in 50% of patients with dose reduction	[26]	2x100 mg / 2x50 mg	28	[20]
AE monitoring		*Unit costs, CHF*	*Source*	*Frequency and % patients PFS*		*Source*
Doctors visits (DV)		243.20	‖, [186]	see Table 16		[19-21], ‖
Blood test (BT)		56.80	[186]	see Table 16		[19-21], ‖
Electrocardiogram		28.71	¶	see Table 16		[19-21], ‖
Adverse events		*Costs (per case or per cycle), CHF*	*Source*	*% patients PFS*		*Source*
treatment for febrile neutropenia (FN)		994.00‡ per case	[173]	10% of patients with FN		‖
treatment of other AEs in ET monotherapy		40.00 per cycle	‖	100% of patients		‖
treatment of other AEs in ET+CDK4/6 combination therapy		80.00 per cycle	‖	100% of patients		‖
Disease Monitoring		*Unit costs, CHF*	*Source*	*Frequency PFS*	*% patients PFS*	*Source*
Computer tomography (thorax)		527.36	¶	16 weeks	85%#	‖
Magnetic resonance imaging		563.13	¶	16 weeks	5%	‖
PET-CT		1,625.20	¶	16 weeks	10%#	‖
Bone scintigraphy		252.07	¶	24 weeks	100%	[171 179]
Follow-up costs after progression (PP)		*Unit costs, CHF*	*Source*	*Frequency PP*	*% patients PP*	*Source*
(lump sum) costs per month		6,104.92‡	[173]	monthly	100%	[164 173]

ABE=abemaciclib; AE=adverse events; AI=aromatase inhibitor; CDK=cyclin-dependent kinase; CHF=Swiss francs; ET=endocrine therapy; FU=follow up; FUL=fulvestrant; mg=miligrams; PAL=palbociclib; PET-CT=positron emission tomography-computed tomography; RIB=ribociclib; PFS=progression free survival; PP=post progression * same price for different doses, † one-time costs in 3rd cycle, ‡ inflated to CHF of 2019, ‖ Expert opinion ¶ data collected from reference hospital, # see explanations in section 8.1.4.4

Table 16 Schedules for AE monitoring

Monitoring	1st cycle	2nd cycle	3nd cycle	following
AI Mono-therapy	DV+BT	-	-	DV+BT cycle 4/7/10 cont.
FUL Mono-therapy	DV+BT	DV*	DV*	DV+BT cycle 4/7/10 cont., DV* 5/6/8/9/ cont.
PAL	2x(DV+BT)	2x(DV+BT)	DV+BT	DV+BT each cycle
RIB	2x(DV+BT)+ECG	2x(DV+BT)+ECG	DV+BT	DV+BT 4/5/6, DV 7/8/9 cont.
ABE	2x(DV+BT)	2x(DV+BT)	DV+BT	DV+BT 4, DV 5/6/7 cont.

AI=aromatase inhibitor; BT=blood test; cont.=continued; DV=doctor's visit; ECG=electrocardiogram
*50% of patients,
Source: Swissmedic medicinal product informations[19-21 166-170], additional assumptions see Section 8.1.4.4

Table 17: Incidence of febrile neutropenia

Treatment	% of patients with febrile neutropenia
AI	0
PAL+AI[51 54]	1.8
RIB+AI[55]	1.5
ABE+AI[69]	0.3
FUL	0
PAL+FUL[71 74]	0.9
RIB+FUL[61]	1
ABE+FUL[76]	0.9

ABE=abemaciclib; AI=aromatase inhibitor; FUL=fulvestrant; PAL=palbociclib; RIB=ribociclib

8.2.4 Findings cost-effectiveness

8.2.5 Base-case analyses

8.2.5.1 AI-related regimens (PICO 1)

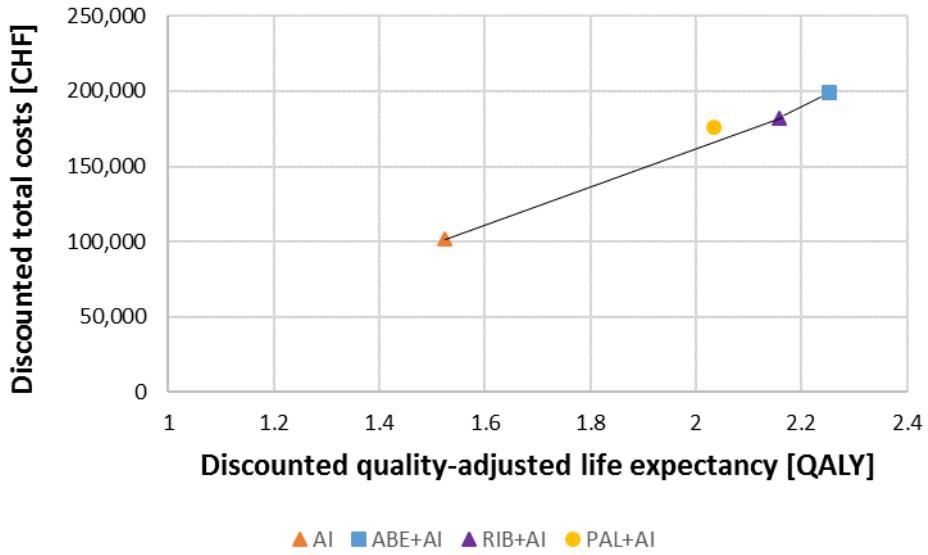
In the base-case analysis of the AI-related regimens (PICO 1), the remaining absolute undiscounted quality-adjusted life expectancies in the respective treatment arms were: 19.64 QALM (1.64 QALY) for AI monotherapy, 26.61 QALM (2.22 QALY) for PAL+AI, 28.42 QALM (2.37 QALY) for RIB+AI and 29.74 QALM (2.48 QALY) for ABE+AI.

Considering costs and health effects, PAL+AI was weakly dominated by AI and RIB+AI. AI led to a discounted mean health effect of 18.29 discounted QALM (1.52 QALY) and to a discounted mean total costs of 101,999 CHF per individual for the remaining lifetime. RIB+AI led to 25.89 discounted QALM (2.16 QALY) and to discounted total costs of 182,324 CHF per individual. ABE+AI led to 27.04 dis-

counted QALM (2.25 QALY) and to discounted total costs of 198,296 CHF per individual. The corresponding discounted ICER of moving from AI to RIB+AI was 126,860 CHF per QALYG. The corresponding discounted incremental cost-effectiveness ratio of moving from RIB+AI to ABE+AI was 166,787 CHF per QALYG.

Figure 29 and Table 18 summarise details on the results of the incremental cost-effectiveness analysis. For details on costs see also Appendix Table 44.

Figure 29: Cost-effectiveness plane for AI-related regimens (PICO 1)



ABE=abemaciclib; AI=aromatase inhibitor; CHF=Swiss francs; PAL=palbociclib; QALY=quality-adjusted life years; RIB=ribociclib; black line represents efficiency frontier

Table 18 Health economic results for AI-related regimens (PICO 1)

Strategy	Disc. total cost [CHF]	Incremental* disc. total cost [CHF]	Disc. quality-adjusted life expectancy [QALY]	Incremental* disc. quality-adjusted life expectancy [QALY]	Incremental* cost- effectiveness ratio [CHF/QALYG]
AI	101,999		1.52		-
PAL+AI	176,159		2.04		D
RIB+AI	182,324	80,324	2.16	0.63	126,860
ABE+AI	198,296	15,972	2.25	0.10	166,787

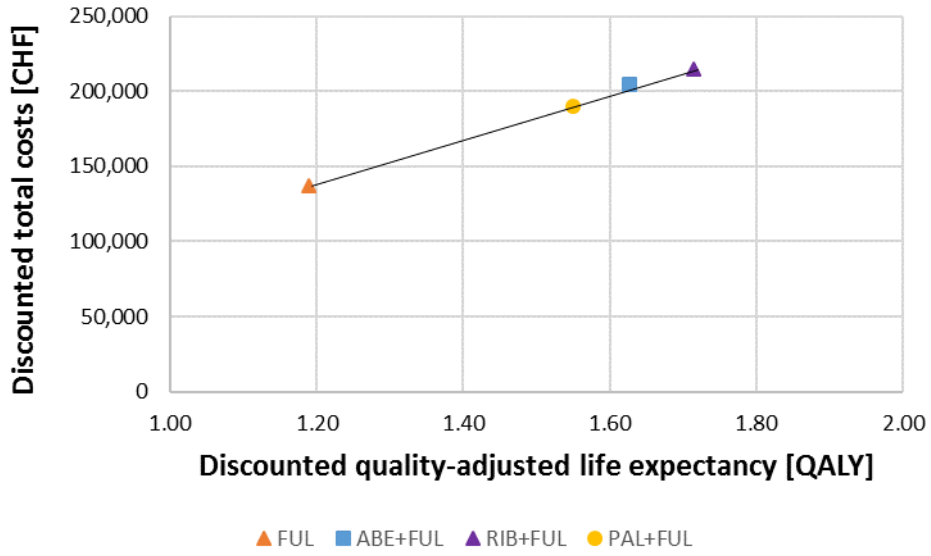
ABE=abemaciclib; AI=aromatase inhibitor; CHF=Swiss francs; D=dominated; disc.=discounted; PAL=palbociclib; QALY=quality-adjusted life years; QALYG=quality-adjusted life years gained; RIB=ribociclib
* compared to the next less costly and non-dominated strategy

8.2.5.2 FUL-related regimens (PICO 2)

In the base-case analysis of the FUL-related regimens (PICO 2), the absolute undiscounted quality-adjusted life expectancies in the respective treatment arms were: 15.22 QALM (1.27 QALY) for FUL monotherapy, 20.05 QALM (1.67 QALY) for PAL+FUL, 21.17 QALM (1.67 QALY) for ABE+FUL and 22.46 QALM (1.87 QALY) for RIB+FUL.

Considering costs and health effects, FUL monotherapy led to 14.28 discounted QALM (1.19 QALY) and to discounted total costs of 136,885 CHF per individual. PAL+FUL led to 18.60 discounted QALM (1.55 QALY) and to discounted total costs of 190,087 CHF per individual. The corresponding discounted incremental cost-effectiveness ratio for moving from FUL monotherapy to PAL+FUL was 147,808 CHF per QALYG. RIB+FUL led to 20.58 discounted QALM (1.72 QALY) and to discounted total costs of 214,633 CHF per individual. The corresponding discounted incremental cost-effectiveness ratio for moving from PAL+FUL to RIB+FUL was 148,342 CHF per QALYG. ABE+FUL was weakly dominated. Figure 30 and Table 19 summarise the results of the incremental cost-effectiveness analysis. For details on costs see also Appendix Table 45.

Figure 30: Cost-effectiveness plane for FUL-related regimens (PICO 2)



ABE=abemaciclib; CHF=Swiss francs; FUL=fulvestrant; PAL=palbociclib; QALY=quality-adjusted life years; RIB=ribociclib, black line represents efficiency frontier

Table 19: Health economic results for FUL-related regimens (PICO 2)

Strategy	Disc. total cost [CHF]	Incremental* disc. total cost [CHF]	Disc. quality-adjusted life expectancy [QALY]	Incremental* disc. quality-adjusted life expectancy [QALY]	Incremental* cost- effectiveness ratio [CHF/QALYG]
FUL	136,885		1.19		-
PAL+FUL	190,087	53,202	1.55	0.36	147,808
ABE+FUL	204,311		1.63		D
RIB+FUL	214,633	24,546	1.72	0.17	148,342

ABE=abemaciclib; CHF=Swiss francs; D=dominated; disc.=discounted; FUL=fulvestrant; PAL=palbociclib; QALY=quality-adjusted life years; QALYG=quality-adjusted life years gained; RIB=ribociclib
* compared to the next less costly and non-dominated strategy

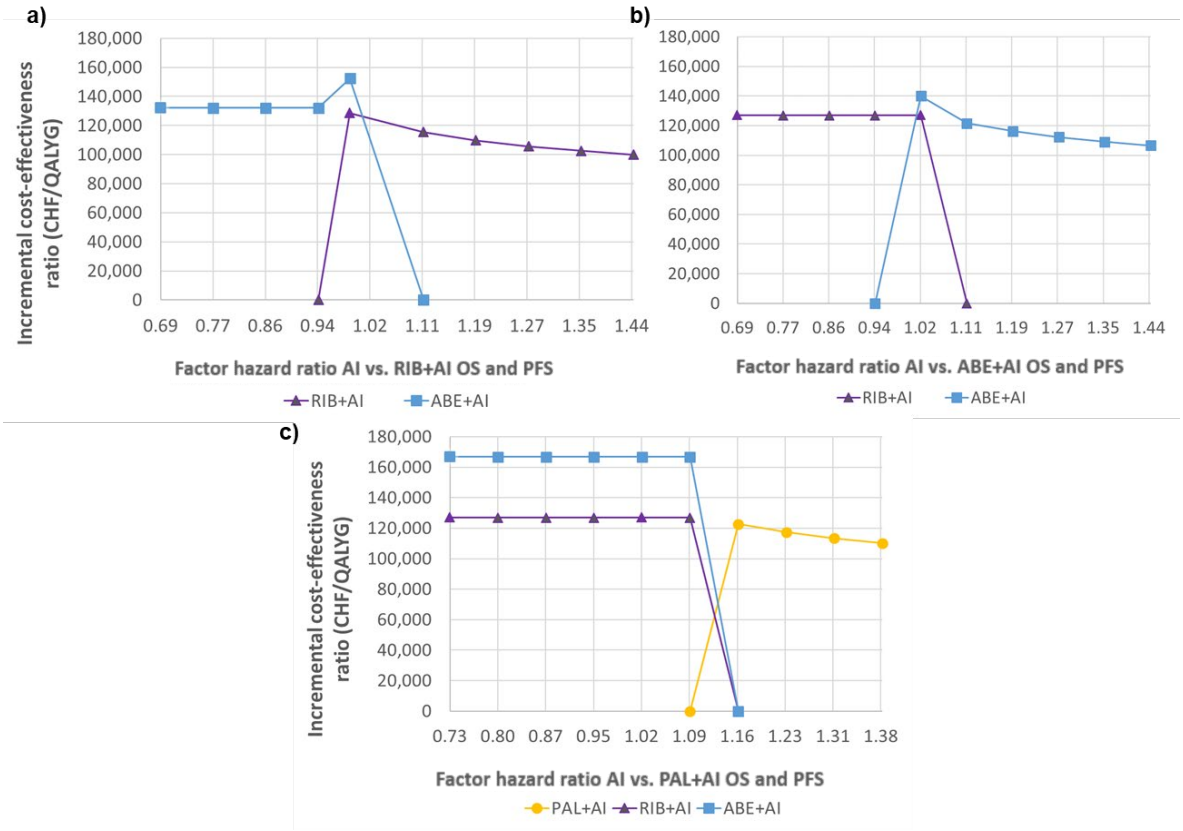
8.2.5.3 Sensitivity and scenario analyses

8.2.5.3.1 Deterministic sensitivity analyses AI-related regimens (PICO 1)

Base-case results of cost-effectiveness of AI-related regimens (PICO 1) were particularly sensitive to the hazard ratios of the compared interventions for overall and progression-free survival. Figure 31 shows ICERs of non-dominated strategies. RIB+AI was dominated (ABE+AI and AI remaining non-dominated) with decreased hazard ratios by a factor less than 0.99 for OS and PFS of AI vs. RIB+AI (corresponding to reduced hazard ratios of 1.741 for PFS and 1.326 for OS for AI vs. RIB+AI) (Figure 31a) or with increased hazard ratios by a factor of 1.065 for the OS and PFS for AI vs. ABE+AI (corresponding to increased hazard ratios of 2.224 for PFS and 1.426 for OS for AI vs. ABE+AI) (Figure 31b). ABE+AI was dominated (RIB+AI and AI remaining non-dominated) with decreased hazard ratios by a factor of 0.94 for OS and PFS of AI vs. ABE+AI (corresponding to reduced hazard ratios of 1.963 for PFS and 1.259 for OS for AI vs. ABE+AI) (Figure 31b) or with increased hazard ratios by a factor of

1.065 for the OS and PFS for AI vs. RIB+AI (corresponding to increased hazard ratios of 1.873 for PFS and 1.425 for OS for AI vs. RIB+AI) (Figure 31a). PAL+AI was no longer dominated with increased hazard ratios by a factor of 1.12 for OS and PFS for AI vs. PAL+AI (corresponding to increased hazard ratios of 2.10 for PFS and 1.34 for OS for AI vs. PAL+AI) (Figure 31c).

Figure 31: Sensitivity analyses on hazard ratios for OS and PFS, AI vs. RIB+AI (a), ABE+AI (b) and PAL+AI (c) (PICO 1)



The factor by which the hazard ratios for both OS and PFS were varied simultaneously in the sensitivity analyses is plotted on the x-axes. Strategies not shown in the graph or with an ICER represented as zero were dominated. If with varying parameter values, a dominated strategy became non-dominated, this is represented by a line moving from zero to the first calculated ICER value. If a non-dominated strategy became dominated, this was represented by a line toward an ICER represented as zero.

ABE=abemaciclib; AI=aromatase inhibitor; CHF=Swiss francs; OS=overall survival; PFS=progression free survival; PAL=palbociclib; QALYG=quality-adjusted life years gained; RIB=ribociclib

RIB+AI became a dominated strategy when we increased follow-up costs for all treatment arms above 7,400 CHF (Appendix Figure 97), or increased follow-up costs only in the CDK4/6 inhibitor treatments (factor 1.092; 6,667 CHF) while holding follow-up costs for AI constant (Appendix Figure 98), decreased the utility of individuals treated with RIB+AI to 0.726 (Appendix Figure 100), or increased the utility of

individuals treated with ABE+AI above 0.747 (Appendix Figure 99). PAL+AI became non-dominated when we increased follow-up costs to 8,097 CHF (Appendix Figure 97). Across sensitivity analyses, results were robust for variations in the proportion of individuals with dose reduction for PAL+AI and ABE+AI, for variations of utility of individuals in post progression (Appendix Figure 101), of utility of individuals in PFS for individuals treated with PAL+AI and for variations of mean OS and PFS for AI.

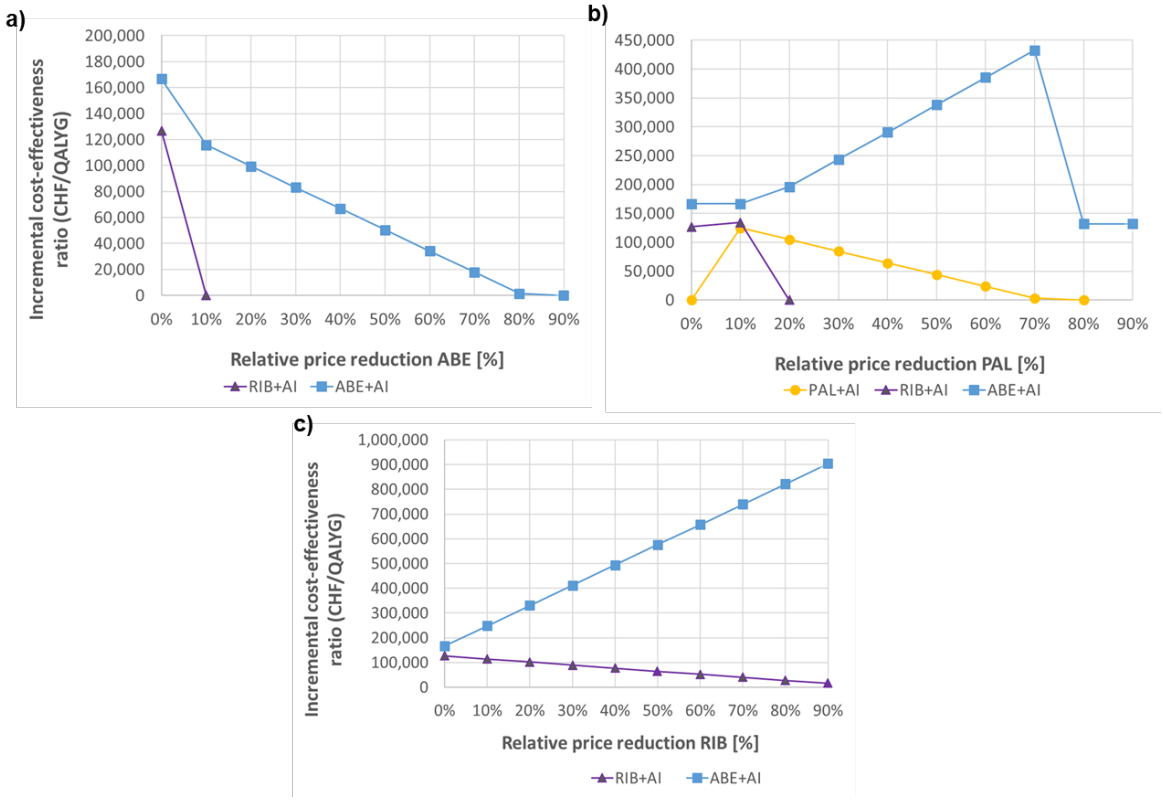
8.2.5.3.2 Scenario analyses AI-related regimens (PICO 1)

Changes in the annual discount rate across a range of 0% to 10% did not have an impact on the ranking of the strategies (Appendix Figure 102). At an annual discount rate of 6%, the ICER of RIB+AI vs. AI was 130,758 CHF/QALYG and the ICER of ABE+AI vs. RIB+AI was 183,278 CHF/QALYG (Appendix Table 46).

Variation of costs for doctors' visits, variations of the percentage of patients receiving CT and the percentage of patients receiving PET-CT had no impact on the ranking of the strategies.

Scenario analyses on relative price reduction of ABE, PAL and RIB are displayed in Figure 32 (excluding dominated strategies). In AI-related regimens (PICO 1), the treatment RIB+AI was dominated when the price of ABE was reduced by at least 10% (Figure 32a) and when the price of PAL was reduced by at least 18% (Figure 32b). PAL+AI was no longer dominated at a 10% price reduction (Figure 32b). At a 10% reduced price of PAL, the ICER of PAL+AI vs. AI was 125,000 CHF per QALY, the ICER of RIB+AI vs. PAL+AI was 134,610 CHF per QALYG and the ICER of ABE+AI vs. RIB+AI was 166,787 CHF per QALYG (Figure 32b). With a price reduction of RIB, the ICER of RIB+AI vs. AI decreased and the ICER of ABE+AI vs. RIB+AI increased (Figure 32c).

Figure 32: Scenario analyses on relative price reduction ABE (a), PAL (b) and RIB (c) (PICO 1)



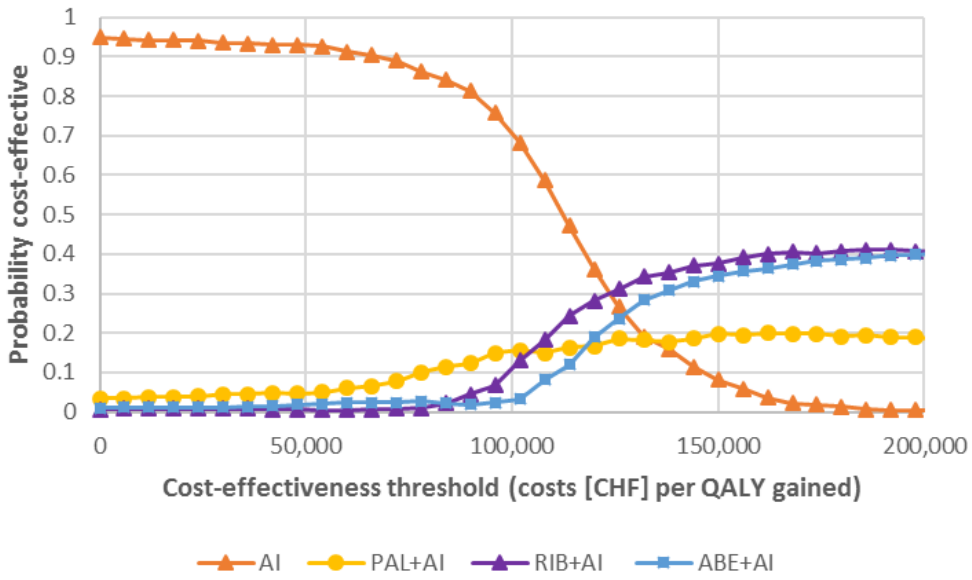
Strategies not shown in the graph or with an ICER represented as zero were dominated. If with varying parameter values, a dominated strategy became non-dominated, this is represented by a line moving from zero to the first calculated ICER value. If a non-dominated strategy became dominated, this was represented by a line toward an ICER represented as zero. ABE = abemaciclib; AI=aromatase inhibitor; CHF = Swiss francs; PAL=palbociclib; QALYG=quality-adjusted life years gained; RIB=ribociclib; at 80% price reduction of PAL or more, AI became dominated and ABE+AI was compared to PAL+AI

In the scenario analysis assuming mean weighted HR OS (PFS) AI alone vs. AI+CDK4/6 inhibitors of 1.326 (1.912), the ICER of RIB+AI vs. AI was 147,400 CHF per QALYG and ABE+AI and PAL+AI were dominated. (Appendix Table 47 and Table 48)

8.2.5.3.3 Probabilistic sensitivity analysis AI-related regimens (PICO 1)

The results of the probabilistic-sensitivity analysis displayed in Figure 33 show that ABE+AI is cost effective in 40% of simulations at a willingness-to-pay (WTP) threshold of 198,000 CHF per QALYG. RIB+AI is cost effective in 41% of the simulations at this threshold. At a WTP of 150.000 CHF per QALYG, AI was cost effective in 9% of the simulations, PAL+AI in 20%, ABE+AI in 34% and RIB+AI in 38% of the simulations. At a WTP of 100.000 CHF per QALYG, AI was cost effective in 68% of the simulations, PAL+AI in 16%, ABE+AI in 3% and RIB+AI in 13% of the simulations.

Figure 33: Cost-effectiveness acceptability curve AI-related regimens (PICO 1)

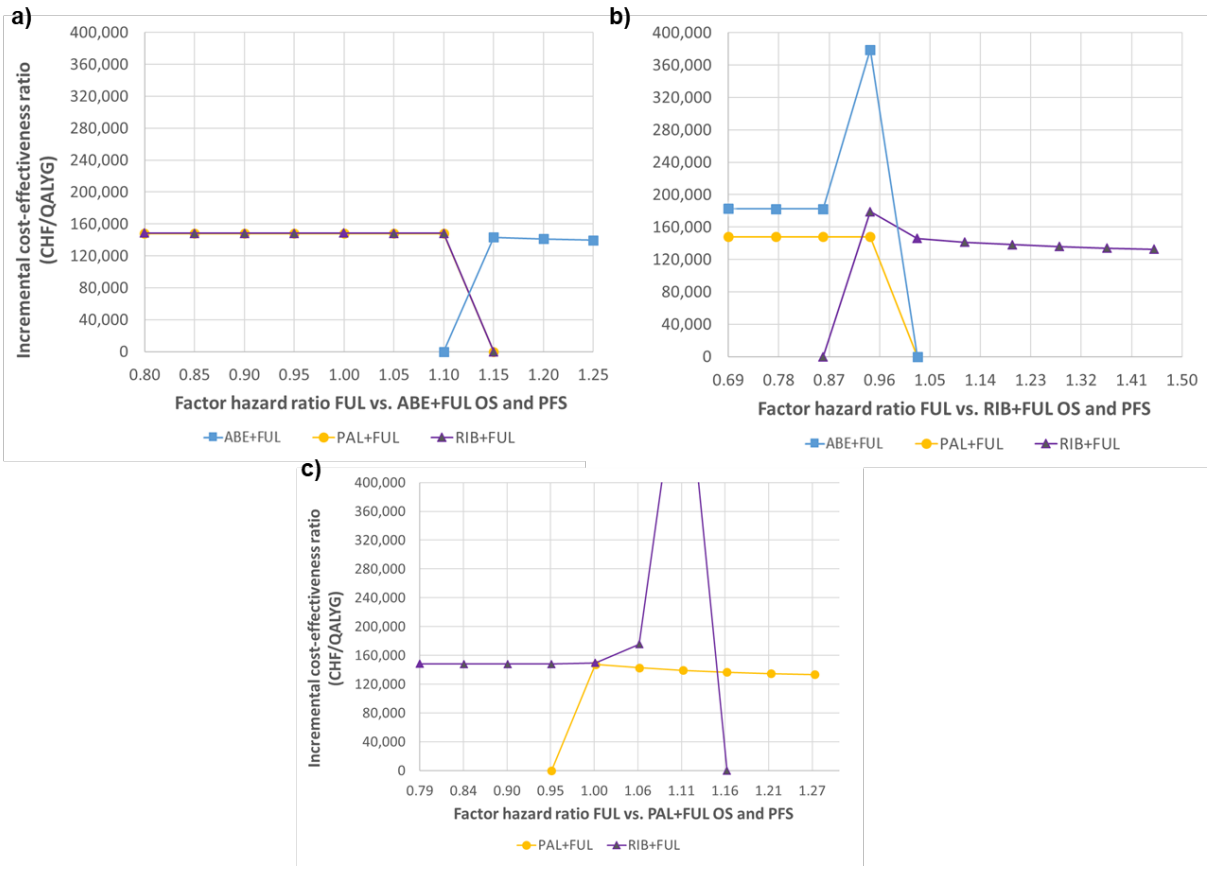


ABE=abemaciclib; CHF=Swiss francs; FUL=fulvestrant; PAL=palbociclib; QALY=quality-adjusted life years; RIB=ribociclib

8.2.5.3.4 Deterministic sensitivity analyses FUL-related regimens (PICO 2)

Base-case results of cost-effectiveness of FUL-related regimens (PICO 2) were particularly sensitive to the hazard ratios for OS and PFS of the compared interventions. Figure 34 shows ICERs of non-dominated strategies. ABE+FUL was no longer (weakly) dominated with increased hazard ratios by a factor of 1.1 for OS and PFS of FUL vs ABE+FUL (Figure 34a) (corresponding to a hazard ratio of 2.16 for PFS and 1.45 for OS) or decreased hazard ratios by a factor of 0.943 for the overall and progression-free survival for FUL vs. RIB+FUL (Figure 34b) (corresponding to a hazard ratio of 1.71 for PFS and 1.35 for OS). PAL+FUL became dominated when decreasing the hazard ratios by a factor of 0.95 for the overall and progression-free survival for FUL vs. PAL+FUL (Figure 34c) (corresponding to a hazard ratio of 1.91 for PFS and 1.17 for OS).

Figure 34: Sensitivity analyses on hazard ratios of OS and PFS, FUL vs. ABE+FUL (a), RIB+FUL (b) and PAL+FUL (c) (PICO 2)



The factor by which the hazard ratios for both OS and PFS were varied simultaneously in the sensitivity analyses is plotted on the x-axes. Strategies not shown in the graph or with an ICER represented as zero were dominated. If with varying parameter values, a dominated strategy became non-dominated, this is represented by a line moving from zero to the first calculated ICER value. If a non-dominated strategy became dominated, this was represented by a line toward an ICER represented as zero.

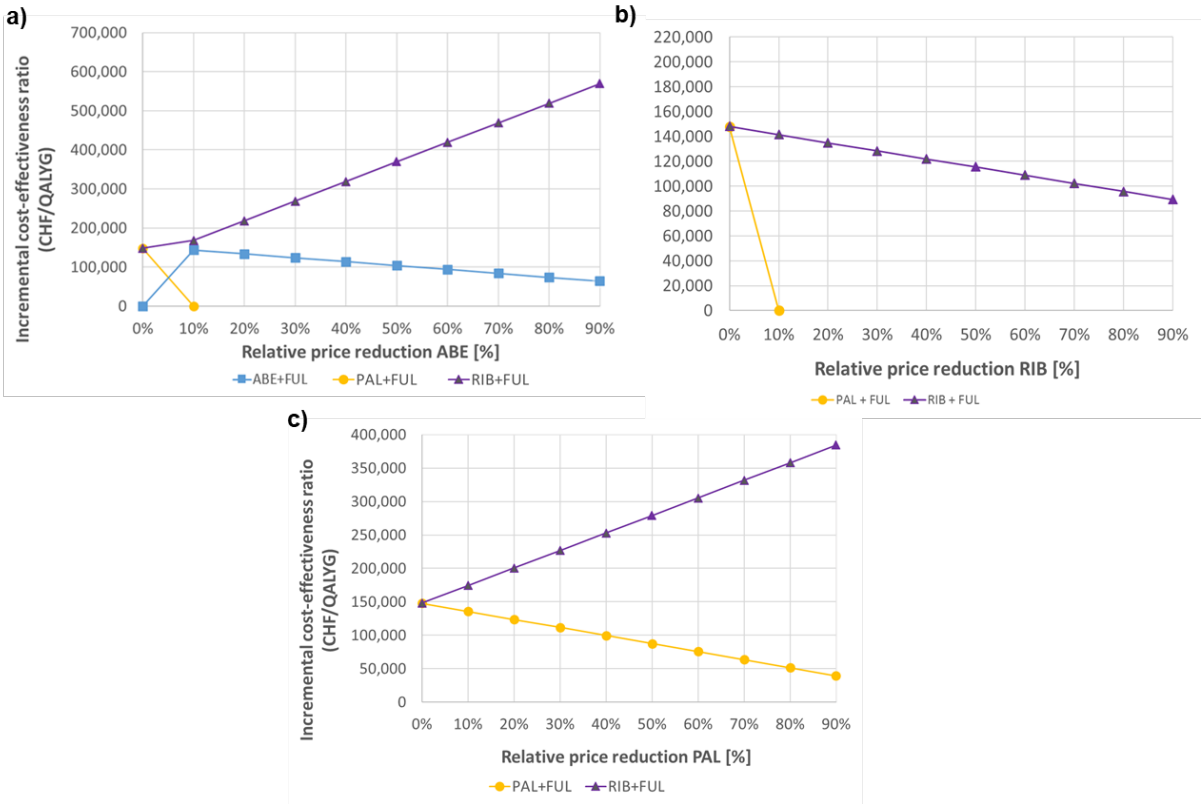
ABE=abemaciclib; CHF=Swiss francs; FUL=fulvestrant; OS=overall survival; PAL=palbociclib; PFS=progresseion free survival; QALYG=quality-adjusted life years gained; RIB=ribociclib

PAL+FUL became a dominated strategy when we decreased follow-up costs below 5,244 CHF (Appendix Figure 109), increasing follow-up costs in the CDK4/6 inhibitor treatment while holding follow-up costs for FUL constant using a factor of 1.025 (corresponding to 6,257 CHF) (Appendix Figure 98), decreased the utility of individuals treated with PAL+FUL to 0.72 (Appendix Figure 106), increased the utility of individuals treated with RIB+FUL in PFS to 0.74 (Appendix Figure 107), increased utility of individuals in post progression above 0.482 (Appendix Figure 108) and increased OS and PFS for FUL by a factor of 1.12 (corresponding to mean PFS of 6.58 month and mean OS of 32.36 month) (Appendix Figure 104). Base-case results were robust for variations in the amount of individuals with dose reduction in PAL+FUL and ABE+FUL. For variations in the amount of individuals with dose reduction in RIB+FUL see (Appendix Figure 103).

8.2.5.3.5 Scenario analyses FUL-related regimens (PICO 2)

Scenario analyses on relative price reduction of ABE, PAL and RIB are displayed in Figure 35 (excluding dominated strategies). Our scenario analysis showed that a 10% price reduction of ABE led to a change in the ranking of the strategies with an ICER of ABE+FUL vs. FUL of 143,937 CHF per QALYG and an ICER of RIB+FUL vs. ABE-FUL of 168,204 CHF per QALYG with PAL+FUL being dominated (Figure 35a). A 10% price reduction of RIB led to a change in the ranking of the strategies with an ICER of RIB+FUL vs. FUL of 141,455 CHF/QALYG and PAL+FUL being dominated (Figure 35b). The impact of price reduction of PAL on ICER values are displayed in Figure 35c.

Figure 35: Scenario analyses on relative price reduction ABE (a), RIB (b) and PAL (c) (PICO 2)



Strategies not shown in the graph or with an ICER represented as zero were dominated. If with varying parameter values, a dominated strategy became non-dominated, this is represented by a line moving from zero to the first calculated ICER value. If a non-dominated strategy became dominated, this was represented by a line toward an ICER represented as zero. ABE=abemaciclib; CHF=Swiss francs; FUL=fulvestrant; PAL=palbociclib; QALYG=quality-adjusted life years gained; RIB=ribociclib

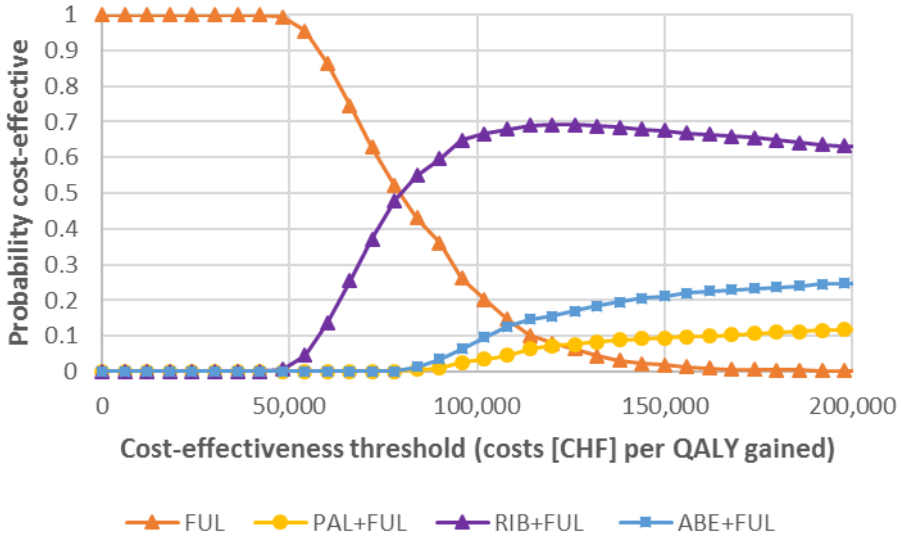
Variations of costs for doctors' visit, the percentage of patients receiving CT and the percentage of patients receiving PET-CT had no impact on the ranking of the strategies.

In the scenario analysis with a HR OS (PFS) of 1.316 (1.947) for FUL alone vs. FUL+CDK4/6 inhibitors, the ICER of RIB+FUL vs. FUL was 138,989 CHF per QALYG and ABE+FUL as well as PAL+FUL were dominated (Appendix Table 50 and Table 51).

8.2.5.3.6 Probabilistic sensitivity analysis FUL-related regimens (PICO 2)

The results of the probabilistic-sensitivity analysis displayed in Figure **36** show that RIB+FUL was cost-effective in 50% of simulations at a threshold of 78,000 CHF per QAL-YG. ABE+FUL and PAL+FUL were cost-effective in 0% of the simulations at this threshold. At a WTP threshold of 150,000 CHF per QALYG, RIB+FUL was cost-effective in 68%, ABE+FUL in 21%, PAL+FUL in 10% and FUL in 2% of the simulations. At a WTP threshold of 100,000 CHF per QALYG, RIB+FUL was cost-effective in 67%, ABE+FUL in 10% and PAL+FUL in 4% of the simulations.

Figure 36: Cost-effectiveness acceptability curve FUL-related regimens (PICO 2)



ABE=abemaciclib; CHF=Swiss francs; FUL=fulvestrant; PAL=palbociclib; QALY=quality-adjusted life years; RIB=ribociclib

8.2.6 Findings budget impact

Table 20 and Table 21 show the results of the budget impact analysis for an incident cohort in the first year of treatment. It was presumed to comprise around 1,160 patients based on several assumptions and sources (listed in Table 52 in the Appendix) and reflects the number of Swiss patients newly diagnosed with HR+/HER2- LA/MBC, either as de novo diagnoses or because of disease recurrence/progression (see Table 52 in the Appendix). It does not reflect the overall number of patients currently living with HR+/HER2- LA/MBC, which might be three to four times as high (the median overall survival of MBC being around 3 years (see Chapter 3).[ix]

[ix] Mariotto et al. 2017[179] estimated the prevalence of MBC for the US population in a 2020 prognosis to amount to 168,292 or 0.05% of US population (https://www.census.gov/). Transferring this result to the Swiss population of around 8.6 million (Swiss federal statistical office), MBC prevalence would approximate 4,400 patients. The proportion of HR+/HER2-BC was estimated by

Current scenario, PICO 1 (see Table 20): Based on expert estimates we assumed that 44% of patients received a treatment with PAL+AI, 19% with RIB+AI, 7% with ABE+AI, 23% with AI monotherapy and 8% with other therapies. We calculated direct treatment costs for patients in the PICO 1 population, newly starting with treatment, to amount to around 29.04 million CHF for the first year of treatment. This includes all costs depicted in Table 15. It does not include costs of treatment regimens other than AI+CDK4/6 inhibitor combination or AI monotherapy. Expected costs for the second, third, fourth and fifth year of treatment amounted to 23.85, 19.20, 15.03 and 11.58 million CHF, respectively (rounded values, not shown in Table 20). These costs include transitions to disease progression and death within the cohort.

Revised scenario 1, PICO 1 (see Table 20): When PAL is delisted patients receive RIB or ABE instead of PAL (which in the model also changes time to disease progression / death and related costs). Direct treatment costs for the incident cohort in the first year of treatment decrease by around 1.32 million CHF compared to the current scenario.

Revised scenario 2, PICO 1 (see Table 20): When RIB is delisted patients receive PAL or ABE instead of RIB (which in the model also changes time to disease progression / death and related costs). Direct treatment costs for the incident cohort in the first year of treatment increase by around 0.92 million CHF compared to the current scenario.

Revised scenario 3, PICO 1 (see Table 20): When ABE is delisted patients receive PAL or RIB instead of ABE (which in the model also changes time to disease progression / death and related costs). Direct treatment costs for the incident cohort in the first year of treatment decrease by around 0.19 million CHF compared to the current scenario.

Current scenario, PICO 2 (see Table 21): Based on expert estimates we assumed that 36% of patients received a treatment with PAL+FUL, 16% with RIB+FUL, 6% with ABE+FUL, 10% with FUL monotherapy and 33% with other therapies. We calculated direct treatment costs for patients in the PICO 2 population, newly starting with treatment, to amount to around 12.42 million CHF for the first year of treatment. This includes all costs depicted in Table 15. It does not include costs of treatment regimens other than FUL+CDK4/6 inhibitor combination or FUL monotherapy. Expected costs for the second, third, fourth and fifth year of treatment amounted to 9.74, 7.27, 5.31 and 3.84 million CHF, respectively (rounded values, not shown in Table 21). These costs include transitions to disease progression and death within the cohort.

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our experts to be 75% in Switzerland, yielding a rough estimate of 3,300 for HR+/HER2- MBC prevalence. This number excludes patients with LA BC for which we did not have prevalence estimates.

Revised scenario 1, PICO 2 (see Table 21): When PAL is delisted patients receive RIB or ABE instead of PAL (which in the model also changes time to disease progression / death and related costs). Direct treatment costs for the incident cohort in the first year of treatment decrease by around 0.11 million CHF compared to the current scenario.

Revised scenario 2, PICO 2 (see Table 21): When RIB is delisted patients receive PAL or ABE instead of RIB (which in the model also changes time to disease progression / death and related costs). Direct treatment costs for the incident cohort in the first year of treatment increase by around 0.10 million CHF compared to the current scenario.

Revised scenario 3, PICO 2 (see Table 21): When ABE is delisted patients receive PAL or RIB instead of ABE (which in the model also changes time to disease progression / death and related costs). Direct treatment costs for the incident cohort in the first year of treatment decrease by around 0.04 million CHF compared to the current scenario.

Univariate sensitivity analyses: Decreasing or increasing incidence estimates directly translated into lower or higher costs within all scenarios (changing absolute, but not relative differences between scenarios). Estimates regarding the proportion of ET+CDK4/6 inhibitor combination therapy versus AI or FUL monotherapy versus the proportion of other treatments in the PICO1 and PICO2 population differed between experts. In both PICO populations expert 1 estimated the proportion of combination therapy to be lower and the proportions of monotherapy and other therapies to be higher. Accordingly all budget impact estimates decreased with expert 1 estimates and increased with expert 2 estimates, with slight changes also in relative differences (see Table 53, Table 54, Table 55 and Table 56 in the Appendix). Decreasing the price of one of the CDK4/6 inhibitors (while keeping the other two at base case level) makes a disinvestment in this inhibitor more costly and, at the same time, a disinvestment in one of the others less costly: Whereas in base case a PAL disinvestment scenario leads to a minus of around 5% in total direct PICO1 treatment costs (1.32 million CHF, see above), it leads to a plus of around 5% when the price of PAL has been reduced by 20% and to a plus of around 24% when the price has been reduced by 50% (see Appendix Figure 112, Figure 113 and Figure 114). The same applies to the other CDK4/6 inhibitors, but with a smaller impact as PAL has the largest market share. This pattern can also be seen in PICO 2 treatment costs. Here the overall impact size in all three CDK 4/6 inhibitors is even smaller (see Appendix Figure 115, Figure 116 and Figure 117).

Table 20: Results budget impact analysis PICO 1 referring to an incident cohort (first year of treatment)

Treatment	direct costs per patient in the 1st year of treatment, CHF	current scenario*			Revised scenario 1*			Revised scenario 2*			Revised scenario 3*		
		% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF
PAL+AI	48,058	44%	355	17,044,970	0%			60%	489	23,510,303	49%	394	18,938,855
RIB+AI	42,368	19%	156	6,611,875	51%	416	17,631,668	0%			21%	173	7,346,528
ABE+AI	49,732	7%	57	2,822,197	19%	151	7,525,860	10%	78	3,892,686	0%		
AI	14,066	23%	182	2,565,674	23%	182	2,565,674	23%	182	2,565,674	23%	182	2,565,674
others	-	8%	61	-	8%	61	-	8%	61	-	8%	61	-
total		100%	811	29,044,717‖	100%	811	27,723,202‖	100%	811	29,968,663‖	100%	811	28,851,058‖
Difference revised vs. current scenario, incident cohort							-1,321,515			923,947			-193,659

ABE=abemaciclib; AI=aromatase inhibitor; CHF = Swiss Francs; PAL=palbociclib; PICO=population, intervention, comparator, outcome; RIB=ribociclib
* see Section 8.1.4.6, †rough estimate see Table **52** in the Appendix, ‖excludes costs of other therapy regimes (row "others"), # source: expert estimates

Table 21: Results budget impact analysis PICO 2 referring to an incident cohort (first year of treatment)

Treatment	direct costs per patient in the 1st year of treatment, CHF	current scenario*			Revised scenario 1*			Revised scenario 2*			Revised scenario 3*		
		% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF
PAL+FUL	56,323	36%	125	7,032,496	0%			50%	172	9,699,995	40%	139	7,813,884
RIB+FUL	54,618	16%	55	3,000,604	42%	147	8,001,611	0%			18%	61	3,334,004
ABE+FUL	57,806	6%	20	1,154,829	15%	53	3,079,545	8%	28	1,592,868	0%		
FUL	35,522	10%	35	1,234,152	10%	35	1,234,152	10%	35	1,234,152	10%	35	1,234,152
others	-	33%	113	-	33%	113	-	33%	113	-	33%	113	-
total		100%	347	12,422,082‖	100%	347	12,315,308‖	100%	347	12,527,015‖	100%	347	12,382,041‖
Difference revised vs. current scenario, incident cohort							-106,774			104,933			-40,040

ABE=abemaciclib; AI=aromatase inhibitor; CHF = Swiss Francs; PAL=palbociclib; PICO=population, intervention, comparator, outcome; RIB=ribociclib
* see Section 8.1.4.6, †rough estimate see Table **52** in the Appendix, ‖excludes costs of other therapy regimes (row "others"), # source: expert estimates

Summary statement costs, cost-effectiveness and budget impact

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For PICO 1, our analysis showed that ABE+AI vs. RIB+AI has an ICER of 166,787 CHF per QALYG and RIB+AI vs. AI monotherapy has an ICER of 126,860 CHF per QALYG. PAL+AI was dominated in the base-case analysis. Accounting for parameter uncertainty in a probabilistic-sensitivity analysis at a WTP of 150.000 CHF per QALYG, AI was cost effective in 9% of the simulations, PAL+AI in 20%, ABE+AI in 34% and RIB+AI in 38% of the simulations. For PICO 2, our analysis showed that PAL+FUL vs. FUL monotherapy has an ICER of 147,808 CHF per QALYG and RIB+FUL vs. PAL+FUL has an ICER of 148,342 CHF per QALYG. ABE+FUL was dominated in the base-case analysis. Accounting for parameter uncertainty in a probabilistic-sensitivity analysis, at a WTP threshold of 150,000 CHF per QALYG, RIB+FUL was cost-effective in 68%, ABE+FUL in 21%, PAL+FUL in 10% and FUL in 2% of the simulations.

With PAL respectively ABE disinvestment scenario cost savings of around 1.32 respectively 0.19 million CHF in the first year can be expected in those HR+/HER2-LA/MBC patients that newly started treatment with CDK4/6+AI or AI monotherapy, and cost savings of around 0.11 respectively 0.04 million CHF in HR+/HER2-LA/MBC patients that newly started treatment with CDK4/6+FUL or FUL monotherapy. With a RIB disinvestment scenario additional costs of around 0.92 in the first year can be expected in those HR+/HER2-LA/MBC patients that newly started treatment with CDK4/6+AI or AI monotherapy, and of around 0.10 million CHF in HR+/HER2-LA/MBC patients that newly started treatment with CDK4/6 + FUL or FUL alone.

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9 Legal, social and ethical issues

9.1 Methodology legal, social and ethical issues

9.1.1 Databases and search strategy

The search strategy and the selection process are described in Subsection 7.1.1.2.

9.1.2 Other sources

Regarding the legal issue we consulted two juridical experts.

9.1.3 Assessment of quality of evidence

We did not conduct a quality assessment of the literature which was included.

9.1.4 Methodology data analysis legal, social and ethical issues

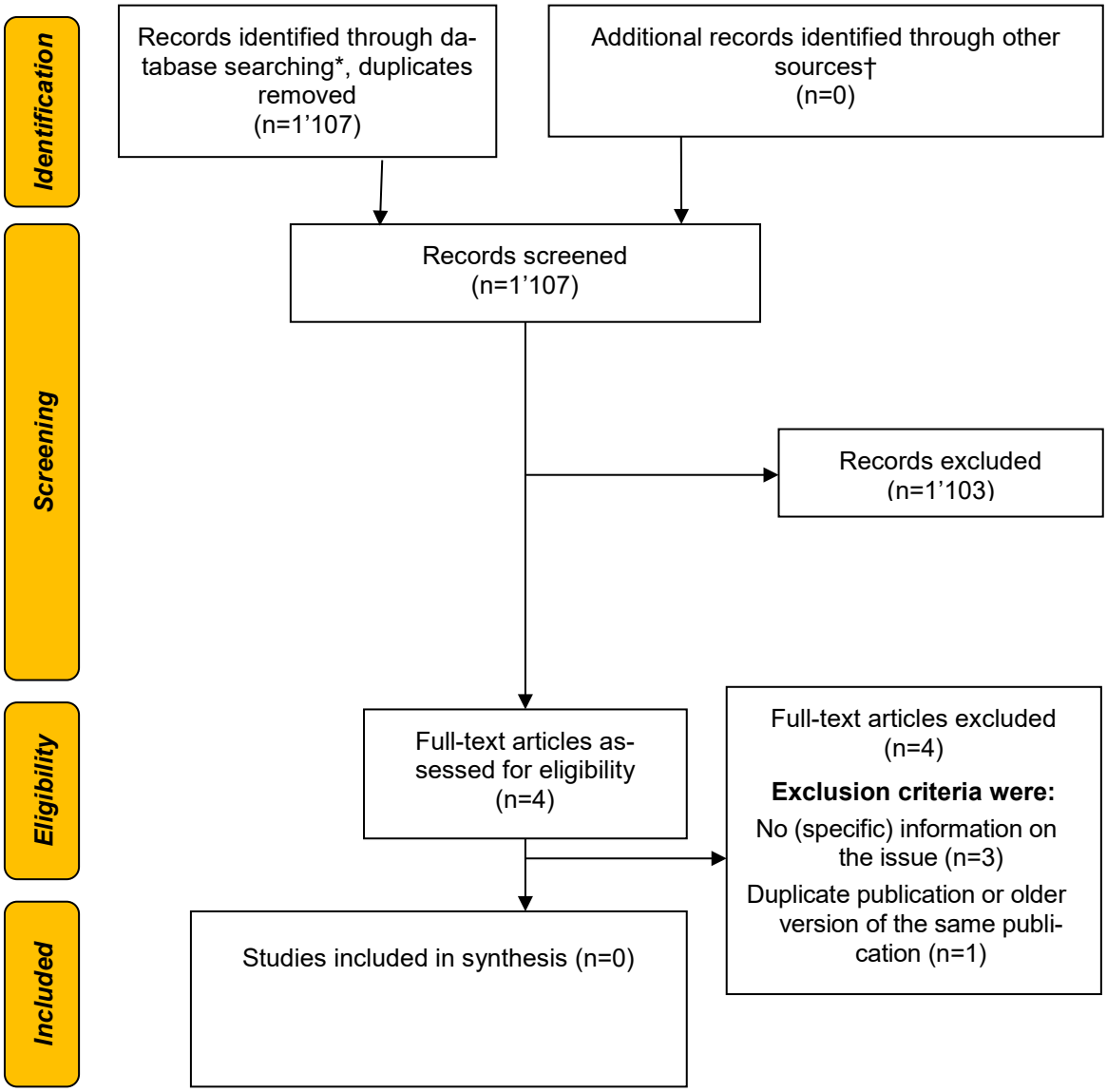
We conducted a narrative synthesis of the relevant ethical aspects discussed in the included papers. There was insufficient evidence regarding the social issue (see Subsection 9.2.4). The statements of the juridical experts were summarised.

9.2 Results legal, social and ethical issues

9.2.1 PRISMA flow diagram

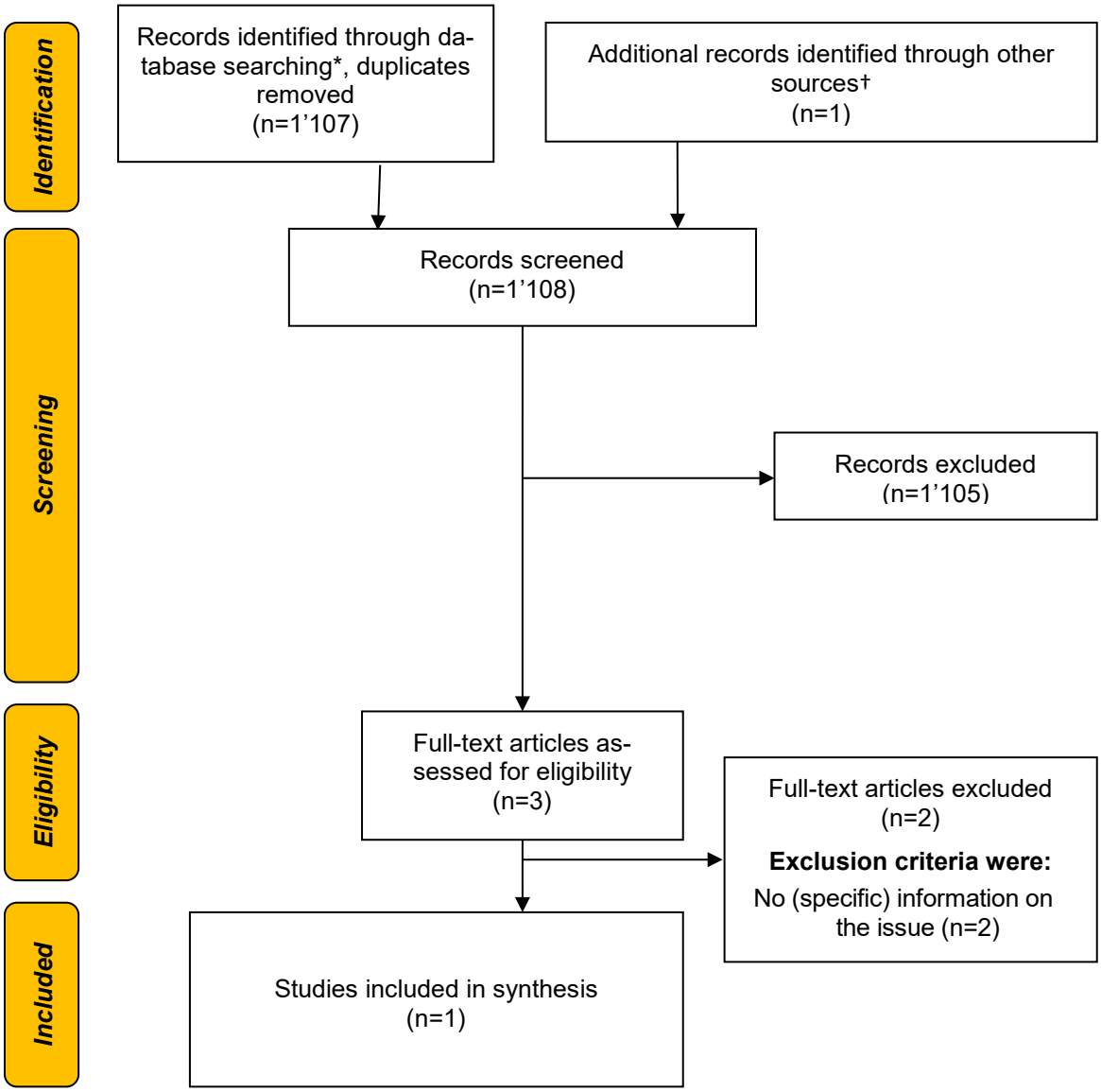
Table 58 in Appendix 15.8.8 shows the number of hits retrieved in the systematic search described in Subsection 7.1.1.2.1 in MEDLINE, EMBASE, The Cochrane Library, TRIP database, CRD and Scopus. After removing duplicates in Endnote, 1’107 hits remained. Figure 37 to Figure 39 show the PRISMA flow charts for publications on legal, social and ethical issues.

Figure 37: PRISMA flow chart for publications on legal issues



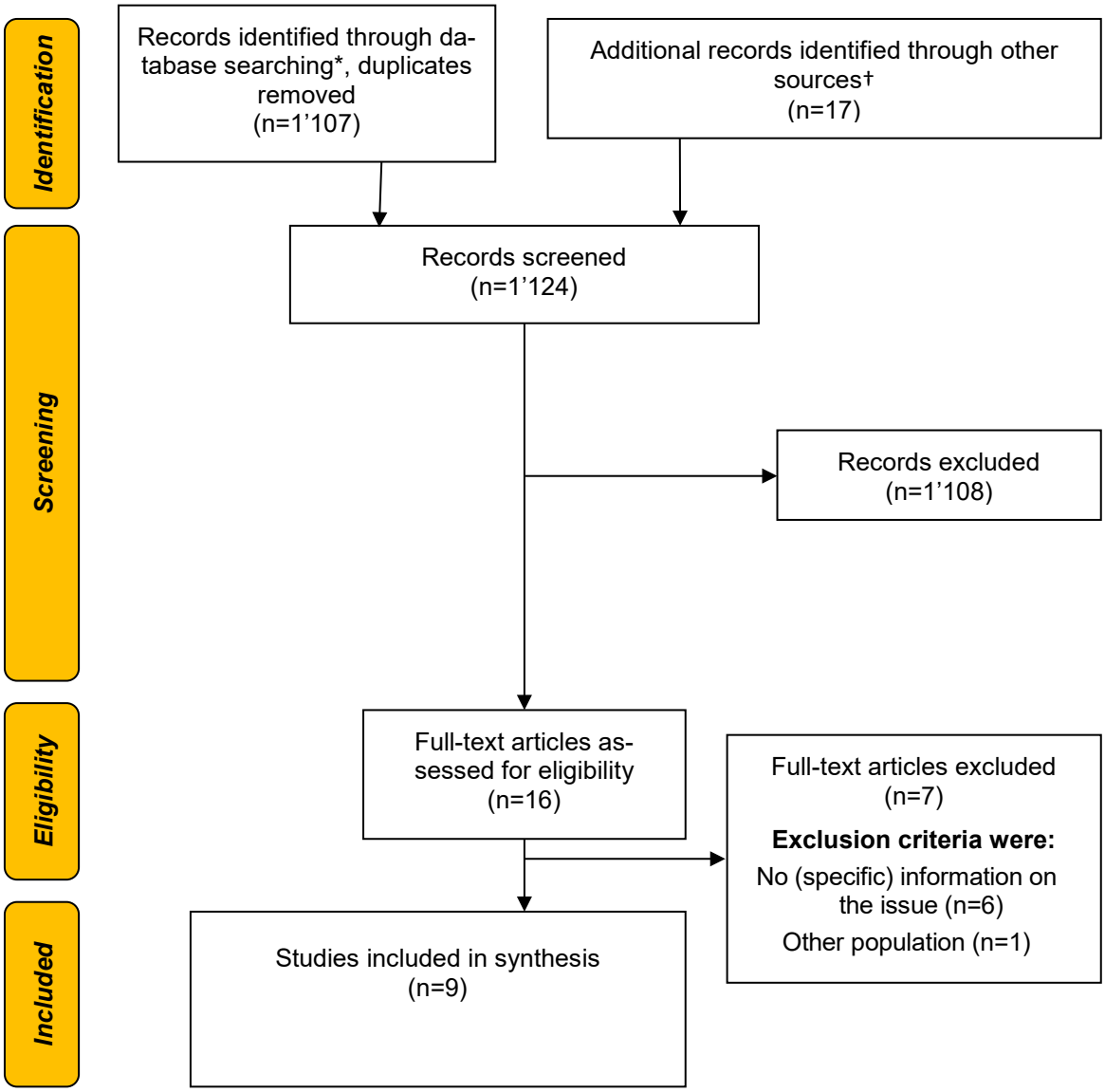
* Literature search for NRSs
† Refers to the literature search for RCTs

Figure 38: PRISMA flow chart for publications on social issues



* Literature search for NRSs
† Refers to the literature search RCTs

Figure 39: PRISMA flow chart for publications on ethical issues



* Literature search for NRSs
† Refers to the literature search for RCTs

9.2.2 Evidence tables

No relevant publications could be identified for the legal issue.

Regarding the social issue, one patient survey on treatment satisfaction was identified.[187]

Table 22: Evidence table for systematic reviews on ethical issues

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[188]	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[189]	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[190]	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 22: Evidence table for systematic reviews on ethical issues (continued)

Lux et al. 2019[191]	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[192]	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[193]	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[191]).
‡ Not 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 23: Evidence table for other publication types on ethical issues

Author Year	Study title	Study design	Relevant ethical issues	Sponsor(s)	Conflict of interest*
Freidlin et al. 2013[194]	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[195]	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[196]	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.

9.2.3 Findings legal issues

The literature search did not yield any publication relevant to the legal issue. According to the consulted juridical experts, article 71a-d of the Swiss regulation on health insurance would apply only in the case of disinvestment in all members of the substance class. Disinvesting in all three CDK4/6 inhibitors is not among the budget impact scenarios that were considered in this report (see 8.2.6). We therefore did not further assess the legal issue.

9.2.4 Findings social issues

The literature search yielded only one publication addressing social issues (a patient satisfaction survey in patients receiving either PAL+AI or PAL+FUL). This was insufficient to address the social issue that was defined in the scoping phase. In the scoping report we considered conducting patient interviews to gather information on patient expectations towards PAL. Before the start of the HTA phase the focus of this report was extended to the assessment of all three CDK4/6 inhibitors. Thus, appropriately assessing the social issue would require information on patient expectations towards all three inhibitors individually. Since PAL, RIB and ABE have been available to patients for very different time spans, gaining comparable information from patients on all three CDK4/6 inhibitors is not feasible. We therefore did not further assess the social issue.

9.2.5 Findings ethical issues

The choice of primary endpoints for clinical trials, especially in oncology, has been widely debated. The articles that we retrieved in the literature search (see Table 22 and Table 23) discuss this issue with a special focus on LA/MBC. In the following paragraphs we summarise the authors' main points.

OS is seen as a reliable endpoint as its measurement is objective and precise and its clinical relevance is obvious. However, trials that use OS as the primary endpoint require extensive follow-up and large cohort sizes, due to low event rates in order to reliably detect the effects of the studied interventions.[195] The detection of significant differences in OS is especially difficult in patient cohorts with relatively long post-progression survival (PPS) such as with LA/MBC patients. On the one hand this is because the relative OS gain decreases in patients with longer PPS and on the other hand because variability in the effectiveness of subsequent therapies can further conceal the potential benefit of a study's intervention.[191 195 196] Choice of post-progression therapies cannot be controlled in clinical trials, for obvious reasons.[189] Nevertheless, it has been argued that, even though the initial effects of the study intervention might be attenuated by the above-mentioned factors, OS is the appropriate endpoint because it reveals whether an intervention is useful to the overall population.[194 196]

The main advantages of PFS as the primary endpoint are the reduced follow-up period and sample size required to detect a significant effect of the study intervention. Disadvantages include potential subjectivity in measurement (investigators' judgement) and questionable clinical relevance. An assessment of tumour progression often measures asymptomatic increases in tumour burden, which are not noticeable to the patient.[194] There might be a possible benefit to prolonged PFS even in the absence of OS prolongation through the postponed necessity for subsequent, more toxic therapies but this argument has been met with scepticism by some authors.[191 194] In general, the benefit of prolonged PFS in the absence of prolonged OS should be measurable by assessing patient-reported outcomes such as QoL. It has been noted though, that the implementation of QoL as a clinical trial endpoint is complicated by the large number of different questionnaires, which hampers the comparability of results. An analysis of clinical trials in patients with ABC up to 2015 found that none used QoL as the primary endpoint.[190] Except for PALOMA-1, MONARCH 3 and MONARCHplus, all clinical trials that investigated CDK4/6 inhibitors and which have been included in this assessment reported QoL data but none of them used QoL as the primary endpoint.[49 51 55 61 68-70 75 146] An industry-sponsored patient survey in 282 MBC patients found that a majority of the patients in the study would prefer a hypothetical treatment with longer PFS even if OS and AEs were the same.[195 197]

While a PFS benefit might translate into an OS benefit, this is not necessarily the case. Validation of the correlation between surrogate and clinically relevant endpoints can be achieved using statistical methods and existing clinical trial data but it has been put forward by several authors that such validation would then only apply to very similar patient groups and treatments with similar modes of action.[191 193 194 196] A recent SR conducted an MA of 16 clinical trials (up to 2016) in HR+/HER2+ LA/MBC patients that used ANA, LET, EXE, FUL or TAM in at least one treatment arm and calculated the correlation between HRs of PFS and OS as r=0.72 (95% CI 0.35 to 0.90). The authors performed a surrogate threshold effect analysis and reported an upper confidence limit of HR_{PFS}<0.60 to ensure the possibility of drawing conclusions as to a significant effect on OS, noting, however, that, nevertheless, only final OS data can confirm the effect.[191] Of the clinical trials investigating CDK4/6 inhibitors that are included in this assessment, only PALOMA-1 and MONARCHplus reported HRs for PFS whose upper confidence limits did not exceed 0.60.[49 68]

Despite the controversies around PFS as a surrogate endpoint for OS, PFS was used as the primary endpoint in 60% of clinical trials in MBC patients between 2002 and 2012, while OS was used as the primary endpoint in only 24% of the trials. The FDA approved at least 19 interventions primarily on the basis of PFS data between 2002 and 2010. The approval of many ET agents was based on TTP or overall response rate (ORR) data.[195] The CDK4/6 inhibitors were approved in Switzerland based on PFS [19-21].

Summary statement legal, social and ethical issues

The legal issue regarding the application of article 71a-d of the Swiss regulation on health insurance is not relevant for this assessment because disinvestment in all three CDK4/6 inhibitors is not among the considered scenarios. The social issue regarding patient expectations could not be assessed because the literature review yielded insufficient evidence. The ethical issue concerning the choice of primary endpoints in clinical trials is a controversial topic in the scientific literature with some authors arguing in favour of and some against using PFS. Further research, including assessments of patients' perspectives, is needed to address the question of the clinical relevance of PFS and how PFS correlates with OS or QoL in patients with LA/MBC.

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10 Organisational issues

10.1 Methodology organisational issues

10.1.1 Databases and search strategy

The search strategy and the selection process are described in Subsection 7.1.1.2.

10.1.2 Other sources

We consulted Swissmedic's product information sheets on the CDK4/6 inhibitors for information about specific monitoring recommendations in Switzerland. In addition, we consulted two Swiss experts in clinical oncology.

10.1.3 Assessment of quality of evidence

We did not conduct a quality assessment of the literature which was included.

10.1.4 Methodology data analysis organisational issues

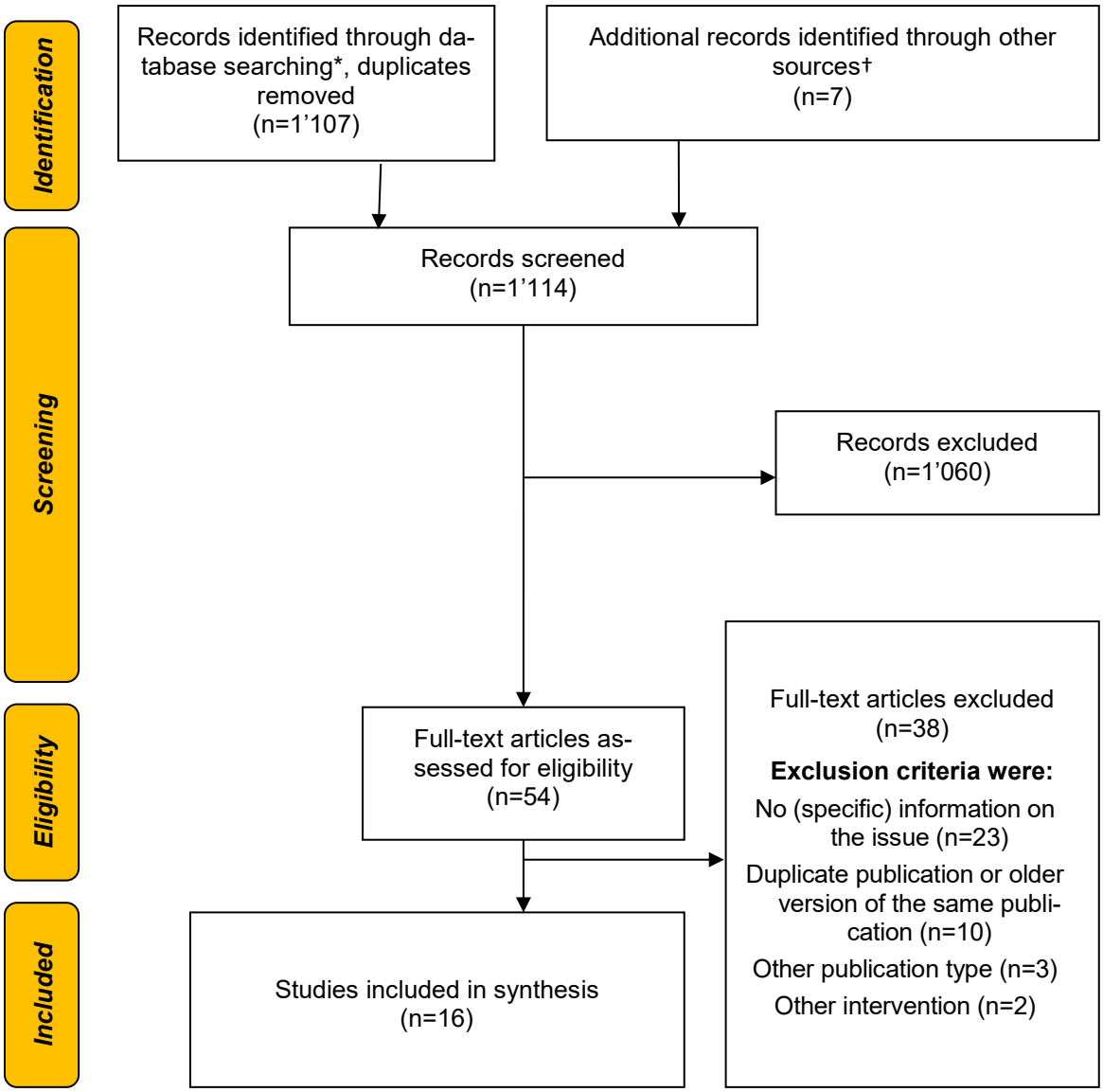
We conducted a narrative synthesis of the relevant issues discussed in the included documents and summarised the statements of the consulted clinical experts.

10.2 Results organisational issues

10.2.1 PRISMA flow diagram

Table 58 in Appendix 15.8.8 shows the number of hits retrieved in the systematic search described in Subsection 7.1.1.2.1 in MEDLINE, EMBASE, The Cochrane Library, TRIP database, CRD and Scopus. After removing duplicates in Endnote, 1'107 hits remained. Figure 40 shows the PRISMA flow chart for publications on organisational issues.

Figure 40: PRISMA flow chart for publications on organisational issues



* Literature search for NRSs
† Refers to the literature search for RCTs as well as other sources described in Subsection 7.1.2

10.2.2 Evidence table

The 16 publications selected in the preliminary synthesis during the scoping phase comprised 7 observational studies, 6 narrative reports and 3 guidelines. While the observational studies were mainly focused on PAL, the narrative reviews and the guidelines addressed the substance class of CDK4/6 inhibitors, including PAL, RIB and ABE. Because PICOs were revised during the scoping phase, we focused the evidence synthesis for organisational issues on the narrative reviews and guidelines. In addition, we consulted Swiss product information sheets for standard monitoring requirements. The literature included is listed in Table 24 and Table 25.

Table 24: Evidence table for narrative reviews on organisational issues

Author Year	**Title**	**Relevant organisational issues**	**Sponsor(s)**	**Conflict of interest***
Boyle et al. 2018[198]	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[181]	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[23]	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[199]	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[180]	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[200]	Managing advanced HR-positive, HER2-negative breast cancer with CDK4/6 inhibitors in postmenopausal 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 25: Evidence table for guidelines on organisational issues

Author Year	Title	Relevant organisational issues	Sponsor(s)	Conflict of interest*
Rugo et al.[201] 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.[202] 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.[12] 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.
† For the assessment we used the recently published 5th ESO-ESMO international consensus guidelines.[8]

10.2.3 Findings organisational issues

Due to their safety profiles, all of the CDK4/6 inhibitors require monitoring for AEs, which is described in the Swiss product information sheets.[19-21] It mainly consists of blood count monitoring, with some differences between substances. No AE monitoring, on the other hand, is recommended for ET agents.[166-170] According to the Swiss experts in clinical oncology who were involved in this report, a patient treated with AI or FUL monotherapy can, however, be assumed to require one doctor's visit including blood tests every three months. In addition, approximately half of the patients treated with FUL can be assumed to require a doctor's visit every month for the injection. All other monitoring requirements for CDK4/6 inhibitors can thus be considered additional organisational needs. An overview of the monitoring schedules for the different treatments, which served as input in the economic model, can be found in Subsection8.2.3, Table 16. The identified narrative reviews partially represent the official recommendations in other countries (Australia and the US) and all of them agree on necessary examinations and schedules that are very similar to the Swiss recommendations as well as the recommendations in the identified guidelines.[8 201 202]

Regarding AE treatment, the authors of the reviews largely agree that treatment with myeloid growth factors is generally not indicated for CDK4/6 inhibitor-induced neutropenia as - in contrast to chemotherapy-induced neutropenia - it is quickly reversible and manageable by dose reductions.[23 180 181] This opinion is also reflected in the product information sheets.[19-21] Optional direct treatments and diagnostic interventions for blood abnormalities at the physician's discretion, such as a bone marrow biopsy and red blood cell transfusion, are mentioned.[180 181] Diarrhoea and nausea should be treated with standard medications (e.g. loperamide and antiemetics). While antiemetics are not indicated prophylactically, diarrhoea should be treated proactively by providing the patients with loperamide and instructing them to take it at the first signs of loose stool, at least for patients treated with ABE.[23 181 198]

One review notes that 'caution should be taken when co-prescribing antiemetics with RIB due to the risk of QT prolongation'.[181] The initiation of treatment with any CDK4/6 inhibitor requires a careful examination and possibly a change in the patient's co-medications to avoid adverse drug interactions with inhibitors or inducers of CYP3A4.[19-21 202]

Summary statement organisational issues

The addition of CDK4/6 inhibitors to treatment with ET leads to additional doctor's visits and examinations for the monitoring of AEs. While CDK4/6 inhibitor-induced abnormal blood counts should be managed with dose modifications, other AEs such as gastrointestinal problems should be treated with standard medication. Special care and potential medication changes are required with CDK4/6 inhibitors in connection with co-medications that interfere with the activity of CYP3A4 and could therefore lead to adverse drug interactions.

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11 Additional issues

Swissmedic recently granted market authorisation for the alpha-specific PI3K inhibitor alpelisib (Picray®).[203] Alpelisib can be prescribed to patients with PIK3CA-mutated tumours, who make up about 40% of all HR+/HER2- LA/MBC patients.[204] While alpelisib is not yet reimbursed by OKP, it might cause a shift in the treatment paradigm of HR+/HER2- LA/MBC patients. In line with the current version of the ESO-ESMO international consensus guidelines, the Swiss experts in clinical oncology we consulted predict that due to the establishment of alpelisib in clinical practice, fewer patients will be treated with CDK4/6 inhibitors in PICO 2.[8] In addition, a substantial proportion of patients who progress on treatment with CDK4/6 inhibitors may be treated with alpelisib in the future.

12 Discussion

12.1 Discussion of analyses for efficacy and safety

Overall, our NMAs suggest superiority of ET+CDK4/6 inhibitor treatment with regards to efficacy (with different certainties and effect sizes for OS, QoL and PFS) but also that CDK4/6 inhibitor combination therapies are associated with an increased risk of AE3+ when compared with ET monotherapy. The data do not conclusively identify any of the CDK4/6 inhibitors as being superior to another. This is mainly due to the scarcity of primary studies. Our results are in line with several recent NMAs, addressing similar research questions.[205-208]

Major concerns in meta-analyses in general and NMA in particular are study heterogeneity, lack of transitivity and inconsistency, which can lead to biased pooled results. We were not able to statistically assess consistency (the statistical manifestation of transitivity) due to the lack of closed loops in our

treatment networks. Therefore, we aimed to ensure transitivity by reducing heterogeneity through rigorous inclusion criteria applied in the primary study selection.

To evaluate the effects of our decisions, we conducted several sensitivity analyses, addressing the effects of 1) patient age, 2) the decision to aggregate individual AIs into one treatment node and 3) the choice of fixed effect versus random effects model. Our results remained largely stable apart from changes in credibility intervals. There were almost no effects on treatment rankings. We could not assess confounders that have not been uniformly reported throughout the trials (such as number and type of prior therapies). Nevertheless, since the primary studies led to market authorisation of CDK4/6 inhibitors and ET agents for similar patient groups, they can be assumed to be jointly randomisable to a certain extent. Sensitivity analyses for the effect of the inclusion of trials from the supplementary set were not necessary because due to the structure of the networks the effect estimates for the decision set were not mediated by those trials.

In most of our analyses, the credibility intervals include 1, highlighting the uncertainty of the results. This can, in part, be attributed to the fact that we often had to use subgroups from the primary studies and the smaller sample sizes led to a reduced test power. The precision of our analysis moreover depends on the selection of fixed versus random effect models. Assuming negligible heterogeneity, the fixed effect model is the most appropriate choice for an NMA. However, the PICO 2 studies in particular showed a large heterogeneity and, consequently, the fixed effect model might overestimate the certainty of our results. On the other hand, the GRADE working group points out that sparse networks can lead to a widening of CIs and therefore recommends using the fixed effect model or a more informative prior.[209]

Our analyses come with several limitations. First and foremost, we were not able to assess consistency due to the lack of closed loops in the treatment networks. This reduces the reliability of indirect comparisons, especially in the presence of study heterogeneity. Further uncertainty derives from the non-proportional hazards that we found in most of the primary studies. Since missing proportionality usually results in a reduced effect size, this bias might result in an underestimation of the differences between the treatments. The available OS data from all of the clinical trials investigating CDK4/6 inhibitors were immature at the time of our assessment, thus the certainty of our OS analysis is limited. In addition, some information provided by the primary studies was inconclusive. For instance, individual articles reporting results from the MONALEESA-2 trial referred to Verma et al. 2017 (a conference abstract) for QoL data. Surprisingly, this abstract reported different values for QoL than the articles.[56] For the NMA we used the more conservative results from the published articles.

The number of available NRSs on patients treated with PAL is much higher than those of NRSs on patients treated with RIB or ABE. This finding was expected, given that PAL received market authorisation significantly earlier than RIB and ABE. The extended safety assessment, therefore, does not allow meaningful comparisons between the three CDK4/6 inhibitors.

Finally, the number of included studies for the individual treatments is very limited. For most treatments only one study was available. Thus, combined with the lack of closed loops, the fixed effect meta-analyses mainly reflect the results of the primary studies.

12.2 Discussion of health-economic analyses and budget impact

In PICO 1, based on our results, ABE+AI was most effective in terms of QALYG compared to RIB+AI and AI monotherapy, resulting in a discounted ICER of ABE+AI vs. RIB+AI of 166,787 CHF per QALYG and discounted ICER of RIB+AI vs. AI of 126,860 CHF per QALYG. The combination therapy PAL+AI was dominated. Our one way-sensitivity analyses showed that these results were sensitive to uncertainty in hazard ratios for OS and PFS. An increase in the hazard ratios of AI vs. RIB+AI from 1.76 to 1.87 for PFS and from 1.34 to 1.42 for OS led to a change in preferred strategies, that is, ABE+AI became a dominated strategy. A decrease in the hazard ratios of AI vs. RIB+AI from 1.76 to 1.74 for PFS and from 1.34 to 1.33 for OS led to a change in preferred strategies, that is, RIB+AI became a dominated strategy. An increase of the hazard ratio of AI vs. PAL+AI from 1.87 to 2.1 for PFS and from 1.19 to 1.34 for OS led to a change in preferred strategies, that is, PAL+AI became a non-dominated strategy. Considering the before-mentioned limited robustness of the comparisons between individual CDK4/6 inhibitors calculated in our NMAs, the cost-effectiveness comparisons between individual CDK4/6 inhibitors therefore have to be interpreted with caution.

A decrease in follow-up costs also had an impact on the ranking of strategies. RIB+AI became dominated when follow-up costs were changed from 6,105 CHF to 7,400 CHF. This is caused by the fact that the patients treated with RIB+AI spent more time in post-progression compared to ABE+AI, and we assumed that ABE+AI has the same mean OS as RIB+AI as the respective data from clinical trials are not yet available. PAL+AI became non-dominated when we increased follow-up costs to 8,097 CHF.

The ICER of 166,787 CHF per QALYG for ABE+AI vs. RIB+AI in the base-case analysis is above commonly accepted WTP for new drugs in other countries. The ICER of 126,860 CHF per QALYG for RIB+AI vs. AI monotherapy in the base-case analysis might be in an acceptable WTP range. For the US and the UK, thresholds ranging from 50,000 USD per QALYG to 150,000 USD per QALYG and above have

been reported.[210 211] [i] At a willingness to pay of 150.000 CHF per QALYG, AI was cost-effective in 9% of the simulations, PAL+AI in 20%, ABE+AI in 34% and RIB+AI in 38% of the simulations.

Our scenario analysis showed that a 10% price reduction of PAL led to a change in the ranking of the strategies with an ICER of 125,000 CHF per QALYG for PAL+AI vs. AI, an ICER of 134,610 CHF per QALYG for RIB+AI vs. PAL+AI and an ICER of 166,787 CHF per QALYG for ABE+AI vs. RIB+AI.

In PICO 2, based on our results, RIB+FUL was most effective in terms of QALYG compared to PAL+FUL and FUL monotherapy, resulting in a discounted ICER of 147,808 CHF per QALYG for PAL+FUL vs. FUL and a discounted ICER of 148,341 CHF per QALYG for RIB+FUL vs. PAL+FUL. The combination therapy ABE+FUL was dominated. Our one-way sensitivity analyses showed that these results were sensitive to uncertainty in hazard ratios for OS and PFS. An increase in the hazard ratios of FUL vs. ABE+FUL from 1.96 to 2.16 for PFS and from 1.32 to 1.45 for OS led to a change in preferred strategies, that is, ABE+FUL became a non-dominated strategy. A decrease of the hazard ratio of FUL vs. PAL+FUL from 2.01 to 1.91 for PFS and from 1.23 to 1.17 for OS led to a change in preferred strategies, that is, PAL+FUL became a dominated strategy. A decrease of the hazard ratio of FUL vs. RIB+FUL from 1.81 to 1.71 for PFS and from 1.43 to 1.35 for OS led to a change in preferred strategies, that is, RIB+FUL became a dominated strategy.

A decrease in follow-up costs also had an impact on the ranking of strategies. PAL+FUL became dominated at follow-up costs below 5,244 CHF. This is caused by the fact that the patients treated with PAL+FUL spent less time in post-progression compared to RIB+FUL.

At a threshold value of 78,000 CHF per QALYG, RIB+FUL was cost-effective in 50% of simulations and ABE+FUL as well as PAL+FUL were cost-effective in 0% of the simulations. At a WTP of 150,000 CHF per QALYG, RIB+FUL was cost-effective in 68% of simulations, ABE+FUL was cost-effective in 21% and PAL+FUL in 10% of the simulations.

Our scenario analysis showed that a 10% price reduction of ABE led to a change in the ranking of the strategies with an ICER of 143,937 CHF per QALYG for ABE+FUL vs. FUL and an ICER of 168,204 CHF per QALYG for RIB+FUL vs. ABE-FUL.

Our analyses have several limitations due to availability of evidence and resulting simplifying assumptions: (1) In PICO 1, we assumed the hazard ratio for OS of AI vs. RIB+AI as a proxy for the hazard ratio for OS for AI vs. ABE+AI due to lacking primary data. This was a conservative assumption because the

[i] "In a US context, the ratio may vary from $50K/QALYG up to $150K/QALYG - or more depending on the individual or the disease. For the National Health Service (NHS) in the UK, the threshold used on behalf of the NHS is £20,000/QALYG, ranging up to £50,000/QALYG for life-threatening conditions."204 Neumann, Cohen and Weinstein205 recommend "if one had to select a single threshold outside the context of an explicit resource constraint or opportunity cost […] either $100,000 or $150,000 per QALY".

hazard ratio for PFS for AI vs. RIB+AI was lower than the hazard ratio for PFS for AI vs. ABE+AI. (2) Utility weights for the time individuals spent in the progression-free health state with CDK4/6 inhibitor treatment were taken from studies evaluating PAL+LET and PAL+FUL, respectively, both using the EQ-5D instrument. Thus, we did not consider the impact of different AEs among the three different CDK4/6 inhibitor regimens, because studies did not report on utility values. Disease-specific questionnaires used in the clinical trials cannot be directly mapped to calculate utility values. The CDK4/6 dependent frequency of severe adverse events (febrile neutropenia) was considered regarding the costs of each treatment arm. (3) We assumed that follow-up costs in the post-progression state are independent of the treatment provided in the progression-free health state. We tested the impact of follow-up costs in the sensitivity analyses. (4) We derived drug costs from the Swiss Specialties List. The current market prices may differ due to discounts provided by the manufacturers. (5) Costs of disease monitoring and treatment of febrile neutropenia were derived from reference hospitals and expert opinions as well as the international literature. Costs of other individual AEs could not be assessed and were therefore considered by assuming a lump sum based on an estimate by a clinical expert. (6) We did not include indirect costs (lost productivity). (7) In both models, mean time-to-event data were aggregated from the clinical trials that were included in the NMAs, and consequently, we did not fit survival curves to clinical trial data but assumed the time to progression or death to be exponentially distributed. We did not explicitly model background mortality because the age-standardised rate mortality was assumed to be included in the estimated OS.

In comparison to other health-economic studies, this is the first decision-analytic modelling assessing the comparative effectiveness and cost effectiveness of treatment regimens with the three CDK4/6 inhibitors PAL, RIB and ABE in combination therapies compared to the respective monotherapies AI (PICO 1) and FUL (PICO 2).

Our results are to a great extend in line with published health-economic studies summarised in this report. Zhang et al. concluded that “despite significant gains in progression-free survival over letrozole alone, the addition of palbociclib or ribociclib […] is not cost-effective in the United States”.[177] Adding PAL to FUL or LET was deemed unlikely to be cost-effective in another study for the United States of Mamiya et al. and in a Swiss study by Matter-Walstra et al.[172-174] In our study in PICO1 adding PAL to AI was dominated, in PICO 2 adding PAL to FUL was cost-effective at a threshold of 150,000 CHF per QALYG but results were sensitive to changes in various parameters. In our study in PICO 1, PAL+AI was weakly dominated by RIB+AI and AI, in PICO 2 RIB+AI was most effective and cost-effective at 150,000 CHF per QALYG. Other studies showed that RIB+AI was dominant compared to PAL+AI in terms of cost-effectiveness.[171 175] However, these international studies varied substantially with respect to costs, utility weights and clinical data that were synthesised in the models. None of these studies were conducted using efficacy data derived in an NMA.

Regarding budget impact, the expected direct costs per year of treatment in an incident cohort were, in the first year, highest for PAL+AI in PICO 1 and PAL+FUL in PICO 2. PAL – within both populations – has the highest market share, followed by RIB. ABE in both populations has the smallest market share. On the other hand, ABE and PAL are associated with higher treatment costs than RIB. Therefore, PAL and ABE disinvestment scenarios lead to cost savings, whereas a RIB disinvestment scenario leads to additional costs. Results of this budget impact analysis refer to an HR+/HER2- LA/MBC incident cohort (newly diagnosed with HR+/HER2- LA/MBC either as de novo diagnoses or because of disease recurrence/progression). The prevalent cohort of patients currently living with HR+/HER2- LA/MBC might be three to four times the number of this incident cohort (see Subsection 8.2.6). Among these patients in later years of treatment for HR+/HER2- LA/MBC, the proportion of patients in post-progression stages is presumably higher than in the incident cohort, thus reducing the overall budget impact of a disinvestment in any one CDK4/6 inhibitor in these patients.

The main limitations of the budget impact analysis – beyond those mentioned above regarding effectiveness and cost parameters – are the lack of (Swiss) data regarding incidence and prevalence of HR+/HER2- LA/MBC, limited availability of utilisation data (also due to time of market authorisation) and the fact that calculations could only be done for a HR+/HER2- LA/MBC incident cohort.

13 Conclusions

Based on the NMA results, the CDK4/6 inhibitors likely provide superior efficacy when compared to ET monotherapies but also a higher risk for AEs. Regarding the comparison of efficacy between individual CDK4/6 inhibitors, our results are too uncertain to draw conclusions. The certainty of the results is limited by the indirectness of the comparisons, partially missing or immature data for OS and QoL and the large credibility intervals. In the future, data from the 67 identified currently ongoing RCTs (24 of which investigate a CDK4/6 inhibitor) will provide important evidence for determining the optimal treatment for patients with HR+/HER2- LA/MBC.

The present study demonstrates that even if cancer drugs are effective, depending on the willingness-to-pay per QALYG, they may not be cost-effective unless the drug price will be reduced substantially. Our results suggest that among the CDK4/6 inhibitor combination treatments, PAL+AI is dominated in PICO 1 and ABE+FUL is dominated in PICO 2 in terms of cost-effectiveness. The certainty of the CEA results is limited due to several input parameters that had to be based on assumptions. Our CEA should be updated when mature OS data for all CDK4/6 inhibitor combination therapies are available from clinical trials, utility studies become available or actual drug prices are provided. The partitioned-survival models should be applied to test the impact of alternative survival distributions on the model outcomes. In the future, an expected value of perfect information (EVPI) analysis may shed light on further research

needed in order to decrease parameter uncertainty. More comparable QoL data for the CDK4/6 inhibitor treatment combinations would benefit the assessment of both, efficacy and cost-effectiveness, in terms of certainty and meaningfulness of the results.

A potential disinvestment in PAL or ABE would lead to reduced direct costs within an incident cohort, whereas a potential disinvestment in RIB would lead to additional costs, given that, in each scenario, patients are allocated to the other two CDK4/6 inhibitors.

14 References

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15 Appendices

15.1 Progression-free survival analyses (PFS)

15.1.1 PFS PICO 1

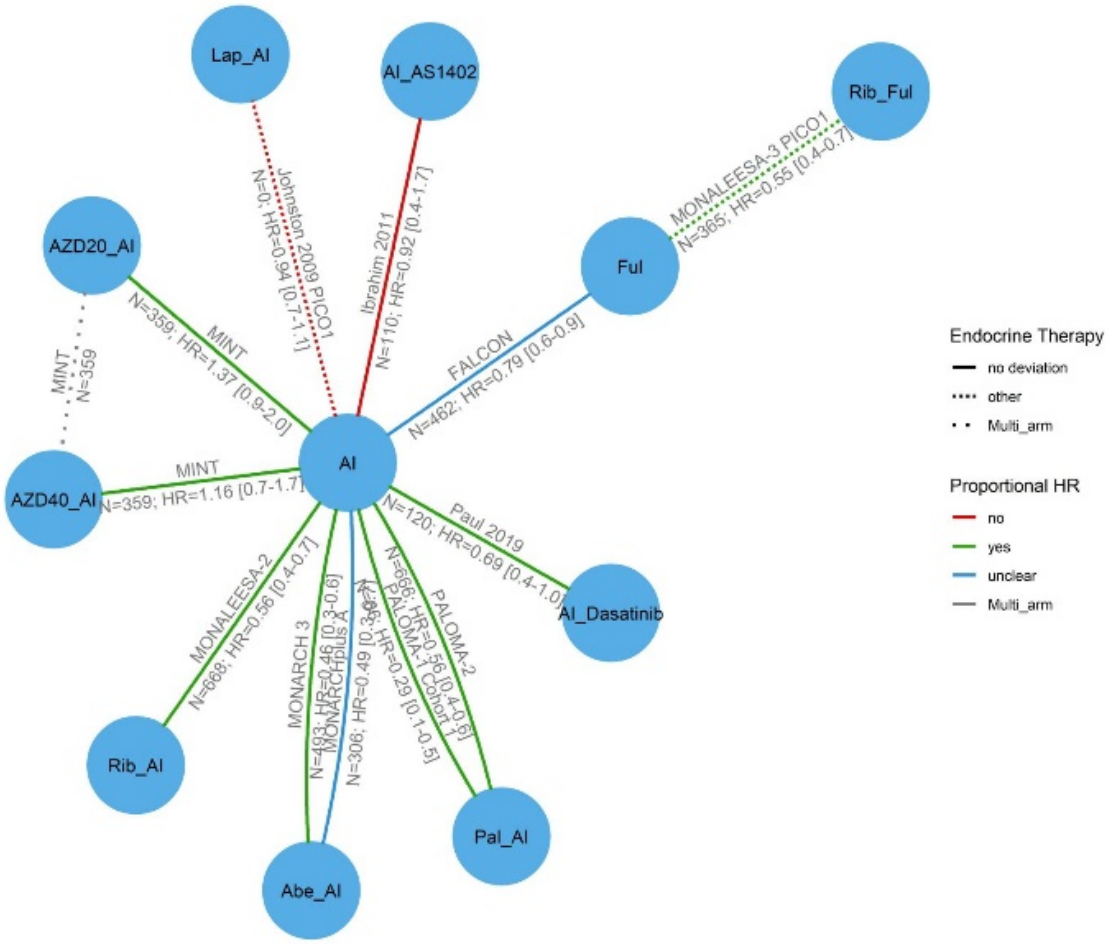
Network characteristics:

All eleven PICO 1 trials reported results on PFS. The network consists of eleven individual treatments. Most treatments were compared to AI. The comparisons ABE+AI vs. AI and PAL+AI vs. AI were each investigated in two trials. All other comparisons were investigated in one single trial each. The mean or

median age per study arm ranged from 60 to 66 years. The most recent articles for each respective trial were published between 2009 and 2019. Only two trials were completed before 2016.

Two studies showed a tendency for non-proportional HRs. We could not evaluate the Kaplan-Meier curves from two studies. Two studies did use a slightly different definition of endocrine resistance or did not provide enough data to assess whether their definition matched ours (Figure 41). Not aggregating

Figure 41: PICO 1 treatment network for PFS



the individual AIs led to a smaller network with six treatments and six trials. ABE+AI dropped out of the network in this scenario (Appendix, Figure 47).

Comparative Efficacy:

The SUCRA and forest plots show a tendency for improved PFS with either one of the CDK4/6 inhibitors combined with AI compared with AI monotherapy. The respective probabilities for each treatment to rank highest are indicated in Figure 42, Table 35 (Appendix) shows the probabilities for each rank for each treatment. The relative efficacy of RIB+FUL is mediated by the FALCON study that compared ANA with FUL and the certainty of this estimate therefore depends on the robustness of both, the MONALEESA-2 and the FALCON trials. The detailed results of the comparisons between all treatments are provided in the heat map (Figure 43).

Figure 42: PICO 1 SUCRA and forest plots for PFS; fixed effect model

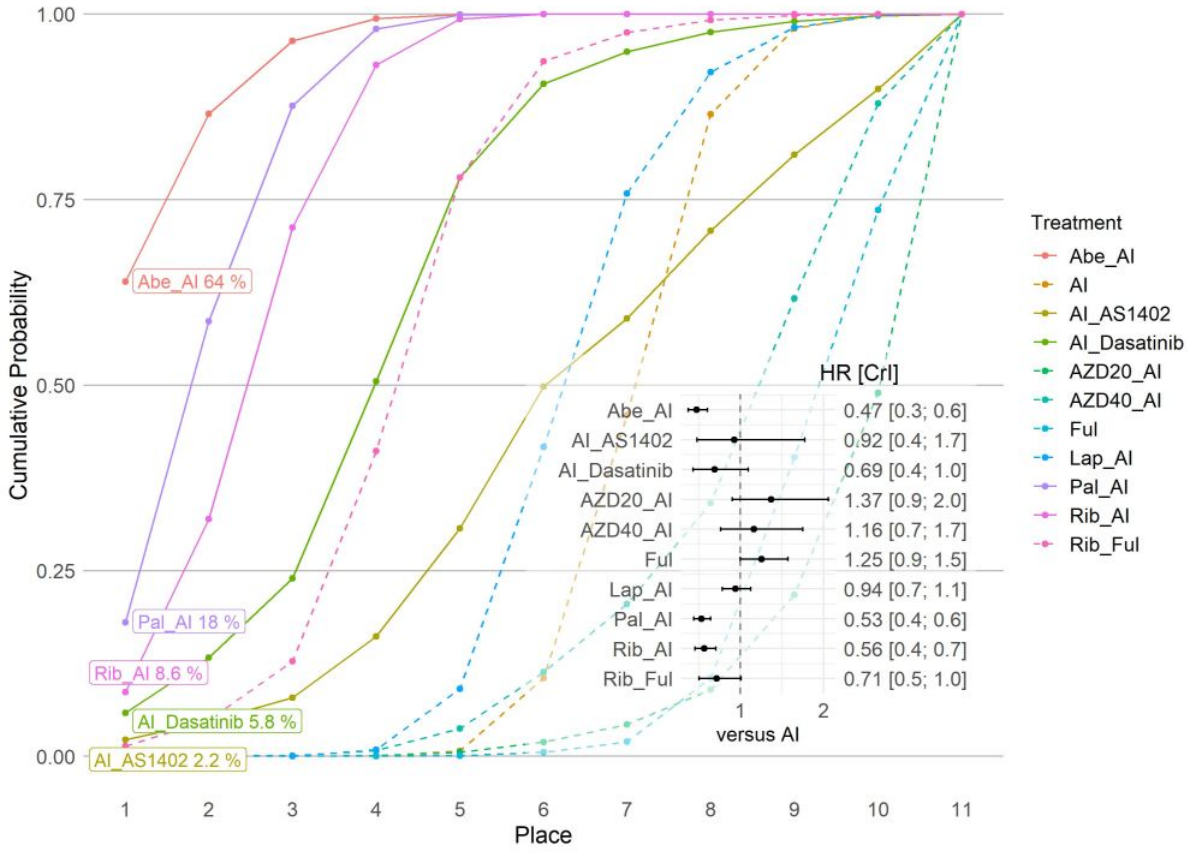
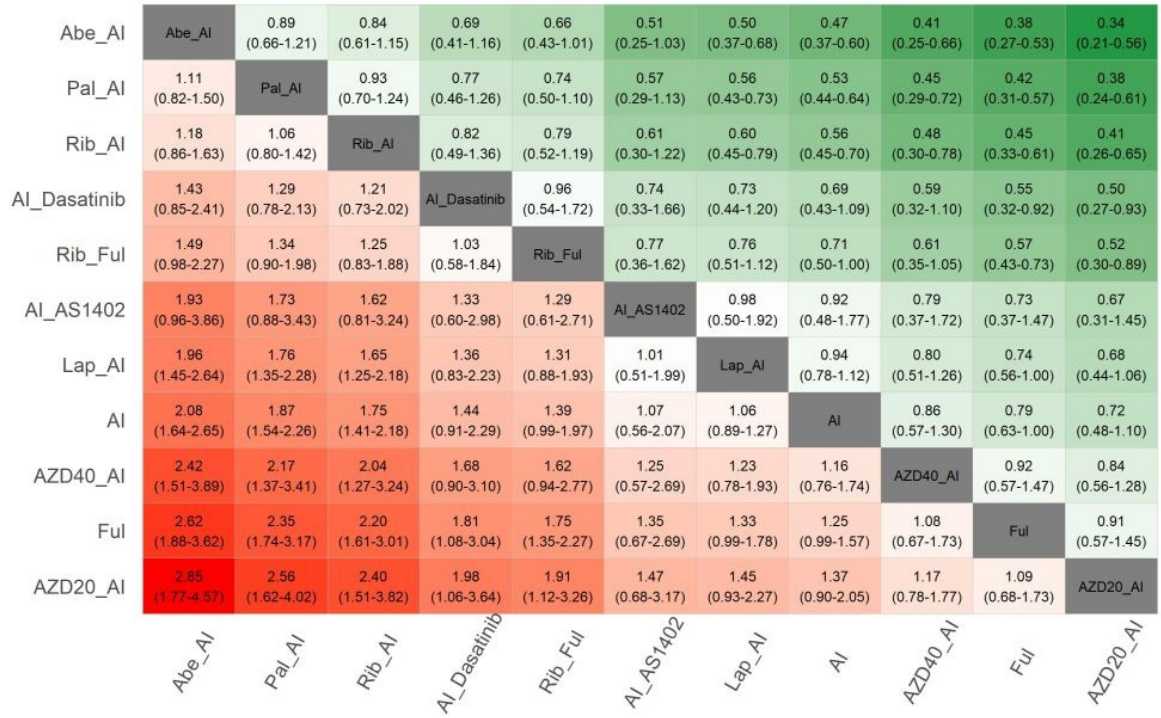


Figure 43: PICO 1 heat map for PFS; fixed effect model



Hazard ratios are indicated for treatments on Y-axis versus treatments on X-axis. Green fields indicate superiority of treatments on Y-axis, red fields inferiority of treatments on Y-axis.

Results remained stable with a tendency for a better efficacy of the CDK4/6 inhibitors in the network with the individual AIs (Appendix, Figure 48).

The random effects model shows comparable results with larger credibility intervals for the individual treatments (Appendix, Figure 49). The inclusion of age as predictor in the network meta regression led to similar results aside from an improved ranking for PAL compared to the other treatments (Appendix, Figure 50 and Figure 51).

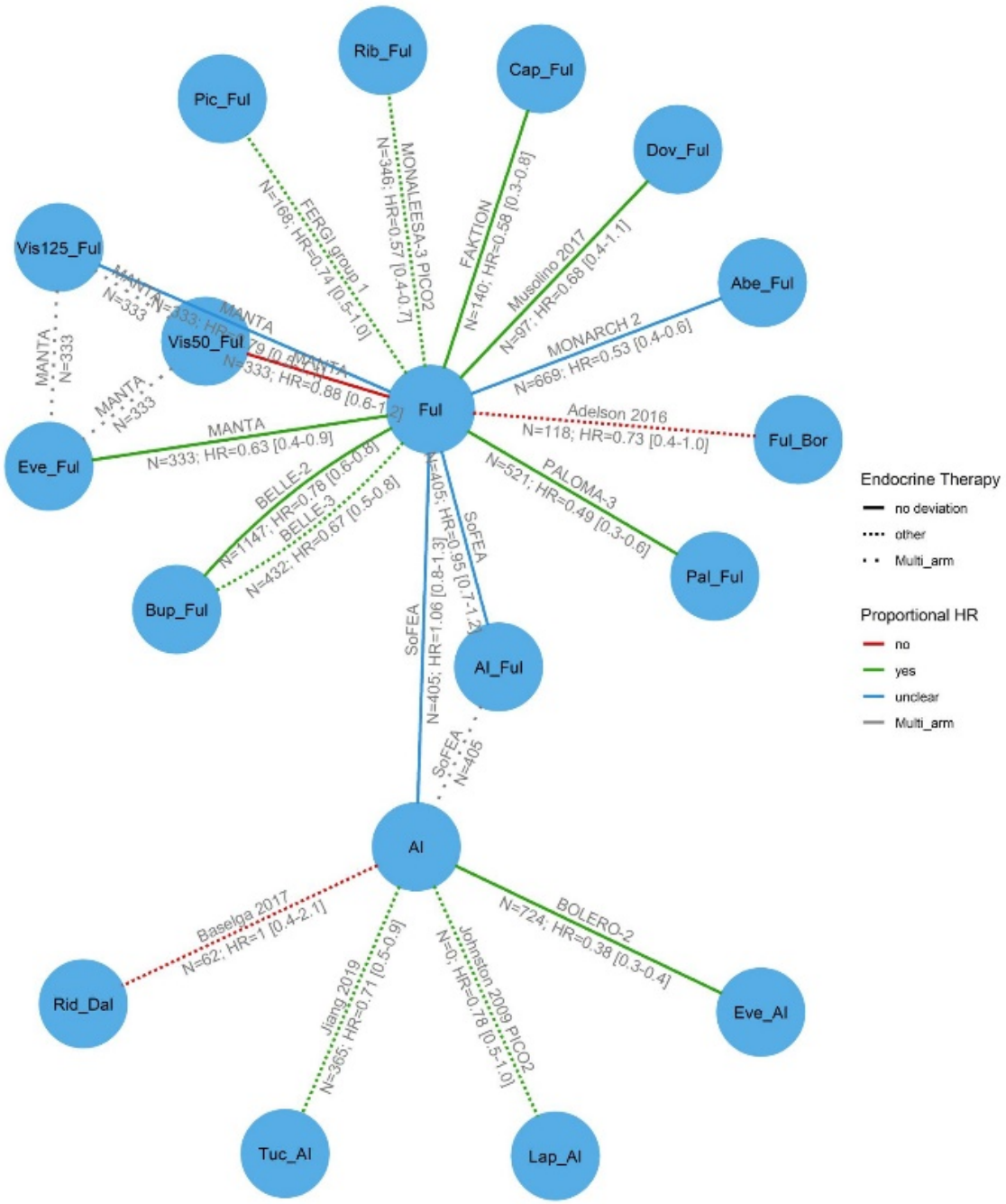
15.1.2 PFS PICO 2

Network characteristics:

All 16 PICO 2 trials reported results on PFS. The network consists of 18 individual treatments, of which 13 were compared to FUL and four to AI. For most comparisons only one trial was available. The only exceptions were the comparisons BUP+FUL vs. FUL and ABE+FUL vs. FUL, which have each been investigated in two trials. The mean or median age per study arm ranged from 55 to 64 years. Aside from NCT00073528[64] and SoFEA[84] all trials had their most recent results published between 2016 and 2020.

The comparisons VIS 50 mg +FUL versus FUL, BOR+FUL versus FUL, and RID+AI versus AI showed a tendency for non-proportional HRs in their Kaplan-Meier curves. Kaplan-Meier curves for VIS 125 mg +FUL versus FUL and ABE+FUL versus FUL were not available. Seven studies did use a different definition of endocrine resistance or did not provide enough data to assess whether their definition matched ours (Figure 44). LAP+LET dropped out of the network if the individual AIs were not aggregated (Appendix, Figure 70).

Figure 44: PICO 2 treatment network for PFS



Comparative Efficacy:

The SUCRA and forest plots show a tendency for improved PFS with any one of the CDK4/6 inhibitors combined with FUL compared with FUL monotherapy. The respective probabilities for each treatment to rank highest are indicated in Figure 45, Table 36 (Appendix) shows the probabilities for each rank for each treatment. The detailed results of the comparisons between all treatments are provided in the heat map (Figure 46).

Figure 45: PICO 2 SUCRA and forest plots for PFS; fixed effect model

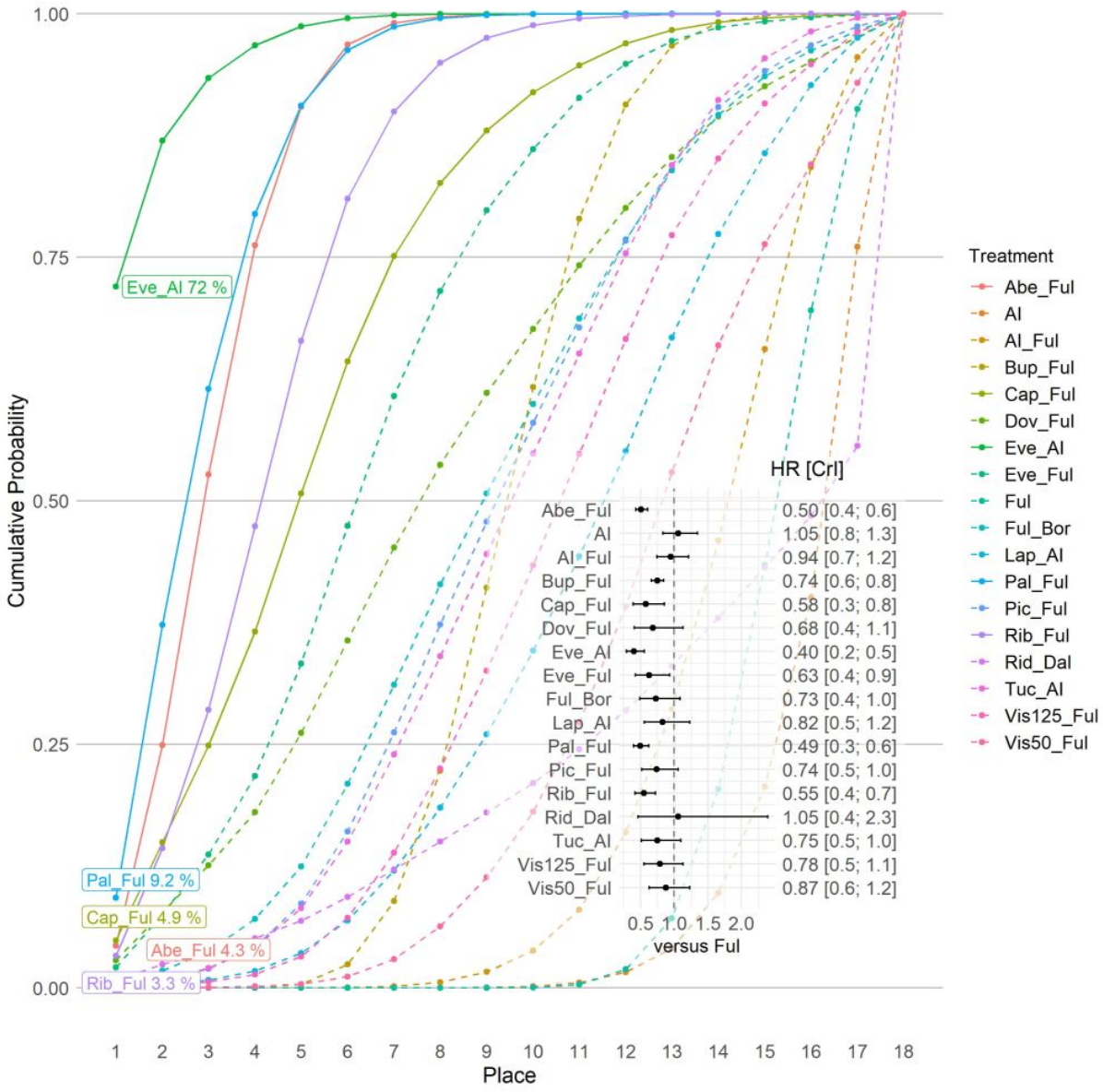
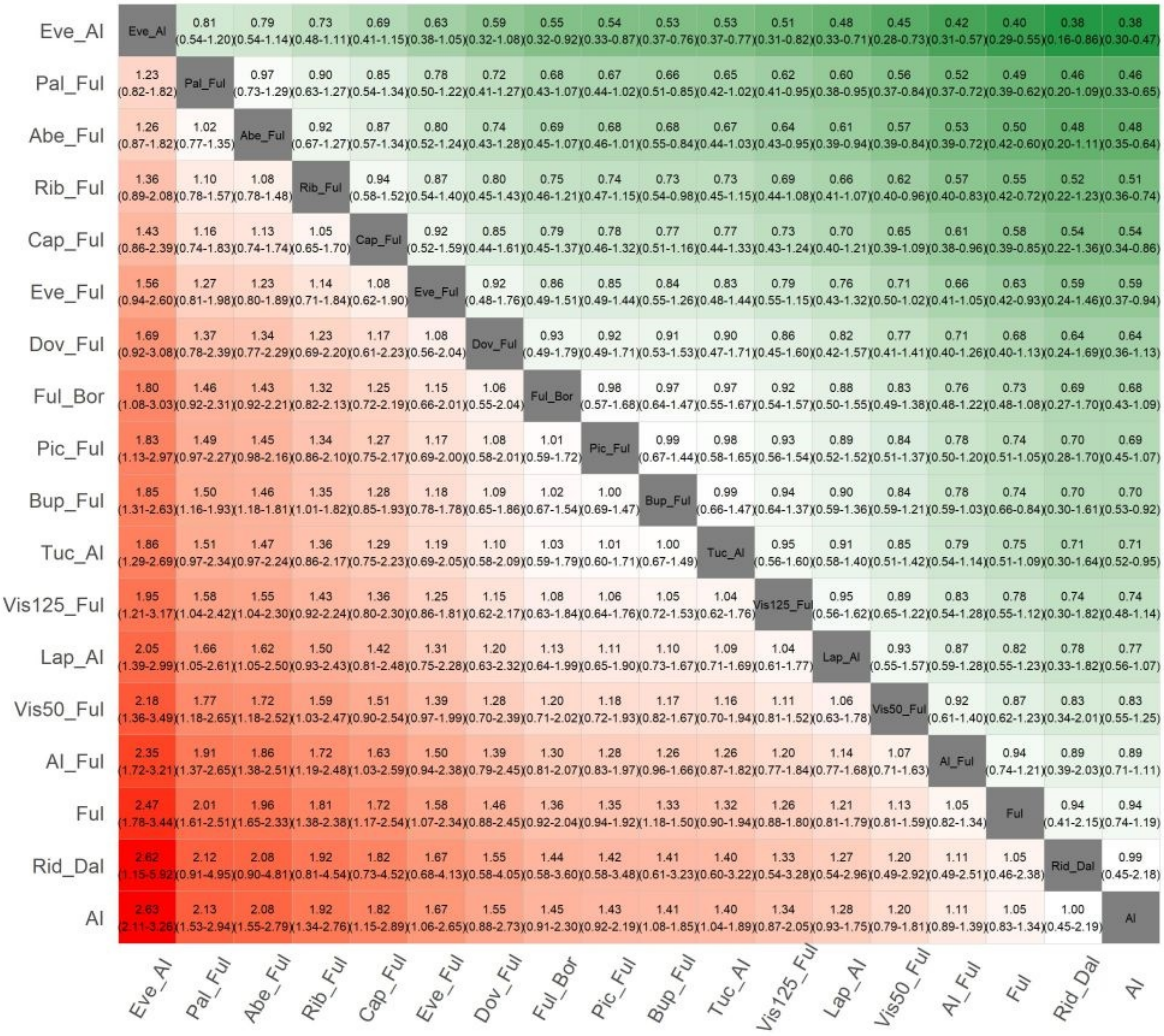


Figure 46: PICO 2 heat map for PFS; fixed effect model



Hazard ratios are indicated for treatments on Y-axis versus treatments on X-axis. Green fields indicate superiority of treatments on Y-axis, red fields inferiority of treatments on Y-axis.

The network with individual AIs led to almost the same results (Figure 71, Appendix). The results derived from the random effects model showed increased uncertainty with larger credibility intervals for the individual treatments (Figure 72, Appendix). The inclusion of age as predictor in the network meta regression increased uncertainty in the rankings further but EVE+AI remained the highest ranking treatment.

15.2 Economic studies identified in systematic literature search

15.2.1 Description of the studies

The systematic literature search for the economic domain retrieved eight cost effectiveness analyses[171-178], of which one study – Matter-Walstra et al. 2017[174] – was an update of the study by Matter-Walstra et al. from 2016.[173] Only one rough estimation of the budget impact was identified; it was included in the study for Switzerland[173 174] and estimated the annual budget impact for the treatment of PAL + LET versus LET alone.

- Galve-Calvo et al.[171] 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.[175] 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.[175] 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.[172] 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.[176] 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.[175] 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.[173] [174] 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.[177] 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.[178] 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.

15.2.2 Quality of the economic studies

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. A detailed quality assessment can be found in Appendix 12.5 of the Scoping report.

15.3 Supplementary tables efficacy and safety

Table 26: Characteristics of relevant ongoing RCTs

Trial ID	Size (pts)*	Treatment (combination) of interest	Primary completion date†	Study completion date†
NCT04031885	300	ABE + FUL	15.04.2021	15.12.2022
NCT03939897	194	ABE + FUL	01.11.2022	01.11.2022
NCT03425838 SONIA	1050	ANA/LET + PAL/RIB/ABE FUL + PAL/RIB/ABE	30.04.2021	31.10.2022
NCT02763566 MONARCH plus	463	ABE + NSAI pbo + NSAI ABE + FUL pbo + FUL	29.03.2019	27.11.2020
NCT03966898	426	pbo + ANA/LET	01.12.2020	01.06.2022
NCT02730091 VICTORIANE	98	ANA/LET	24.02.2021	28.02.2022
NCT02072512 PROOF	180	FUL ANA	30.11.2015	31.12.2016
NCT02767661 MECCA	240	ANA/LET/EXE	31.05.2021	31.05.2023
NCT01654185	60	AI	31.07.2014	31.07.2016
UMIN000025156	130	AI	N/A (anticipated start 2017)	N/A (anticipated start 2017)
NCT02511639 EUCTR2013-004153-24-IT MAIN-A	110	ANA/LET/EXE	31.12.2019	30.06.2020
NCT03778931 EMERALD	466	FUL/ANA/LET/EXE	31.08.2021	31.08.2022
NCT02646735 FRIEND	148	FUL EXE	31.12.2019	31.12.2020
NCT03538171	327	pbo + EXE	28.02.2021	31.08.2021
NCT03291886	124	pbo + EXE	31.12.2019	30.11.2021
NCT02115282	600	pbo + EXE	14.01.2021	N/A
NCT02007512	247	pbo + EXE	30.09.2016	31.03.2020
NCT01151046	118	pbo + EXE	30.06.2014	30.09.2014

Trial ID	Size (pts)*	Treatment (combination) of interest	Primary completion date†	Study completion date†
JapicCTI-173703	124	pbo + EXE	N/A (anticipated start 2017)	N/A (anticipated start 2017)
EUCTR2010-019867-13-SE NCT01234857	400	EXE	N/A (anticipated start 2010)	N/A (anticipated start 2010)
ChiCTR-IPR-17010455	260	EXE	N/A (anticipated start 2017)	N/A (anticipated start 2017)
NCT02958852 EUCTR2016-000494-20-SE ABC-SE	126	LET	30.04.2022	30.04.2022
NCT03927456	288	pbo + FUL	01.06.2020	01.04.2021
NCT03584009	100	FUL	03.03.2022	03.03.2022
NCT03781063	100	FUL	31.07.2020	30.09.2020
NCT03280563 MORPHEUS HR+BC	126	FUL	19.02.2021	05.10.2022
NCT02756364	141	FUL	25.11.2019	25.11.2019
NCT02569801 HydranGea	71	FUL	28.03.2020	28.03.2020
NCT02374099	97	FUL	13.12.2016	21.11.2017
NCT02530411 FURVA	160	pbo + FUL	31.12.2018	31.12.2020
NCT02340221 SANDPIPER	631	pbo + FUL	15.10.2017	03.07.2021
NCT02394496 OVER	396	pbo + FUL	31.12.2016	31.01.2017
NCT01992952 FAKTION	149	pbo + FUL	31.03.2019	31.10.2020
NCT01560416	50	FUL	30.06.2016	30.06.2016
NCT01202591 GLOW	127	pbo + FUL	30.09.2014	31.10.2014
NCT02404051 EUCTR2014-004035-38-IT FEVEX	745	FUL	31.01.2018	31.01.2019
EUCTR2014-003220-52-ES	92	FUL	N/A (anticipated start 2015)	N/A (anticipated start 2015)

Trial ID	Size (pts)*	Treatment (combination) of interest	Primary completion date†	Study completion date†
NCT02344550 LEO	137	LET	31.12.2017	31.08.2018
NCT02313051 MIRACLE	200	LET	31.12.2016	31.12.2017
NCT03905343	400	RIB + ET	31.12.2026	31.12.2026
NCT03822468 PMR	350	RIB + ANA/LET	02.02.2026	02.02.2026
NCT03462251 RIBBIT	158	RIB + AI/FUL	30.06.2025	30.06.2026
NCT03671330	315	RIB + NSAI pbo + NSAI	28.10.2020	14.04.2022
NCT03555877 AMICA	150	RIB + ET ET	31.10.2019	31.01.2019
NCT01857193 EUCTR2012-005461-13-FR	132	RIB + EXE	14.03.2018	11.09.2020
NCT01872260EUCTR2013-001219-57-ES	256	RIB + LET	01.12.2020	31.12.2020
NCT03423199 PATHWAY	180	pbo + TAM	28.02.2022	28.02.2022
NCT02311933	80	TAM	01.07.2020	N/A
NCT01622361 NEST	290	TAM	29.02.2016	29.02.2016
NCT02285179 EUCTR2013-003947-51-GB Poseidon	290	pbo + TAM	31.07.2020	31.07.2022
NCT02297438 PALOMA-4	339	PAL + LET pbo + LET	31.08.2020	02.12.2022
NCT02028507 PEARL	596	PAL + EXE/FUL	14.01.2019	31.07.2020
NCT02491983 PARSIFAL	486	PAL + LET PAL + FUL	31.12.2019	31.05.2020
NCT02384239	70	PAL + FUL/TAM	31.12.2020	31.12.2023
NCT02690480 FLIPPER	189	PAL + FUL pbo + FUL	11.01.2020	31.12.2023

Trial ID	Size (pts)*	Treatment (combination) of interest	Primary completion date†	Study completion date†
NCT02917005 FATIMA	160	PAL + EXE EXE	30.11.2021	31.12.2023
NCT02913430	150	PAL + FUL PAL + TAM	31.03.2020	31.03.2020
NCT03079011 EUCTR2016-004360-18-FR PADA-1	800	PAL + ANA/LET/EXE PAL + FUL	15.04.2022	15.04.2024
NCT03322215 PASIPHAE	196	PAL + FUL	31.10.2021	31.10.2021
NCT03355157 PADMA	260	PAL + ANA/LET/EXE/FUL	31.12.2021	31.12.2021
NCT04060862 IPATunity150	370	pbo + PAL + FUL	19.05.2023	30.01.2026
NCT04047758 ChiCTR1900024998	420	PAL + LET LET	30.09.2021	30.09.2022
EUCTR2016-004191-22-DE	960	PAL + ET +/- CANKADO	N/A (anticipated start 2017)	N/A (anticipated start 2017)

Trial ID	Size (pts)*	Treatment (combination) of interest	Primary completion date†	Study completion date†
2018-003648-22‡ SAKK_2118	400	RIB + ET	N/A (anticipated start 10.01.2020)	N/A (anticipated start 10.01.2020)
NCT04305496 CAPItello-291	834	pbo + FUL	14.12.2022	12.07.2024
NCT04220476 CIMER	204	PAL + LET	31.12.2025	31.12.2028
NCT04214288 SERENA-2	288	FUL	30.03.2022	04.01.2023
NCT04191499	400	pbo + PAL + FUL	01.11.2025	30.11.2025
NCT04158362‡ AMBRE	378	ABE + ET	30.06.2022	30.06.2026
NCT03839823‡ LBCTR2019060241 CTRI/2019/09/021333 RIGHT Choice	222	RIB + LET	31.10.2022	31.10.2022

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.
‡ This trial recruits patients with visceral metastasis, high burden disease or rapidly progressing disease, for whom the standard of care is chemotherapy.

Table 27: Articles excluded from the NMA

Clinical Trial	Complete exclusion of trial?	Excluded article (Author, Year)	Reasons for exclusion
GINECO	yes	Bachelot et al. 2012[212]	No connection to treatment network.
PALOMA-1	no	Bell et al. 2016[213]	Special population (biomarker) PALOMA-1 analyzed two different cohorts. In cohort 2 patients were screened for CCND1 amplification and/or loss of p16. Consequently, we only used cohort 1 for our analysis which was only provided in Finn et al. 2015[49] and Finn et al. 2017[50].
PALOMA-2	no	Durairaj et al. 2018[214]	No relevant outcomes reported
PALOMA-3	no	Loibl et al. 2016[163]	Dataset duplicate
BOLERO-2	no	Campone et al. 2013[215]	No relevant outcomes reported
FALCON	no	Robertson et al. 2018[63]	No relevant outcomes reported
FLAG	yes	Kim et al. 2018[216]	Premenopausal patients
NCT00075764	yes	Mehta et al. 2012[217]	No separate data for relevant subgroup
		Mehta et al. 2019[218]	No separate data for relevant subgroup
NCT00229697	yes	Osborne et al. 2011[219]	No separate data for relevant subgroup
NCT00390455	yes	Burstein et al. 2014[220]	No separate data for relevant subgroup
LEA	yes	Martin et al. 2015[221]	No connection to treatment network
NCT01160718	yes	Zaman et al. 2015[222]	No relevant outcomes reported
NCT02437318	yes	Andre et al. 2019[204]	No separate data for relevant subgroup
YoungPearl	yes	Park et al. 2019[223]	Premenopausal patients
		Lee et al. 2019[224]	Premenopausal patients
Unclear NCT	yes	Lipton et al. 2008[225]	No RCT
MONALEESA-7	yes	Tripathy et al. 2018[146]	Premenopausal patients
		Im et al. 2019[148]	Premenopausal patients
		Lu et al. 2019[147]	Premenopausal patients
MONALEESA-2 MONALEESA-3 MONALEESA-7	no	Beck et al. 2019	Dataset duplicate Wrong population (in presented dataset) Premenopausal

Table 28: RoB assessment of RCTs for PFS

+	Low RoB
?	Some concerns
-	High RoB

Trial Name	Trial ID	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	**Overall**
ACE	NCT02482753	+	+	+	+	+	**+**
Bachelot 2012	Bachelot 2012	-	+	+	?	?	**-**
BELLE-2	NCT01610284	+	+	+	+	?	**?**
BELLE-3	NCT01633060	+	+	+	+	?	**?**
BOLERO-2	NCT00863655	+	+	+	+	+	**+**
FAKTION	NCT01992952	+	+	+	+	+	**+**
FALCON	NCT01602380	+	+	+	+	+	**+**
FERGI	NCT01437566	+	+	+	+	?	**?**
MANTA	NCT02216786	+	?	+	+	+	**?**
MINT	NCT01151215	+	+	+	+	?	**?**
MONALEESA-2	**NCT01958021**	**+**	**+**	**+**	**+**	**+**	**+**
MONALEESA-3	**NCT02422615**	**+**	**+**	**+**	**+**	**+**	**+**
MONALEESA-7	**NCT02278120**	**+**	**+**	**+**	**+**	**+**	**+**
MONARCH 2	**NCT02107703**	**+**	**+**	**+**	**+**	**+**	**+**
MONARCH 3	**NCT02246621**	**+**	**+**	**+**	**+**	**+**	**+**
NCT00073528	NCT00073528	?	+	+	+	?	**?**
NCT00075764	NCT00075764	+	+	+	?	+	**?**
NCT00229697	NCT00229697	+	+	+	+	?	**?**
NCT00390455	NCT00390455	+	?	+	+	+	**?**
NCT00696072	NCT00696072	?	-	+	?	?	**-**
NCT00770354	NCT00770354	?	+	+	+	?	**?**
NCT01142401	NCT01142401	?	?	+	?	?	**?**
NCT01234857	NCT01234857	-	+	+	+	?	**-**
NCT01528345	NCT01528345	+	+	+	+	?	**?**
PALOMA-1	**NCT00721409**	**+**	**+**	**+**	**+**	**?**	**?**
PALOMA-2	**NCT00721409**	**+**	**+**	**+**	**+**	**+**	**+**
PALOMA-3	**NCT01942135**	**+**	**+**	**+**	**+**	**+**	**+**
SoFEA 1	NCT00253422	+	+	+	+	?	**?**
SOLAR-1	NCT02437318	+	+	+	+	+	**+**

Table 29: RoB assessment of RCTs for OS

+	Low RoB
?	Some concerns
-	High RoB

Trial Name	Trial ID	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	**Overall**
BELLE-2	NCT01610284	+	+	+	+	?	**?**
BOLERO-2	NCT00863655	+	+	+	+	+	**+**
FAKTION	NCT01992952	+	+	+	+	+	**+**
MANTA	NCT02216786	+	?	+	+	+	**?**
MONALEESA-2	NCT01958021	+	+	+	+	+	**+**
MONALEESA-3	NCT02422615	+	+	+	+	+	**+**
MONALEESA-7	NCT02278120	+	+	+	+	+	**+**
MONARCH 2	NCT02107703	+	+	+	+	+	**+**
NCT00075764	NCT00075764	+	+	+	+	+	**+**
NCT00390455	NCT00390455	+	?	+	+	+	**?**
NCT00696072	NCT00696072	?	-	+	+	?	**-**
NCT01528345	NCT01528345	+	+	+	+	?	**?**

PALOMA-1	NCT00721409	+	+	+	+	?	?
PALOMA-3	NCT01942135	+	+	+	+	+	+
SoFEA 1	NCT00253422	+	+	+	+	?	?

Table 30: RoB assessment of RCTs for AEs

+	Low RoB
?	Some concerns
-	High RoB

Trial Name	Trial ID	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	**Overall**
ACE	NCT02482753	+	+	+	+	+	+
BELLE-2	NCT01610284	+	+	+	+	?	?
BELLE-3	NCT01633060	+	+	+	+	?	?
BOLERO-2	NCT00863655	+	+	+	+	?	?
FAKTION	NCT01992952	+	+	+	+	+	+
FALCON	NCT01602380	+	+	+	+	?	?
FERGI	NCT01437566	+	+	+	+	?	?
MANTA	NCT02216786	+	+	+	+	?	?
MINT	NCT01151215	+	+	+	+	?	?
MONALEESA-2	NCT01958021	+	+	+	+	?	?
MONALEESA-3	NCT02422615	+	+	+	+	?	?
MONALEESA-7	NCT02278120	+	+	+	+	+	+
MONARCH 2	NCT02107703	+	+	+	+	?	?
MONARCH 3	NCT02246621	+	+	+	+	?	?
NCT00073528	NCT00073528	?	?	+	+	?	?
NCT00075764	NCT00075764	+	-	+	?	+	-
NCT00229697	NCT00229697	+	+	+	+	?	?
NCT00390455	NCT00390455	+	+	+	+	+	+
NCT00696072	NCT00696072	?	-	+	+	?	-
NCT00770354	NCT00770354	?	+	+	+	?	?
NCT01142401	NCT01142401	?	+	+	+	?	?
NCT01234857	NCT01234857	-	+	+	+	?	-
PALOMA-1	NCT00721409	+	+	+	+	?	?
PALOMA-2	NCT00721409	+	+	+	+	?	?
PALOMA-3	NCT01942135	+	+	+	+	?	?
SoFEA 1	NCT00253422	+	+	+	+	?	?
SOLAR-1	NCT02437318	+	+	+	+	?	?

Table 31: RoB assessment of RCTs for QoL

+	Low RoB
?	Some concerns
-	High RoB

Trial Name	Trial ID	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	**Overall**
BOLERO-2	NCT00863655	+	+	-	+	+	-
FALCON	NCT01602380	+	+	?	+	+	?
MONALEESA-2	NCT01958021	+	+	-	+	+	-
MONALEESA-7	NCT02278120	+	+	?	+	+	?
MONARCH 2	NCT02107703	+	?	+	+	+	?
PALOMA-2	NCT00721409	+	+	+	+	+	+
PALOMA-3	NCT01942135	+	?	+	+	+	?

Table 32: RoB assessment for cohort studies and single-arm trials

Author, Year	Study design	(i) Prospective planning with a protocol defining inclusion criteria, interventions and endpoints of interest?	(ii) Consecutive patient inclusion?	(iii) Transparent, non-selective reporting in regard to patient characteristics, intervention and outcome?
Ban et al. 2018[90]	retr. cohort	no	yes	yes
Battisti et al. 2019[91]	retr. cohort	no	yes	yes
Bui et al. 2019[92]	retr. cohort	no	yes	yes
Clifton et al. 2019[93]	retr. cohort	no	yes	no
Demir et al. 2020[94]	retr. cohort	no	yes	no
Dickler et al. 2017[112]	single arm	yes	yes	yes
du Rusquec et al. 2018[95]	prosp. cohort	yes	yes	yes
Gervaso et al. 2020[114]	retr. cohort	no	yes	yes
Herrscher et al. 2019[96]	retr. cohort	no	yes	yes
Iwamoto et al. 2018[97]	retr. cohort	no	yes	yes
Kikuchi et al. 2020[98]	retr. cohort	no	yes	yes
Kish et al. 2018[99]	retr. cohort	no	yes	yes
Masuda et al. 2018[100]	single arm	yes	yes	yes
Maurer et al. 2018[101]	retr. cohort	no	yes	no
Mendes et al. 2020[102]	prosp. cohort	yes	yes	yes
Nigro et al. 2020[103]	retr. cohort	no	yes	yes
Patnaik et al. 2016[113]	single arm	yes	yes	no
Pizzuti et al. 2019[104]	retr. cohort	no	yes	unclear
Schickli et al. 2019[105]	retr. cohort	no	yes	unclear
Stearns et al. 2018[106]	prosp. cohort	yes	yes	yes
Tamura et al. 2016[107]	single arm	yes	unclear	yes
Varella et al. 2019[108]	retr. cohort	no	yes	yes
Watson et al. 2019[109]	retr. cohort	no	yes	yes
Wilkie et al. 2019[110]	retr. cohort	no	yes	no
Xi et al. 2019[111]	retr. cohort	no	yes	yes

Table 33: Description of the extracted variables

Trial/study metrics	
Excluded	Whether the article was excluded from the NMA during data extraction
Trial	The Name of the Trial
ID ClinicalTrials.gov	The NCT number
Author	Name of the first author
Year	Year of publication

Treatment	The treatments that were compared
n	Sample sizes (ITT population; randomized patients)
n safety	Sample size that we used for our analyses on adverse events and discontinuations. If reported, we used the number of patients that received the treatment. Second choice was the number of patients in the safety analysis reported by the primary study.
Sponsor	Study sponsor
Comments	Additional comments in regard to the study including reasons for exclusion.
Patient characteristics	
Prior ET	Proportion of patients with relapse/progression during ET for advanced-stage disease or during adjuvant ET or within 12 months after end of adjuvant ET. no = 0; yes = all patients had prior ET. If the time frame was not reported we used the proportion regardless of the time.
HER2-	The proportion of HER2- patients. Negative = all patients had HER2- status
Outcomes/results	
Discontinuations	The number of patients that discontinued treatment (without patients that discontinued due to treatment progression or death since these patients are already in PFS taken into account).
Dis AE	Discontinuations due to adverse event
AE	The number of patients with any adverse event regardless of severity.
AE TR	The number of patients with any treatment related adverse event regardless of severity.
AE3	The number of patients with any adverse event grade 3 or worse. If the studies grouped the cases in regard to individual severity levels, we summarized the reported numbers on grade 3, 4 and 5 (as far as the overall sum was not higher than n safety).
AE3 TR	The number of patients with any treatment related adverse event grade 3 or worse. If the studies grouped the cases in regard to individual severity levels, we summarized the reported numbers on grade 3, 4 and 5 (as far as the overall sum was not higher than n safety).
OS HR	Overall survival hazard ratio. OS were regularly reported as interim analysis.
OS HR CI low	Lower confidence interval of the overall survival hazard ratio
OS HR CI up	Upper confidence interval of the overall survival hazard ratio
OS statistics	The statistical method that was used to calculate the HR and the confidence interval.
PFS HR	Progression free survival hazard ratio

PFS HR CI low	Lower confidence interval of the progression free survival hazard ratio
PFS HR CI up	Upper confidence interval of the progression free survival hazard ratio
PFS statistics	The statistical method that was used to calculate the HR and the confidence interval.
QoL instrument	Instrument that was used to assess quality of life. We exclusively extracted HRs on time to deterioration.
QoL HR CI low	Lower confidence interval of the time to deterioration* hazard ratio.
QoL HR CI up	Upper confidence interval of the time to deterioration* hazard ratio
Potential effect modifiers	
Menopausal status	The menopausal status. We additionally extracted which methods were used for premenopausal patients to artificially make them postmenopausal. However, these results were sometimes inconclusive. For instance, Mehta (2012) and Mehta (2019) reported a lower age range of 27 years. However, they defined the population as “postmenopausal” without any description of used methods to achieve this status for premenopausal women.
OS not proportional	x = the Kaplan-Meier curves showed signs of non-proportional hazards (crossing of curves or delayed separation). Our assessment might differ from formal methods like the use of statistical tests. Unclear = Kaplan-Meier curves were not reported.
PFS not proportional	x = the Kaplan-Meier curves showed non-proportional hazards. Unclear = Kaplan-Meier curves were not reported.
QoL not proportional	x = the Kaplan-Meier curves showed non-proportional hazards. Unclear = Kaplan-Meier curves were not reported.
Age type	Measure that was used to report age (i.e. median or mean; range, IQR or SD)
Age	Median or mean age of included patients
Age deviation low	Lower range, IQR or SD of median/mean patient age
Age deviation high	Upper range, IQR or SD of median/mean patient age

* Time to deterioration was not assessed uniformly in the individual studies. For instance, the threshold that defined a deterioration differed as well as the instruments used to assess QoL.

Table 34: Treatment schemes and assigned nodes

Treatment scheme	Node
Abemaciclib 150 mg + Fulvestrant 500 mg	Abe + Ful
Abemaciclib 150 mg + Fulvestrant 500 mg loading and 250 mg	Abe + Ful
Abemaciclib 150 mg + NSAI (Anastrozole or Letrozole)	Abe + Ana or Let
Alpelisib 300 mg + Fulvestrant 500 mg	Alp + Ful
Anastrozole 1 mg	Ana
Anastrozole 1 mg + Fulvestrant 500 mg loading and 250 mg	Ana + Ful
Anastrozole 1 mg + Goserelin 3,6mg	Ana + Gos

Anastrozole 1 mg + Placebo	Ana
AZD8931 20 mg + Anastrozole 1 mg	AZD 20 + Ana
AZD8931 40 mg + Anastrozole 1 mg	AZD 40 + Ana
Buparlisib 100 mg + Fulvestrant 500 mg	Bup + Ful
Capecitabine	Cape
Capecitabine 1250 mg	Cape
Capivasertib 400 mg + Fulvestrant 500 mg	Cap + Ful
Dovitinib 500 mg + Fulvestrant 500 mg	Dov + Ful
Entinostat 5 mg + Exemestane 25 mg	Ent + Exe
Everolimus 10 mg + Fulvestrant 500 mg	Eve + Ful
Everolimus 10 mg + Exemestane 25 mg	Eve + Exe
Exemestane 25 mg	Exe
Exemestane 25 mg + Placebo	Exe
Fulvestrant 500 mg	Ful
Fulvestrant 500 mg + Bortezomib 1.6 mg	Ful + Bor
Fulvestrant 500 mg + Goserelin 3,6mg	Ful + Gos
Fulvestrant 500 mg + Placebo	Ful
Fulvestrant 500 mg + Selumetinib	Ful + Sel
Fulvestrant 500 mg loading and 250 mg + Placebo	Ful
Goserelin + NSAI + Placebo	Gos + NSAI
Goserelin 3.6mg	Gos
Lapatinib 1.500 mg + Fulvestrant 500 mg loading and 250 mg	Lap + Ful
Lapatinib 1.500 mg + Letrozole 2.5 mg	Lap + Let
Letrozole	Let
Letrozole 2.5 mg	Let
Letrozole 2.5 mg + AS1402 9 mg	Let + AS1402
Letrozole 2.5 mg + Dasatinib 100 mg	Let + Dasatinib
Letrozole 2.5 mg + Placebo	Let
Letrozole 2.5 mg or Fulvestrant 250 mg	Let or Ful 250
Letrozole 2.5 mg or Fulvestrant 250 mg + Bevacizumab 15 mg	Let or Ful 250 + Bev
NSAI (Anastrozole or Letrozole) + Placebo	Ana or Let
Palbociclib + Exemestane + GnRH agonist	Pal + Exe + GnRH ag
Palbociclib 125 mg + Exemestane 25 mg + Leuprolide	Pal + Exe + Leu
Palbociclib 125 mg + Fulvestrant 500 mg	Pal + Ful
Palbociclib 125 mg + Letrozole 2.5 mg	Pal + Let

Pictilisib 340 mg + Fulvestrant 500 mg	Pic + Ful
Ribociclib + Goserelin + NSAI	Rib + Gos + NSAI
Ribociclib 600 mg + Fulvestrant 500 mg	Rib + Ful
Ribociclib 600 mg + Letrozole 2.5 mg	Rib + Let
Ridaforolimus 30 mg + Dalotuzumab 10 mg	Rid + Dal
Tamoxifen	Tam
Tamoxifen 20 mg	Tam
Tamoxifen 20 mg + Everolimus 10 mg	Tam + Eve
Tamoxifen 20 mg + Gefitinib 250 mg	Tam + Gef
Tamoxifen 20 mg + Placebo	Tam
Tucidinostat 30 mg + Exemestane 25 mg	Tuc + Exe
Vistusertib 50 mg + Fulvestrant 500 mg	Vis 50 + Ful
Vistusertib intermittent 125 mg + Fulvestrant 500 mg	Vis 125 + Ful

Table 35: NMAs PICO 1 ranking probabilities

OS											
Treatment	Rank 1	Rank 2	Rank 3								
AI	0.01	0.18	0.81								
Pal_AI	0.32	0.54	0.14								
Rib_AI	0.67	0.27	0.05								
QoL											
Treatment	Rank 1	Rank 2	Rank 3	Rank 4							
AI	0.06	0.37	0.53	0.04							
Ful	0.01	0.04	0.11	0.83							
Pal_AI	0.59	0.25	0.12	0.04							
Rib_AI	0.33	0.34	0.24	0.09							
PFS											
Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9	Rank 10	Rank 11
Abe_AI	0.64	0.23	0.10	0.03	0.01	0.00	0.00	0.00	0.00	0.00	0.00
AI	0.00	0.00	0.00	0.00	0.01	0.10	0.35	0.41	0.12	0.02	0.00
AI_AS1402	0.02	0.02	0.03	0.08	0.15	0.19	0.09	0.12	0.10	0.09	0.10
AI_Das	0.06	0.07	0.11	0.27	0.27	0.13	0.04	0.03	0.01	0.01	0.00
AZD20_AI	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.05	0.13	0.27	0.51
AZD40_AI	0.00	0.00	0.00	0.01	0.03	0.08	0.09	0.14	0.28	0.26	0.12
Ful	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.09	0.30	0.33	0.26
Lap_AI	0.00	0.00	0.00	0.01	0.08	0.33	0.34	0.16	0.06	0.02	0.00
Pal_AI	0.18	0.41	0.29	0.10	0.02	0.00	0.00	0.00	0.00	0.00	0.00
Rib_AI	0.09	0.23	0.39	0.22	0.06	0.01	0.00	0.00	0.00	0.00	0.00
Rib_Ful	0.01	0.04	0.08	0.28	0.37	0.16	0.04	0.02	0.01	0.00	0.00
AE3+											
Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8			
Abe_AI	0.00	0.00	0.00	0.01	0.30	0.31	0.21	0.16			
AI	0.00	0.65	0.32	0.03	0.00	0.00	0.00	0.00			
AI_AS1402	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00			
AZD20_AI	0.00	0.25	0.30	0.43	0.01	0.00	0.00	0.00			
AZD40_AI	0.00	0.00	0.00	0.02	0.42	0.16	0.14	0.26			
Ful	0.00	0.10	0.38	0.50	0.02	0.00	0.00	0.00			
Pal_AI	0.00	0.00	0.00	0.00	0.06	0.16	0.33	0.46			
Rib_AI	0.00	0.00	0.00	0.00	0.19	0.36	0.32	0.12			

Discontinuations											
Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7				
Abe_AI	0.00	0.00	0.00	0.00	0.00	0.20	0.80				
AI	0.15	0.59	0.22	0.03	0.00	0.00	0.00				
AI_AS1402	0.06	0.04	0.05	0.06	0.10	0.49	0.20				
AI_Das	0.71	0.16	0.08	0.04	0.01	0.00	0.00				
Ful	0.05	0.12	0.29	0.31	0.18	0.05	0.00				
Pal_AI	0.02	0.08	0.32	0.39	0.16	0.02	0.00				
Rib_AI	0.00	0.00	0.04	0.17	0.55	0.24	0.00				

This table shows the probabilities – as calculated in the NMAs – for each treatment to be ranked on a specific rank. Treatment nodes are explained in Table 34.

Table 36: NMAs PICO 2 ranking probabilities

OS											
Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9	Rank 10	Rank 11
Abe_Ful	0.05	0.18	0.26	0.22	0.14	0.08	0.04	0.01	0.00	0.00	0.00
AI	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.03	0.19	0.61	0.16
AI_Ful	0.02	0.07	0.12	0.15	0.18	0.19	0.16	0.10	0.02	0.00	0.00
Bup_Ful	0.00	0.02	0.06	0.14	0.24	0.28	0.19	0.06	0.02	0.00	0.00
Cap_Ful	0.54	0.19	0.09	0.06	0.04	0.03	0.02	0.02	0.01	0.00	0.00
Dov_Ful	0.17	0.15	0.10	0.08	0.07	0.07	0.07	0.09	0.06	0.08	0.06
Eve_AI	0.00	0.00	0.01	0.01	0.03	0.05	0.09	0.17	0.45	0.16	0.03
Ful	0.00	0.00	0.00	0.00	0.01	0.07	0.28	0.43	0.16	0.05	0.01
Pal_Ful	0.02	0.09	0.17	0.21	0.20	0.16	0.09	0.04	0.01	0.00	0.00
Rib_Ful	0.19	0.29	0.19	0.12	0.08	0.06	0.04	0.02	0.01	0.00	0.00
Rid_Dal	0.00	0.01	0.01	0.01	0.01	0.02	0.02	0.03	0.07	0.09	0.73
QoL											
Treatment	Rank 1	Rank 2	Rank 3								
Abe_Ful	0.16	0.81	0.03								
Ful	0.00	0.04	0.96								
Pal_Ful	0.84	0.15	0.01								
PFS											
Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9	Rank 10	Rank 11
Abe_Ful	0.04	0.21	0.28	0.24	0.14	0.06	0.02	0.01	0.00	0.00	0.00
AI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
AI_Ful	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.04
Bup_Ful	0.00	0.00	0.00	0.00	0.00	0.02	0.07	0.13	0.19	0.21	0.17
Cap_Ful	0.05	0.10	0.10	0.12	0.14	0.14	0.11	0.08	0.05	0.04	0.03
Dov_Ful	0.03	0.05	0.05	0.05	0.08	0.09	0.10	0.09	0.07	0.07	0.07
Eve_AI	0.72	0.15	0.06	0.03	0.02	0.01	0.00	0.00	0.00	0.00	0.00
Eve_Ful	0.02	0.05	0.06	0.08	0.12	0.14	0.13	0.11	0.08	0.06	0.05
Ful	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ful_Bor	0.00	0.01	0.02	0.03	0.05	0.08	0.10	0.10	0.09	0.09	0.09
Lap_AI	0.00	0.00	0.01	0.01	0.02	0.03	0.05	0.06	0.08	0.09	0.10
Pal_Ful	0.09	0.28	0.24	0.18	0.11	0.06	0.02	0.01	0.00	0.00	0.00
Pic_Ful	0.00	0.01	0.01	0.02	0.04	0.07	0.10	0.11	0.11	0.10	0.10
Rib_Ful	0.03	0.11	0.14	0.19	0.19	0.15	0.09	0.05	0.03	0.01	0.01
Rid_Dal	0.01	0.02	0.01	0.01	0.02	0.02	0.03	0.03	0.03	0.03	0.03
Tuc_AI	0.00	0.01	0.01	0.02	0.04	0.07	0.09	0.10	0.10	0.10	0.10
Vis125_Ful	0.00	0.00	0.00	0.01	0.02	0.04	0.07	0.09	0.10	0.11	0.11
Vis50_Ful	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.03	0.05	0.07	0.09
Treatment	Rank 12	Rank 13	Rank 14	Rank 15	Rank 16	Rank 17	Rank 18				
Abe_Ful	0.00	0.00	0.00	0.00	0.00	0.00	0.00				
AI	0.01	0.02	0.06	0.11	0.19	0.36	0.24				
AI_Ful	0.08	0.13	0.17	0.20	0.19	0.11	0.04				
Bup_Ful	0.12	0.06	0.02	0.01	0.00	0.00	0.00				
Cap_Ful	0.02	0.01	0.01	0.00	0.00	0.00	0.00				

Dov_Ful	0.06	0.05	0.04	0.03	0.03	0.03	0.02				
Eve_AI	0.00	0.00	0.00	0.00	0.00	0.00	0.00				
Eve_Ful	0.03	0.02	0.01	0.01	0.00	0.00	0.00				
Ful	0.02	0.05	0.13	0.23	0.26	0.21	0.10				
Ful_Bor	0.08	0.07	0.06	0.04	0.03	0.02	0.02				
Lap_AI	0.11	0.12	0.11	0.08	0.07	0.05	0.02				
Pal_Ful	0.00	0.00	0.00	0.00	0.00	0.00	0.00				
Pic_Ful	0.09	0.08	0.06	0.04	0.03	0.02	0.01				
Rib_Ful	0.00	0.00	0.00	0.00	0.00	0.00	0.00				
Rid_Dal	0.04	0.05	0.05	0.05	0.05	0.07	0.44				
Tuc_AI	0.10	0.09	0.07	0.04	0.03	0.01	0.00				
Vis125_Ful	0.12	0.11	0.08	0.06	0.04	0.03	0.02				
Vis50_Ful	0.12	0.14	0.13	0.10	0.08	0.08	0.07				
AE3+											
Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7				
Abe_Ful	0.00	0.00	0.01	0.13	0.29	0.51	0.06				
Bup_Ful	0.00	0.00	0.02	0.27	0.50	0.21	0.00				
Cap_Ful	0.02	0.84	0.12	0.01	0.00	0.00	0.00				
Dov_Ful	0.00	0.11	0.68	0.16	0.03	0.02	0.00				
Ful	0.98	0.02	0.00	0.00	0.00	0.00	0.00				
Pal_Ful	0.00	0.00	0.00	0.00	0.01	0.08	0.90				
Pic_Ful	0.00	0.02	0.17	0.42	0.17	0.18	0.04				
Discontinuations											
Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9	Rank 10	Rank 11
Abe_Ful	0.00	0.00	0.00	0.00	0.01	0.02	0.03	0.06	0.32	0.39	0.16
Bup_Ful	0.00	0.00	0.02	0.08	0.13	0.16	0.25	0.27	0.08	0.01	0.00
Cap_Ful	0.00	0.01	0.03	0.03	0.03	0.04	0.04	0.06	0.19	0.31	0.27
Dov_Ful	0.00	0.02	0.13	0.13	0.11	0.13	0.15	0.18	0.10	0.04	0.01
Eve_Ful	0.02	0.03	0.13	0.16	0.17	0.15	0.13	0.11	0.07	0.03	0.01
Ful	0.63	0.34	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ful_Bor	0.01	0.01	0.02	0.02	0.02	0.02	0.03	0.04	0.10	0.19	0.55
Pal_Ful	0.32	0.50	0.11	0.04	0.03	0.01	0.00	0.00	0.00	0.00	0.00
Pic_Ful	0.00	0.03	0.25	0.16	0.13	0.16	0.12	0.09	0.04	0.01	0.00
Vis125_Ful	0.02	0.04	0.16	0.19	0.18	0.15	0.12	0.09	0.04	0.01	0.00
Vis50_Ful	0.01	0.03	0.12	0.17	0.19	0.16	0.13	0.10	0.06	0.02	0.00

This table shows the probabilities – as calculated in the NMAs – for each treatment to be ranked on a specific rank. Treatment nodes are explained in Table 34.

Table 37: Incidence of AEs in patients receiving PAL reported in two or more NRSs, with grades

			Reported incidence			
Adverse Event	**Grade**	**N (studies)**	**lowest**	**highest**	**median**	**mean**
Anaemia	Any Grade	12	5.9%	66.9%	41.5%	38.4%
	Grade 1	3	7.8%	40.3%	21.3%	23.1%
	Gade 2	4	5.1%	10.9%	7.8%	7.9%
	Grade 3	5	2.4%	5.0%	2.9%	3.4%
	Grade 3-4	4	2.9%	4.8%	3.6%	3.7%
Leukopenia	Any grade	6	1.9%	100.0%	70.2%	58.5%
	Grade 1	2	0.5%	4.2%	2.4%	2.4%
	Gade 2	2	0.7%	7.5%	4.1%	4.1%
	Grade 3	2	0.7%	8.1%	4.4%	4.4%
	Grade 3-4	4	20.0%	83.0%	41.5%	46.5%
Lymphopenia	Any grade	3	17.0%	30.0%	23.0%	23.3%
	Grade 3-4	2	23.0%	30.0%	26.5%	26.5%
Neutropenia	Any grade	22	2.1%	100.0%	84.0%	76.3%

	Grade 1	5	1.5%	15.5%	10.4%	8.8%
	Grade 2	5	10.5%	31.5%	20.6%	22.3%
	Grade 3	11	27.9%	76.9%	49.7%	49.1%
	Grade 4	10	3.0%	16.7%	7.7%	9.0%
	Grade 3-4	8	47.0%	90.5%	62.5%	67.1%
	Febrile neutropenia	11	1.3%	5.1%	3.0%	3.0%
Thrombocytopenia	Any Grade	13	10.9%	55.0%	42.3%	36.4%
	Grade 1	3	9.9%	35.1%	14.7%	19.9%
	Grade 2	3	3.9%	4.5%	4.5%	4.3%
	Grade 3	8	2.1%	12.5%	5.6%	6.4%
	Grade 4	4	1.3%	3.3%	2.2%	2.3%
	Grade 3-4	3	2.4%	11.8%	9.3%	7.8%
Alopecia	Any Grade	5	1.6%	16.7%	5.0%	7.2%
	Grade 1	2	1.4%	6.5%	4.0%	4.0%
	Grade 2	2	0.2%	1.3%	0.8%	0.8%
Decreased appetite	Any Grade	3	3.1%	37.0%	11.1%	17.1%
Arthralgia	Any Grade	3	1.4%	12.3%	2.0%	5.2%
	Grade 1	2	0.9%	7.8%	4.4%	4.4%
	Grade 2	2	0.5%	3.9%	2.2%	2.2%
Constipation	Any Grade	4	3.9%	21.4%	8.9%	10.8%
	Grade 1	3	3.5%	9.3%	5.2%	6.0%
	Grade 2	2	0.2%	3.3%	1.8%	1.8%
Cutaneous toxicity	Any Grade	2	2.6%	15.6%	9.1%	9.1%
	Grade 1	2	2.1%	10.4%	6.3%	6.3%
	Grade 2	2	0.5%	5.2%	2.9%	2.9%
Diarrhoea	Any grade	6	1.5%	17.4%	6.3%	8.5%
	Grade 1	3	1.3%	14.1%	4.0%	6.5%
	Grade 2	3	0.7%	2.7%	1.3%	1.6%
	Grade 3	2	0.2%	0.6%	0.4%	0.4%
Dizziness	Any Grade	2	2.6%	26.0%	14.3%	14.3%
Emergency room encounters, hospitalisation		2	10.4%	18.8%	14.6%	14.6%
Fatigue	Any grade	12	3.5%	59.0%	35.7%	34.3%
	Grade 1	2	25.7%	27.2%	26.5%	26.5%
	Grade 2	2	8.1%	14.2%	11.2%	11.2%
	Grade 3	3	2.1%	4.2%	3.3%	3.2%
	Grade 3-4	2	1.7%	11.8%	6.8%	6.8%
Headache	Any Grade	4	0.7%	14.3%	8.4%	7.9%
	Grade 1	3	0.7%	11.1%	1.3%	4.4%
	Grade 2	2	1.3%	2.4%	1.9%	1.9%
Infections	Any Grade	6	19.3%	35.0%	24.4%	25.4%
	Requiring antibiotics	2	19.3%	23.7%	21.5%	21.5%
ALT increased	Any grade	2	13.0%	19.0%	16.0%	16.0%
AST increased	Any grade	2	16.7%	28.0%	22.4%	22.4%
	Grade 3-4	2	2.4%	4.0%	3.2%	3.2%
Hypertransaminasaemia	Any grade	5	1.5%	58.1%	2.4%	14.7%
LFTs elevated	Any grade	2	4.7%	32.2%	18.4%	18.4%
Malaise	Any Grade	2	15.0%	16.7%	15.9%	15.9%
Mucositis	Any Grade	3	4.0%	7.1%	5.6%	5.6%
Nausea	Any grade	7	5.2%	69.7%	19.5%	25.1%
	Grade 1	2	5.2%	15.0%	10.1%	10.1%
Nausea/Vomiting	Any Grade	3	2.0%	14.2%	3.3%	6.5%
Renal failure		2	1.7%	3.8%	2.8%	2.8%
(Skin) rash	Any grade	5	1.5%	19.0%	3.4%	5.9%
Stomatitis	Any grade	6	3.3%	73.8%	16.4%	23.5%

Table 38: Incidence of AEs in patients receiving PAL reported in one NRS

Adverse Event	Grade	Incidence
Abscess	Any Grade	2.0%
ALT increased	Grade 3-4	9.5%
Altered defaecation (other than diarrhoea and constipation)		15.0%
Anorexia	Any Grade	2.6%
	Grade 1	2.4%
	Grade 2	0.2%
Arthralgia	Grade 3	0.6%
Asthenia	Any Grade	28.6%
	Grade 1	7.8%
	Grade 2	10.4%
	Grade 3	10.4%
Ascites	Any Grade	4.0%
	Grade 3-4	4.0%
Cerebral haemorrhage		2.4%
Conjunctivitis	Any Grade	14.3%
	Grade 1	9.1%
	Grade 2	5.2%
Constipation	Grade 3	0.2%
Cramps in lower limbs		13.0%
Decreased appetite	Grade 1	7.5%
	Grade 2	3.0%
	Grade 3	0.6%
Diarrhoea	Grade 3+4	0.8%
Difficulty or pain when walking		15.0%
Dizziness	Grade 1	2.6%
Dysgeusia	Any Grade	22.0%
Epistaxis	Any grade	4.1%
Fatigue	Grade 1-2	44.1%
Flu-like symptoms		17.0%
Gastrointestinal complaints		26.6%
Gastrointestinal bleeding	Any Grade	1.7%
	Grade 3	1.7%
Headache	Grade 3	0.3%
Herpes virus reactivation	Any Grade	3.9%
	Grade 1	2.6%
	Grade 2	1.3%
Hypertension	Any Grade	4.0%
	Grade 3-4	4.0%
Infections	Grade 1	8.4%
	Grade 2	13.5%
	Grade 3	3.0%
	Grade 4	0.3%
	Grade 5	0.3%
	lethal (concurrent Sepsis)	0.3%
Hepatic Dysfunction		3.8%
Hypertransaminasemia	Grade 1	7.8%
	Grade 2	1.9%
	Grade 3	0.2%
Itchy Skin		3.0%
LFTs elevated	Grade 3-4	5.1%
Muscle stiffness		17.0%
Mucositis	Grade 1	6.4%
	Grade 2	0.5%

	Grade 3	0.2%
	Grade 4	4.5%
Nausea	Grade 2	6.0%
	Grade 3	1.5%
	Grade 3-4	1.7%
Nausea/Vomiting	Grade 1	12.8%
	Grade 2	1.4%
Neutropenia	lethal	1.7%
Neuropathy	Any Grade	1.5%
Numbness and tingling		17.0%
Oral mucositis	Grade 1	6.5%
	Grade 2	5.2%
Pain, abdominal	Any Grade	5.2%
	Grade 1	4.5%
	Grade 2	0.7%
Pain, bone		13.0%
Pain, injection-side		15.0%
Pain, other		20.0%
Pleural effusion	Grade 3-4	7.0%
Pneumonia	Grade 3-4	7.0%
Psychological and behavioural changes		22.0%
QT prolongation	Any Grade	0.5%
	Grade 1	0.5%
Stomatitis	Grade 1	13.2%
	Grade 2	2.7%
	Grade 3	1.7%
	Grade 3-4	0.8%
Subarachnoid haemorrhage	Leading to death	2.4%
Venous thromboembolic event	Any grade	11.0%
	Grade 2	9.4%
	Grade 3	1.6%
Vertigo		1.7%
Watering eye	Any Grade	15.0%
Weight loss		3.8%

Table 39: Incidence of AEs in patients receiving ABE reported in NRSs, with grades

Adverse event	**Grade**	**Dickler et al. 2017 (n = 132)**	**Patniak et al. 2016 (n = 19)**
ALT increased	Any grade	30.0%	N/A
	Grade 1	24.6%	N/A
	Grade 2	1.5%	N/A
	Grade 3	3.8%	N/A
Anaemia	Any Grade	68.5%	11.0%
	Grade 1	30.0%	N/A
	Gade 2	38.5%	N/A
	Grade 3	N/A	11.0%
Anorexia	Any Grade	N/A	32.0%
	Grade 1	N/A	16.0%
	Grade 2	N/A	16.0%
Constipation	Any Grade	N/A	11.0%
	Grade 1	N/A	11.0%
Cramps in lower limbs		98.5%	
Creatinine levels increased	Any Grade	46.9%	11.0%
	Grade 1	50.8%	5.0%
	Grade 2	0.8%	5.0%

Decreased appetite	Any Grade	45.5%	N/A
	Grade 1	28.0%	N/A
	Grade 2	14.4%	N/A
	Grade 3	3.0%	N/A
Dehydration	Any Grade	N/A	16.0%
	Grade 1	N/A	5.0%
	Grade 2	N/A	11.0%
Diarrhoea	Any grade	90.2%	79.0%
	Grade 1	41.7%	37.0%
	Grade 2	28.8%	37.0%
	Grade 3	19.7%	5.0%
Dyspepsia	Any Grade	N/A	11.0%
	Grade 2	N/A	11.0%
Fatigue	Any grade	65.2%	68.0%
	Grade 1	21.2%	37.0%
	Grade 2	31.1%	26.0%
	Grade 3	12.9%	5.0%
Headache	Any Grade	20.5%	N/A
	Grade 1	13.6%	N/A
	Grade 2	6.8%	N/A
Hypokaliaemia	Any Grade	26.2%	16.0%
	Grade 1	N/A	5.0%
	Grade 2	20.8%	11.0%
	Grade 3	5.4%	N/A
Hyponatriaemia	Any Grade	20.8%	N/A
	Grade 1	17.7%	N/A
	Grade 3	3.1%	N/A
Infections	Any Grade	31.1%	N/A
	Any grade	26.2%	N/A
	Grade 1	16.9%	N/A
	Grade 2	7.7%	N/A
	Grade 3	1.5%	N/A
Leukopenia	Any grade	90.8%	32.0%
	Grade 1	18.5%	N/A
	Gade 2	44.6%	5.0%
	Grade 3	27.7%	26.0%
Nausea	Any grade	64.4%	63.0%
	Grade 1	39.4%	32.0%
	Grade 2	20.5%	32.0%
	Grade 3	4.5%	N/A
Neutropenia	Any grade	87.7%	42.0%
	Grade 1	17.7%	N/A
	Grade 2	43.1%	11.0%
	Grade 3	22.3%	32.0%
	Grade 4	4.6%	N/A
	Grade 3-4	0.8%	N/A
Pain, abdominal	Any Grade	38.6%	21.0%
	Grade 1	22.0%	5.0%
	Grade 2	14.4%	5.0%
	Grade 3	23.3%	11.0%
Thrombocytopenia	Any Grade	41.4%	11.0%
	Grade 1	28.9%	11.0%
	Grade 2	10.2%	N/A
	Grade 3	2.3%	N/A
Vomiting	Any Grade	34.8%	42.0%
	Grade 1	22.7%	21.0%
	Grade 2	10.6%	16.0%
	Grade 3	1.5%	5.0%

Watering eye	Any Grade	N/A	16.0%
	Grade 1	N/A	5.0%
	Grade 2	N/A	11.0%

15.4 Supplementary figures efficacy and safety

Figure 47: PICO 1 treatment network for PFS; individual AIs

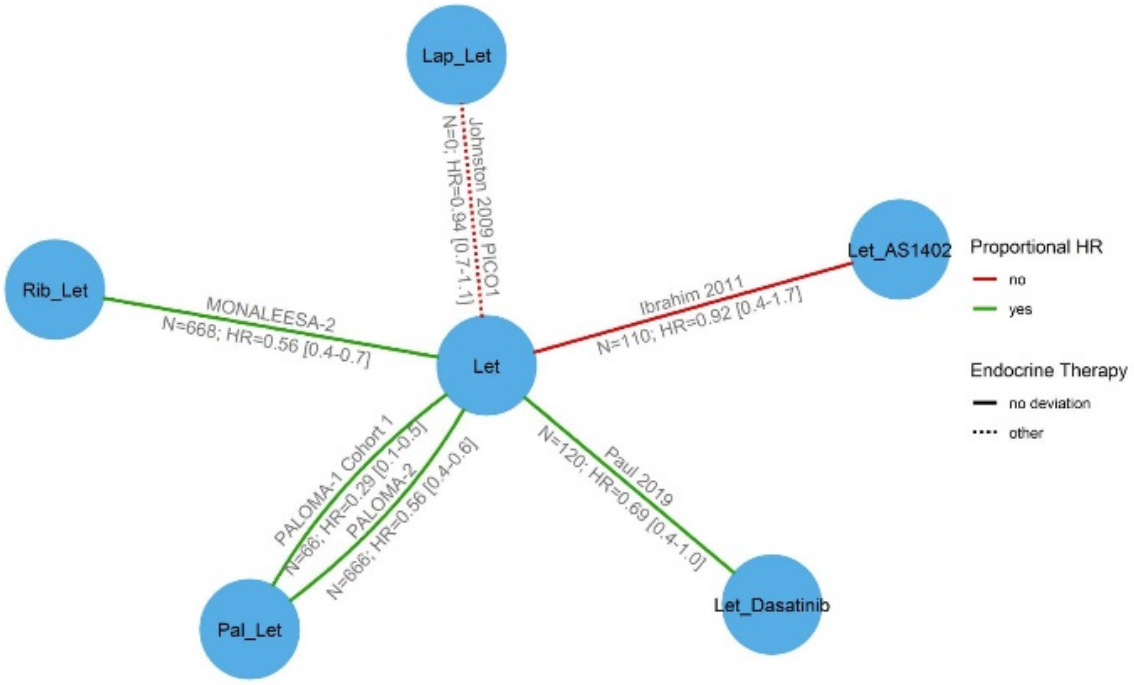


Figure 48: PICO 1 SUCRA and forest plots for PFS; individual AIs; fixed effect model

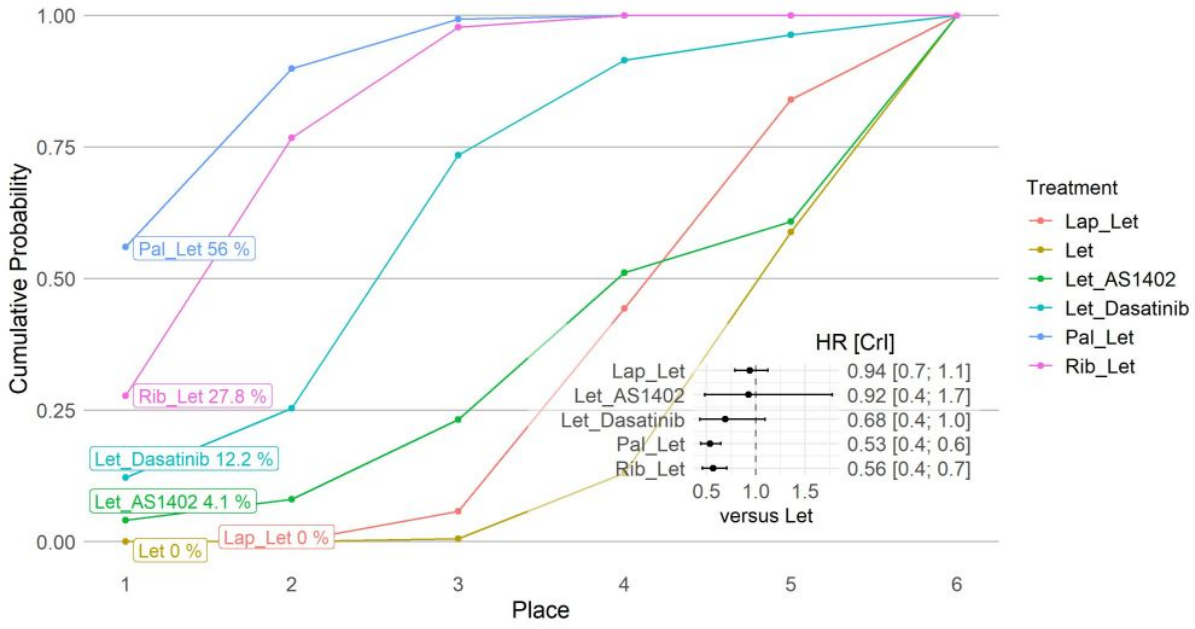


Figure 49: PICO 1 SUCRA and forest plots for PFS; random effects model

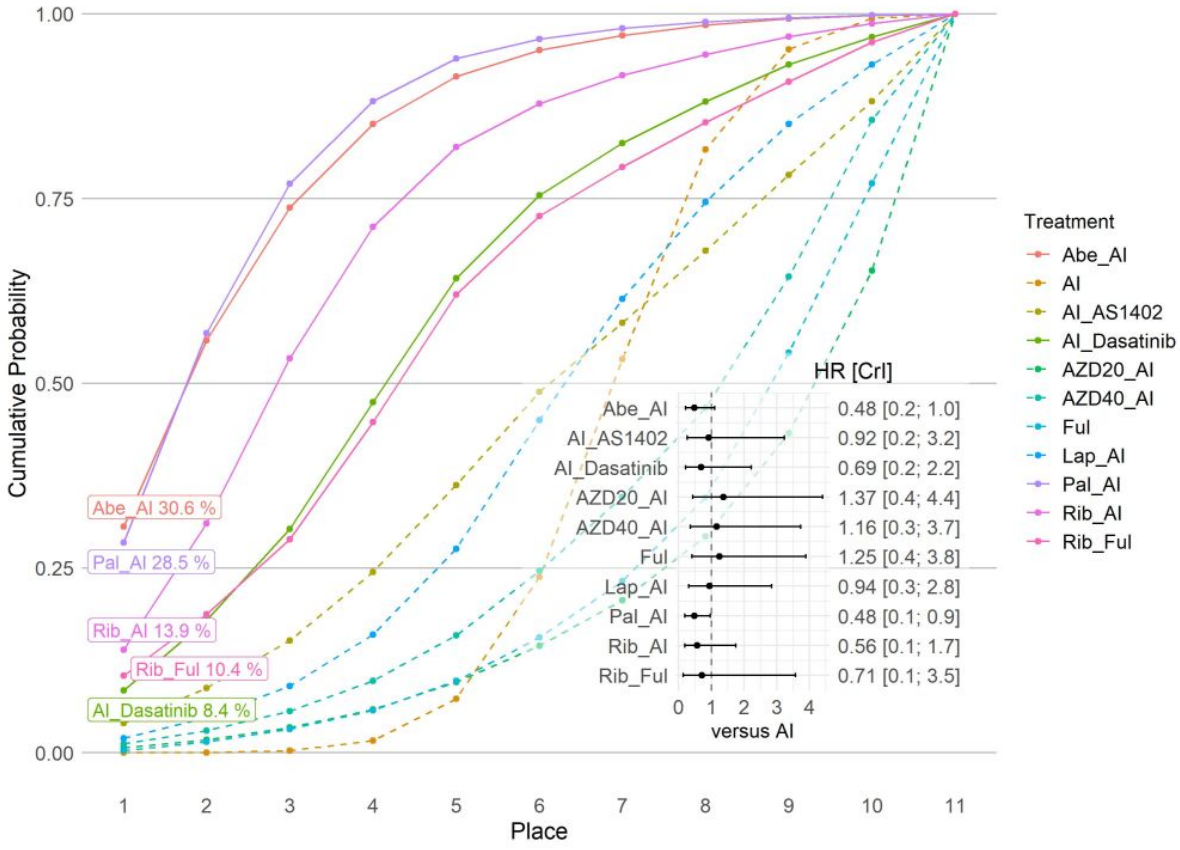


Figure 50: PICO 1 SUCRA and forest plots for PFS; network meta-regression for age; fixed effect model

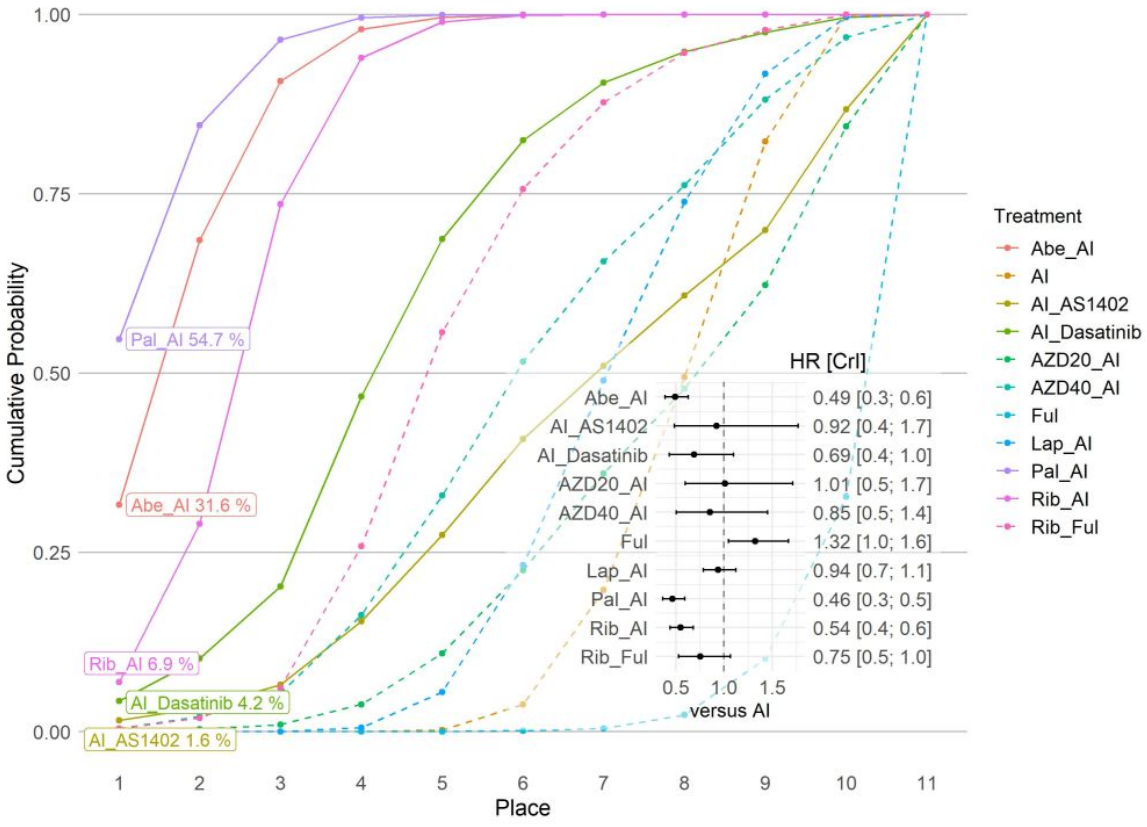


Figure 51: PICO 1 SUCRA and forest plots for PFS; network meta-regression for age; random effects model

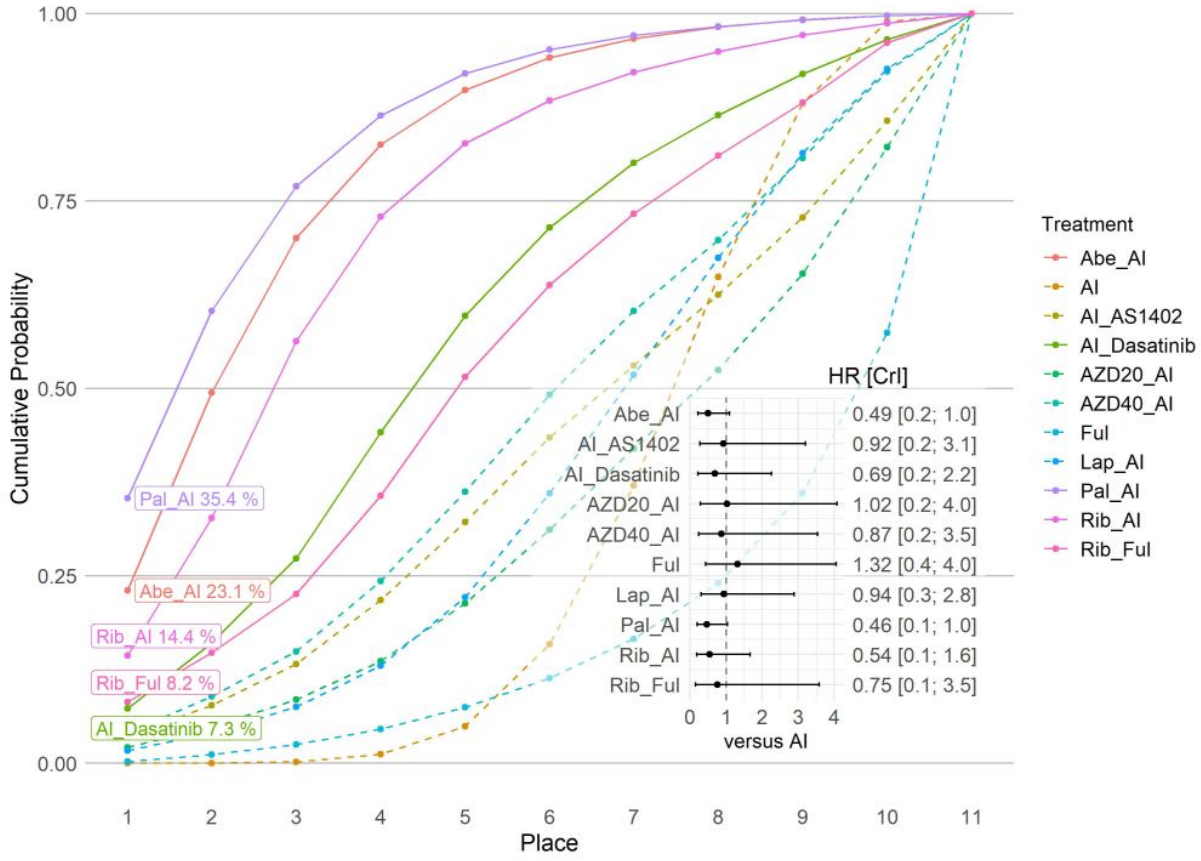


Figure 52: PICO 1 SUCRA and forest plots for OS; random effects model

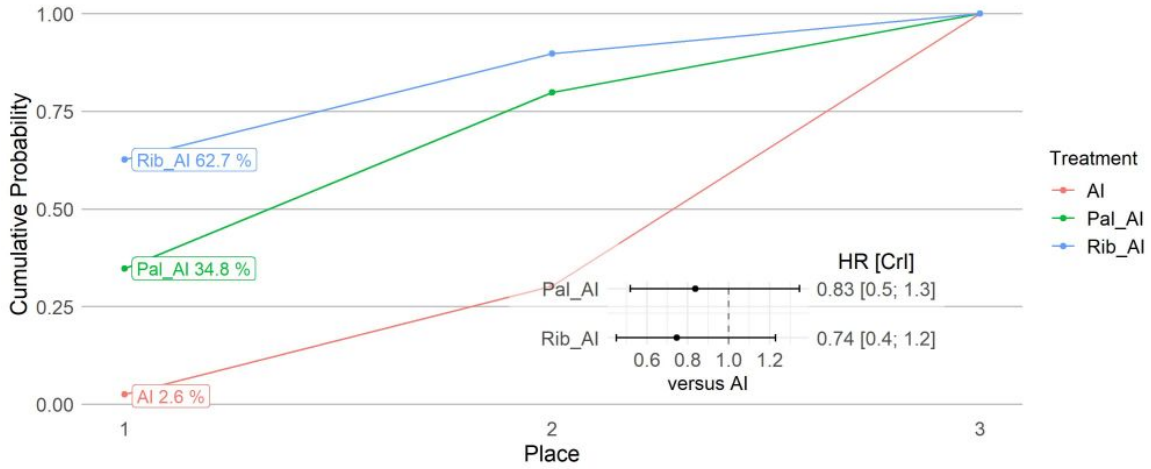


Figure 54: PICO 1 SUCRA and forest plots for OS; network meta-regression for age; random effects model

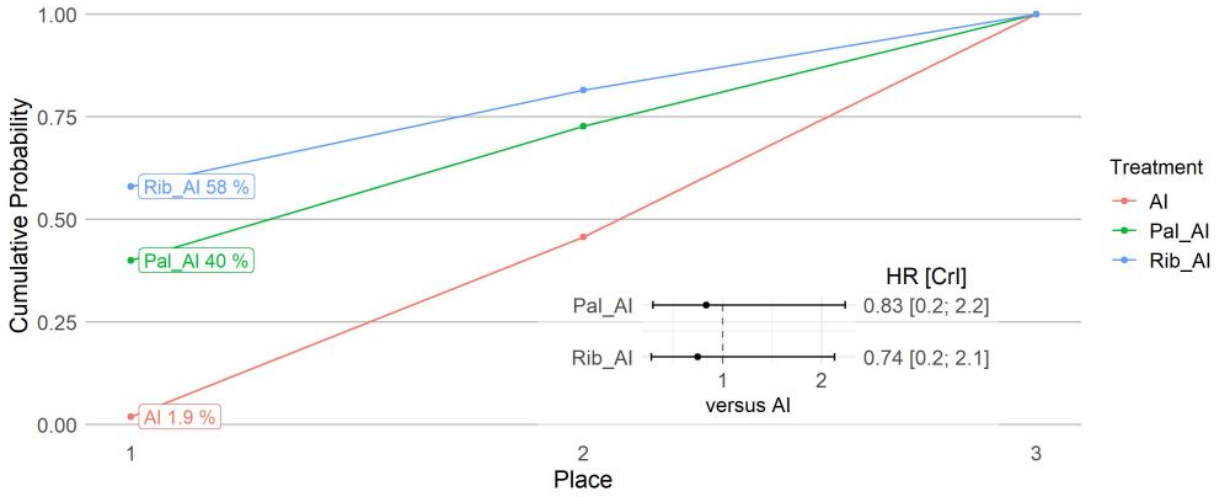


Figure 53: PICO 1 SUCRA and forest plots for OS; network meta-regression for age; fixed effect model

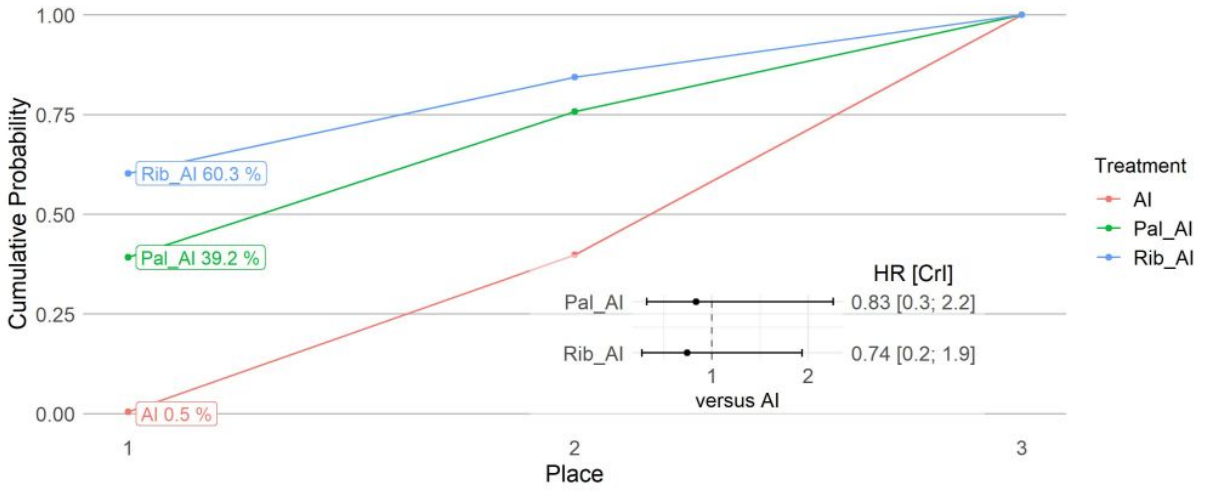


Figure 56: PICO 1 treatment network for QoL; individual AIs

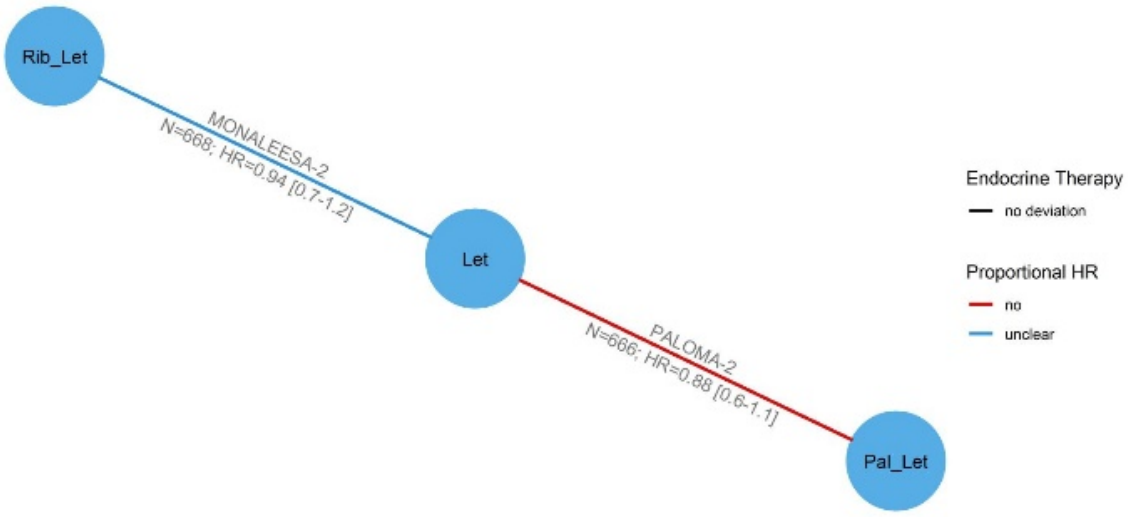


Figure 55: PICO 1 SUCRA and forest plots for QoL; individual AIs

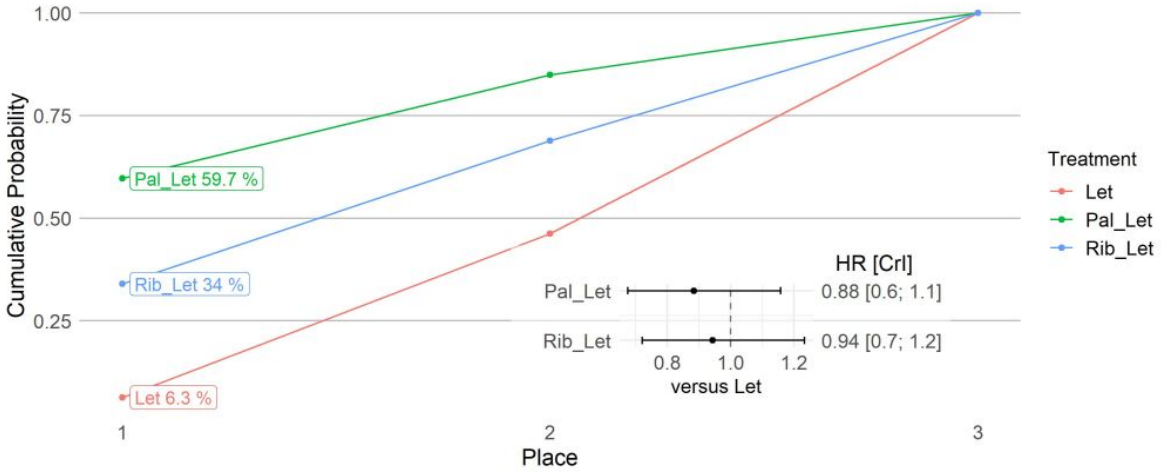


Figure 57: PICO 1 SUCRA and forest plots for QoL; random effects model

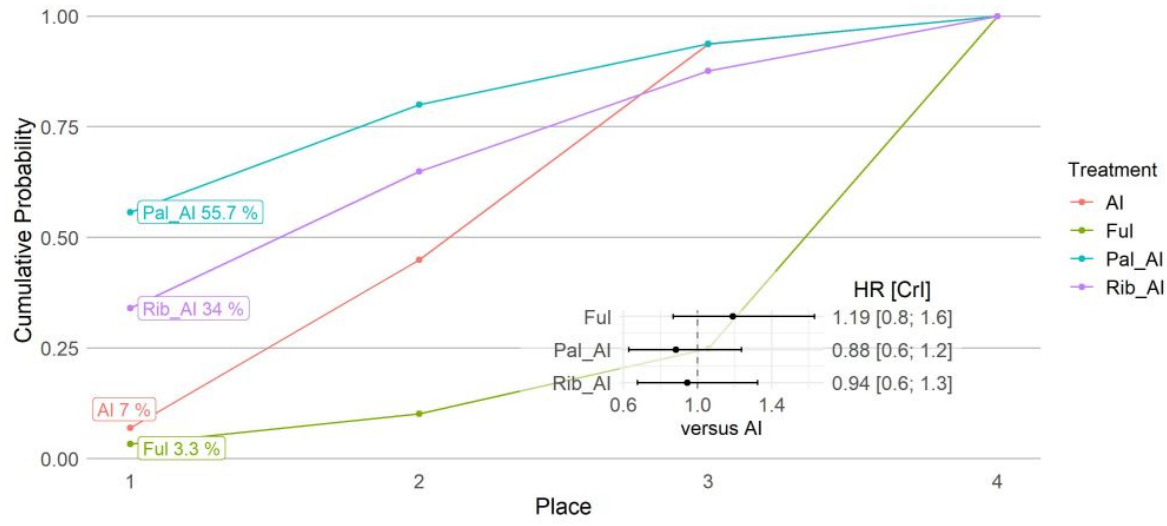


Figure 58: PICO 1 SUCRA and forest plots for QoL; network meta-regression for age; fixed effect model

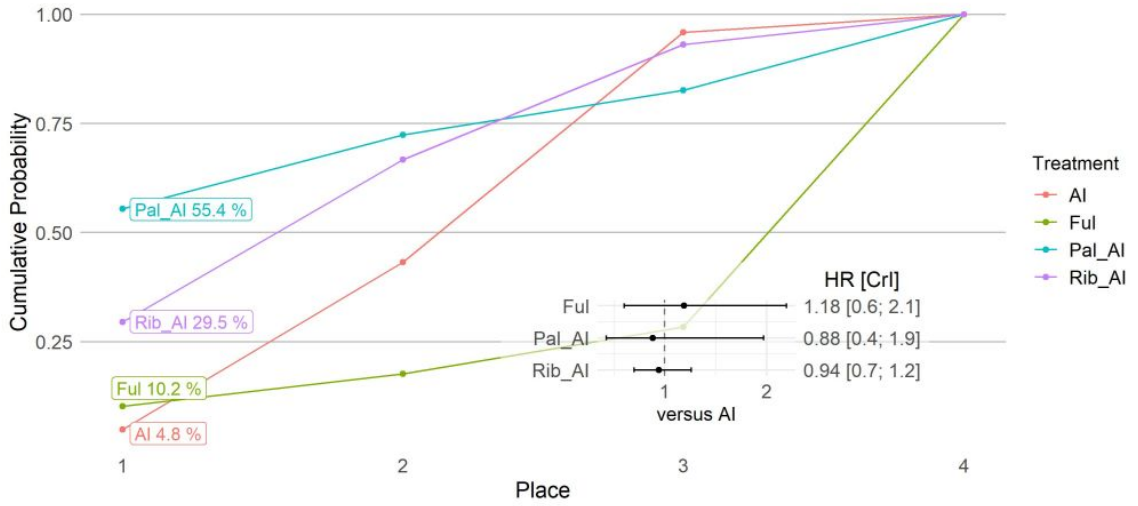


Figure 59: PICO 1 SUCRA and forest plots for QoL; network meta-regression for age; random effects model

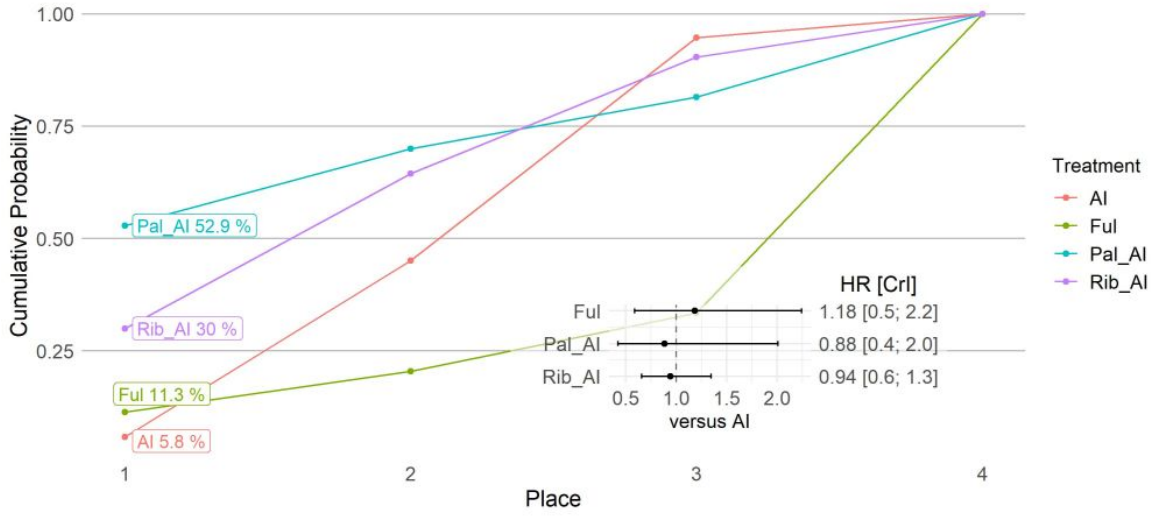


Figure 61: PICO 1 treatment network for AE3+; individual AIs

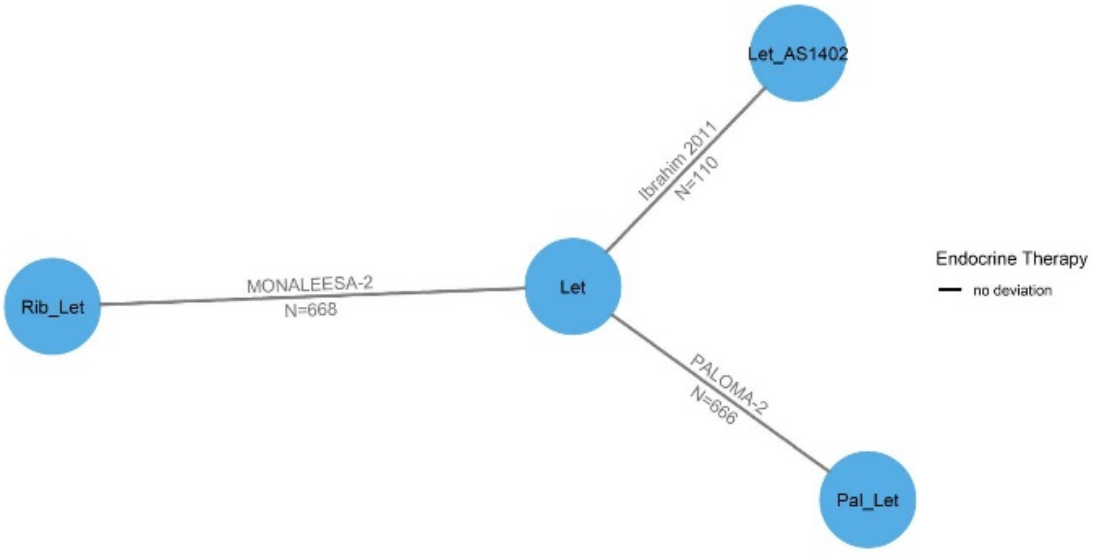


Figure 60: PICO 1 SUCRA and forest plots for AE3+; individual AIs

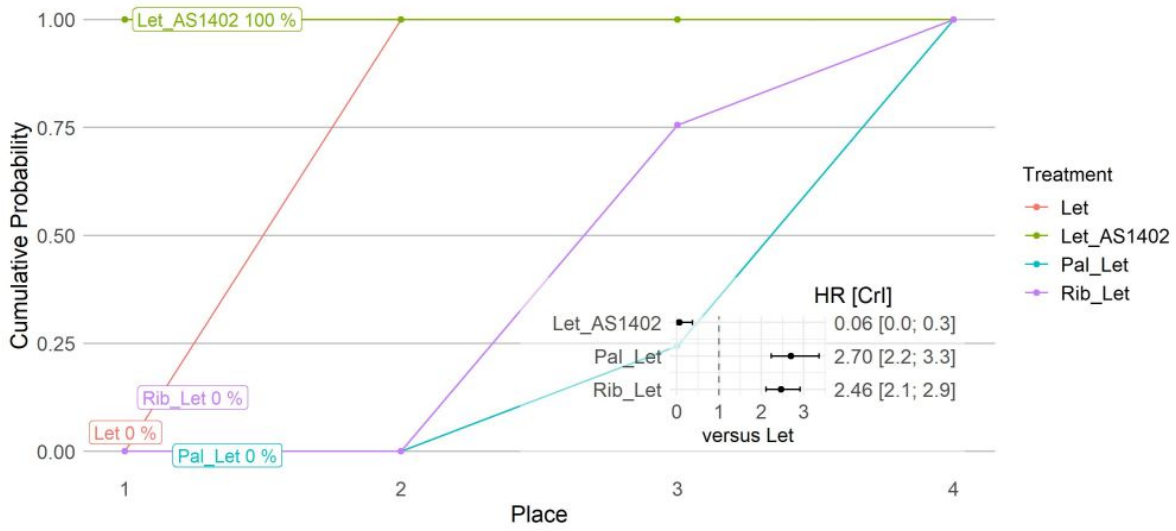


Figure 62: PICO 1 SUCRA and forest plots for AE3+; random effects model

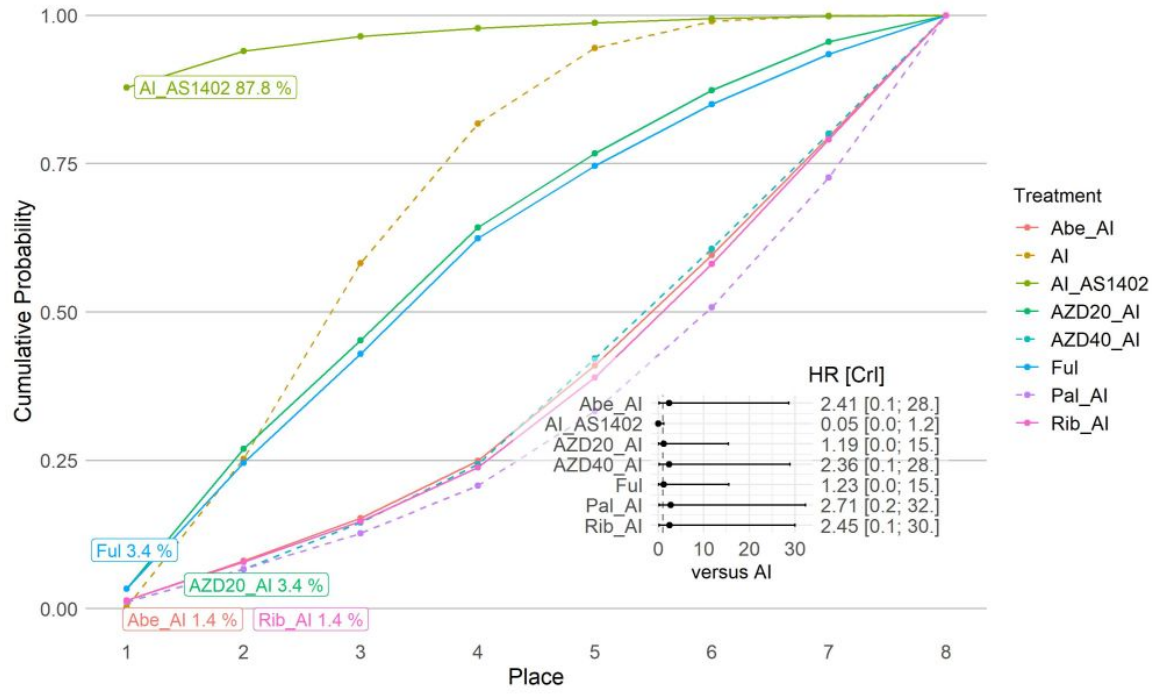


Figure 63: PICO 1 SUCRA and forest plots for AE3+; network meta-regression for age; fixed effect model

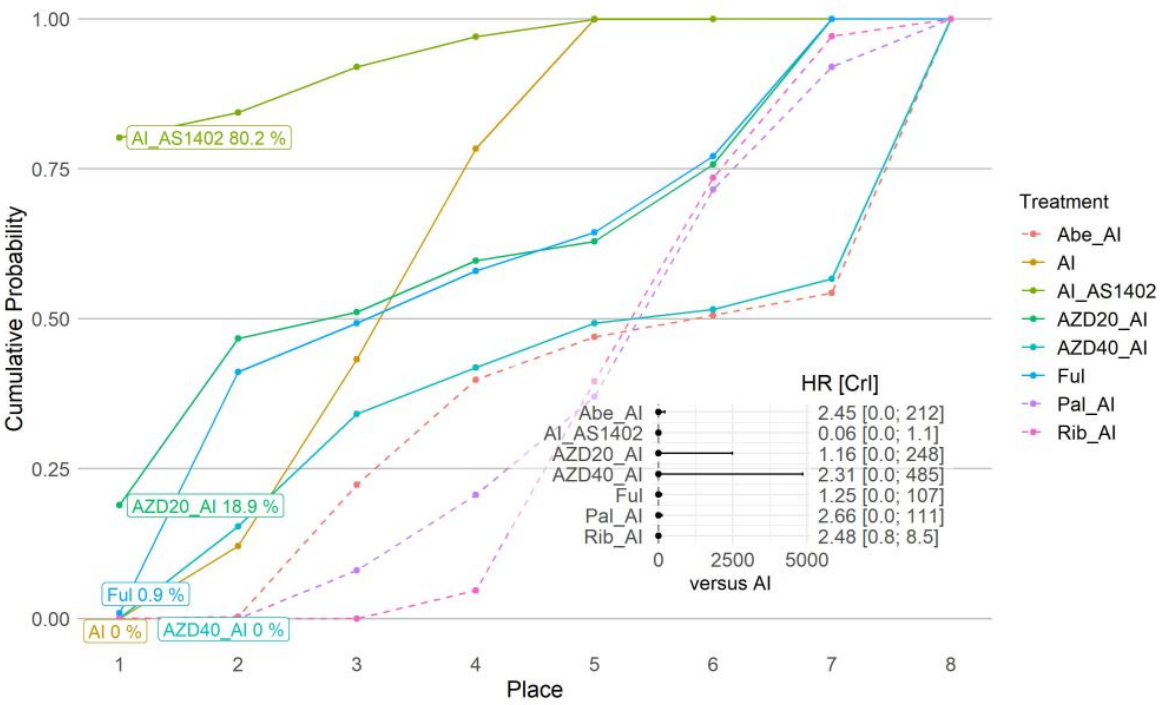


Figure 65: PICO 1 SUCRA and forest plots for AE3+; network meta-regression for age; random effects model

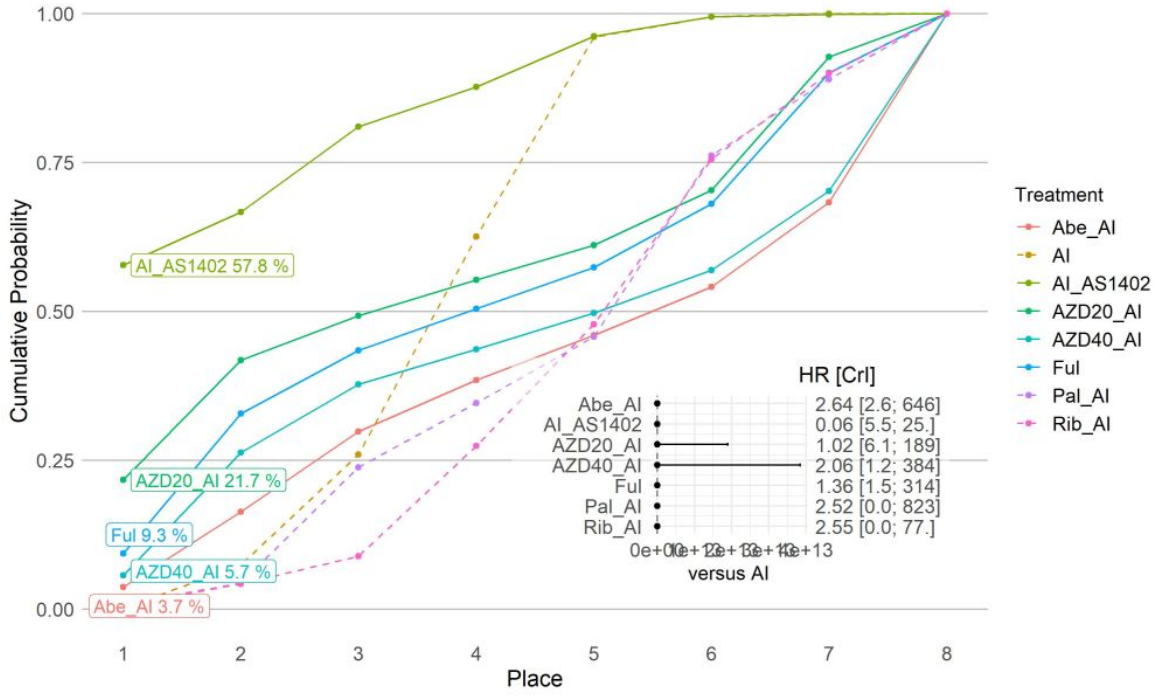


Figure 64: PICO 1 treatment network for discontinuations; individual AIs

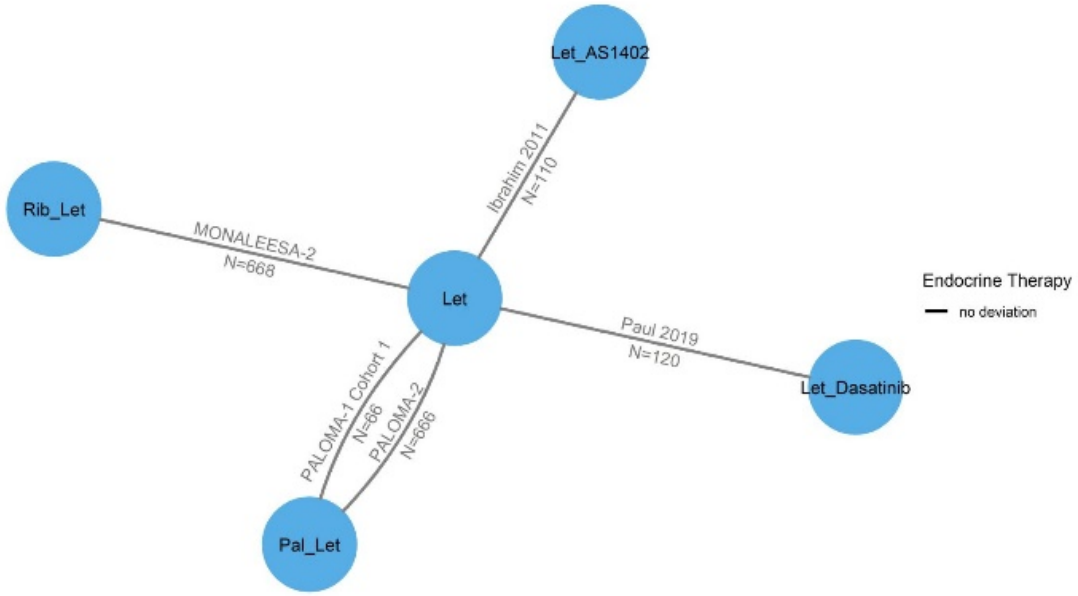


Figure 67: PICO 1 SUCRA and forest plots for discontinuations; individual AIs

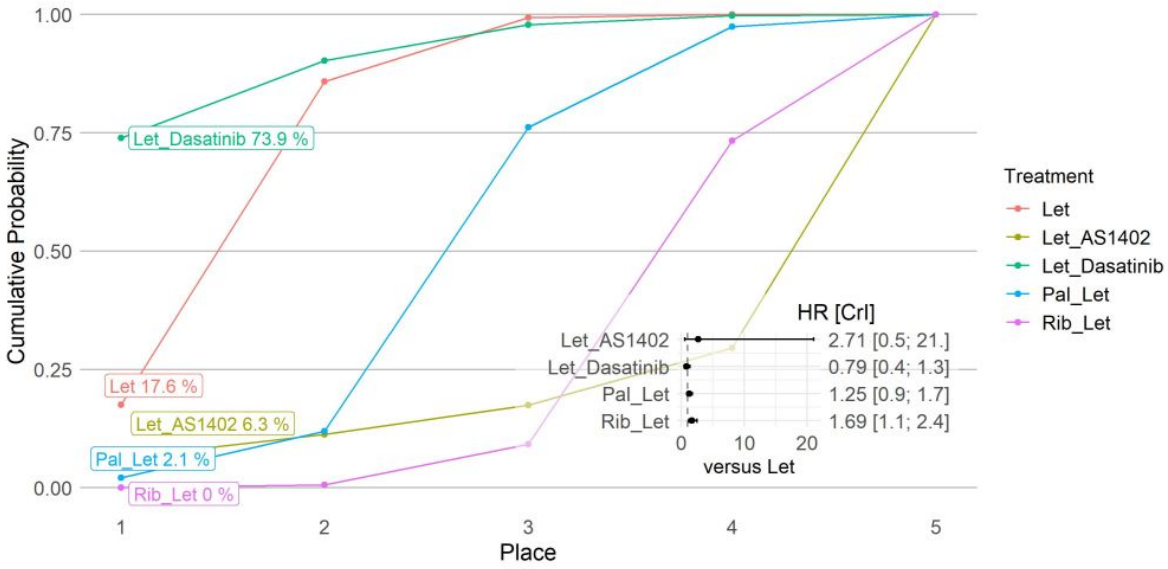


Figure 66: PICO 1 SUCRA and forest plots for discontinuations; random effects model

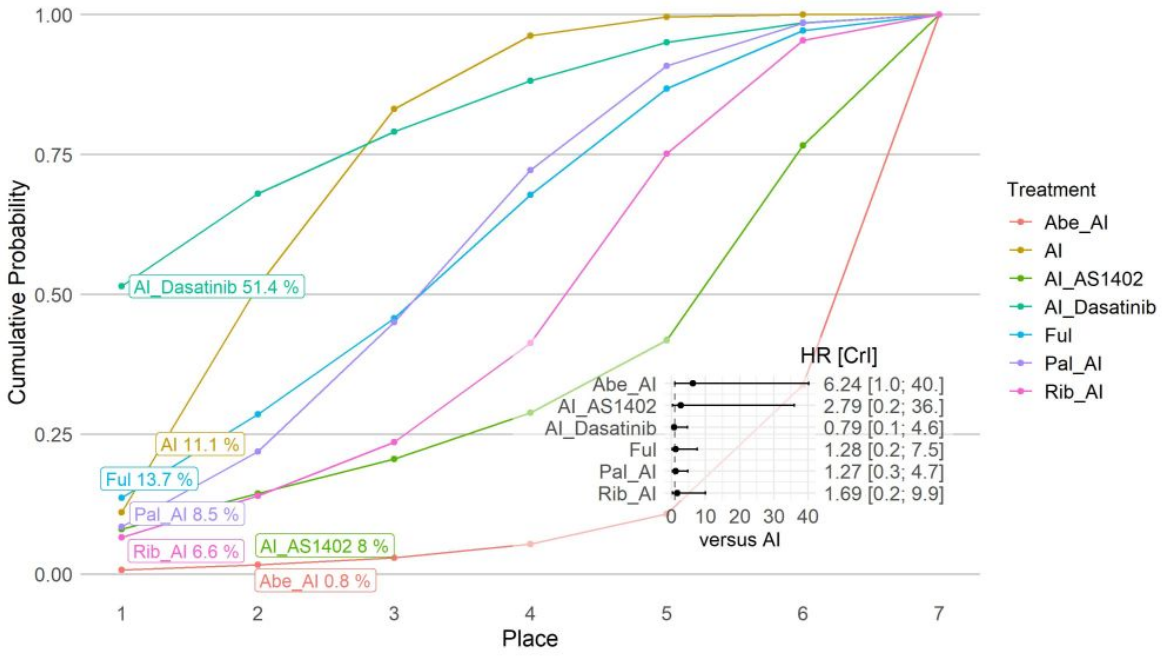


Figure 69: PICO 1 SUCRA and forest plots for discontinuations; network meta-regression for age; random effects model

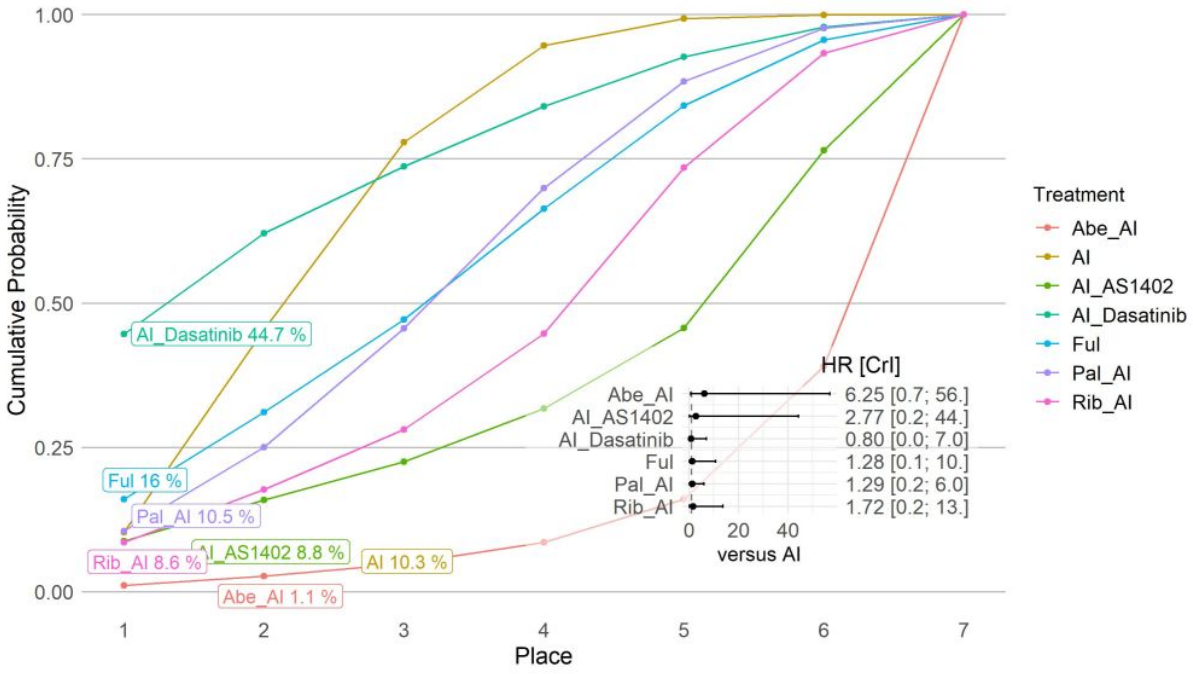


Figure 68: PICO 1 SUCRA and forest plots for discontinuations; network meta-regression for age; fixed effect model

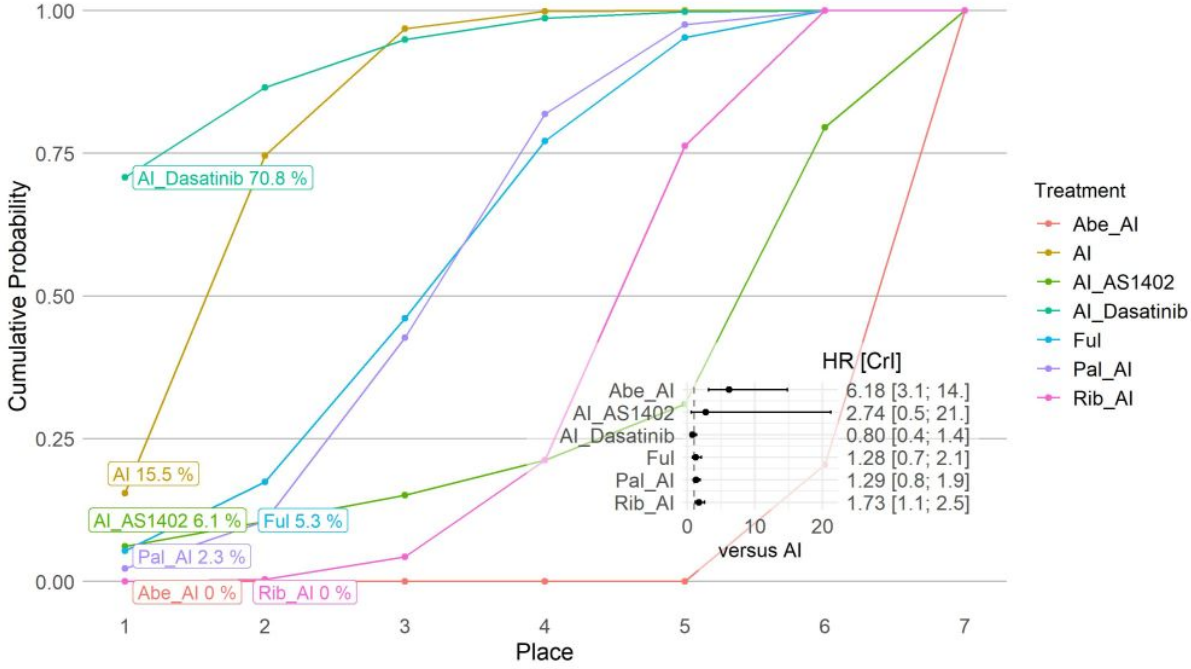


Figure 70: PICO 2 treatment network for PFS; individual AIs

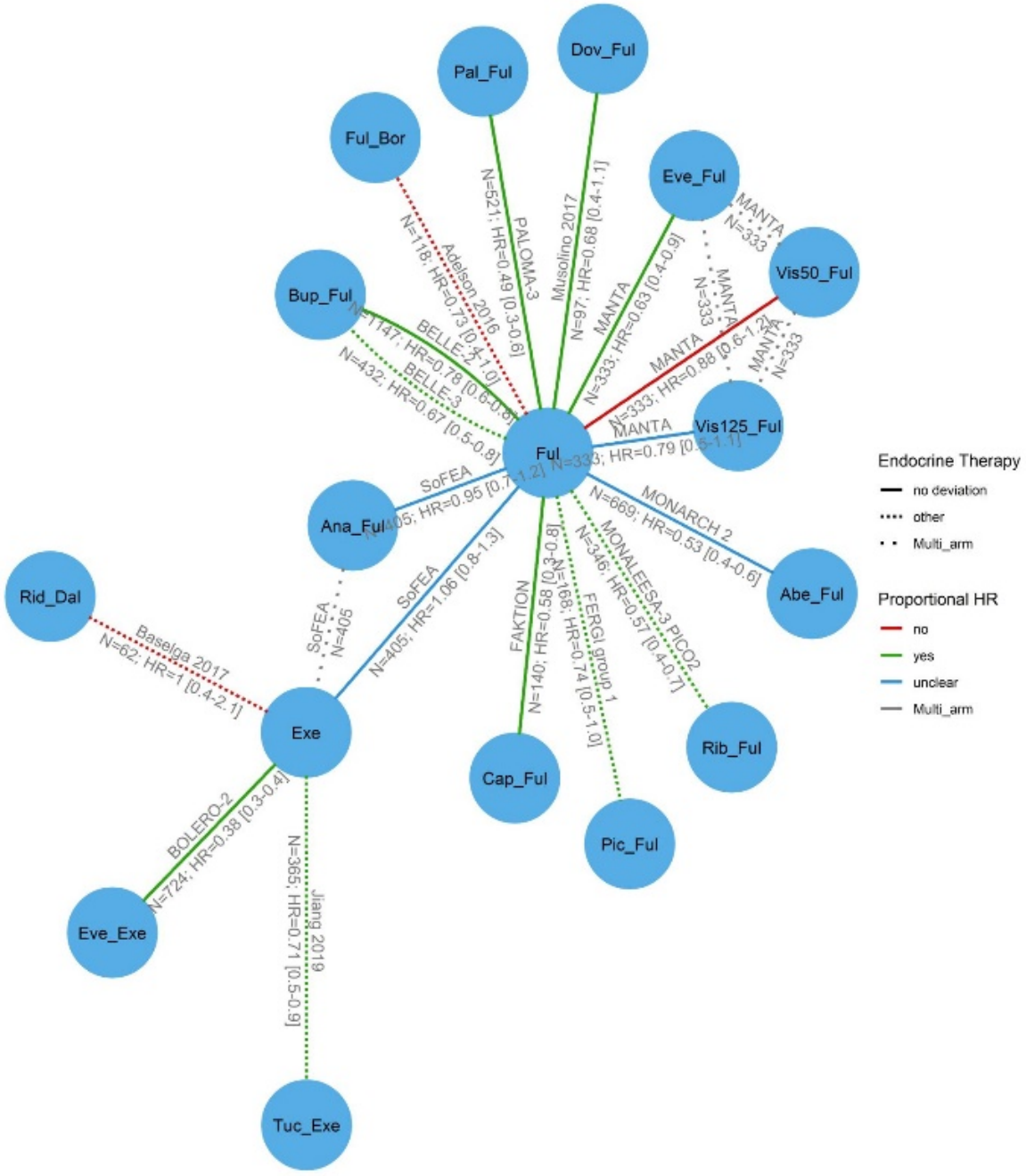


Figure 71: PICO 2 SUCRA and forest plots for PFS; individual AIs

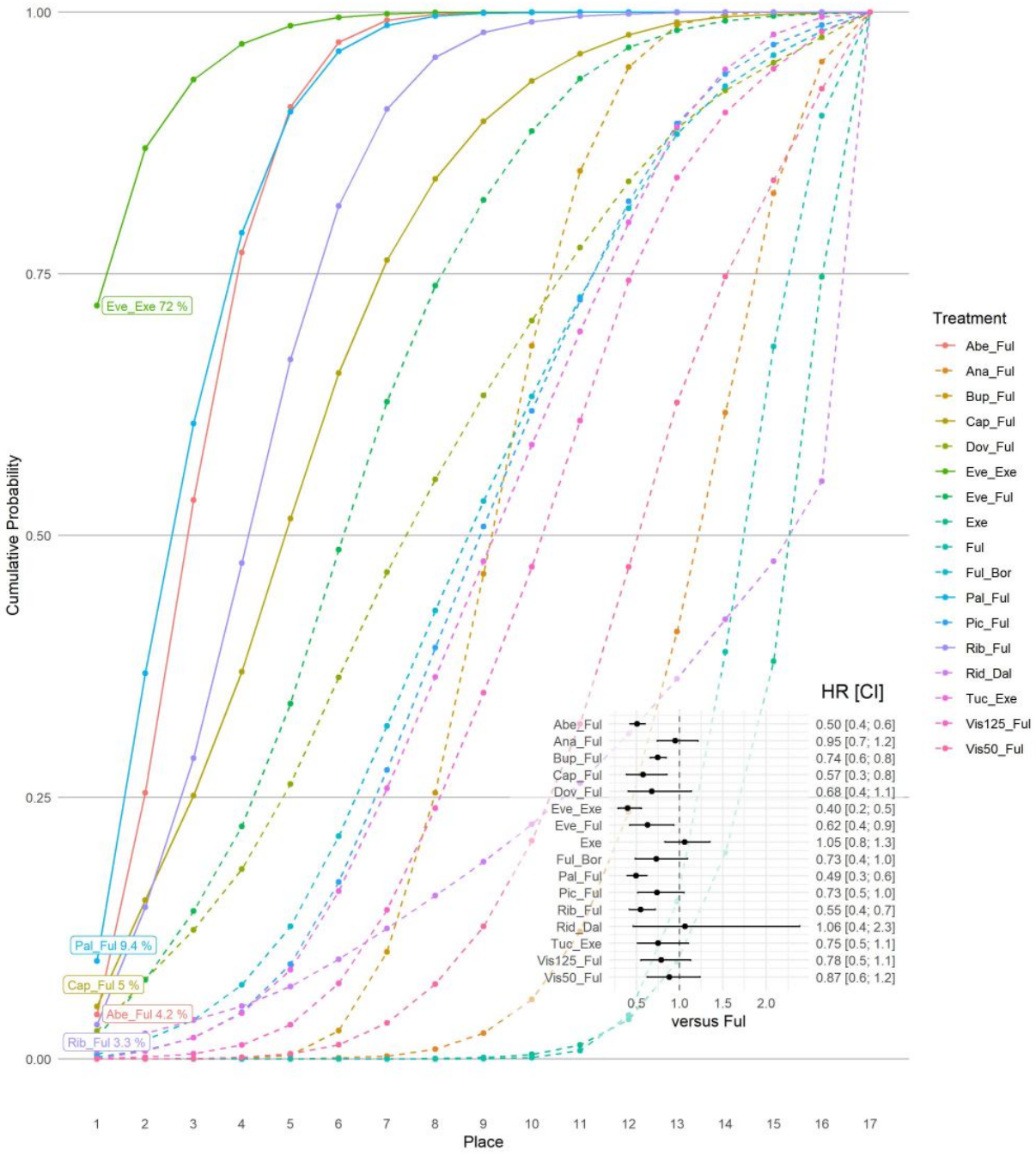


Figure 72: PICO 2 SUCRA and forest plots for PFS; random effects model

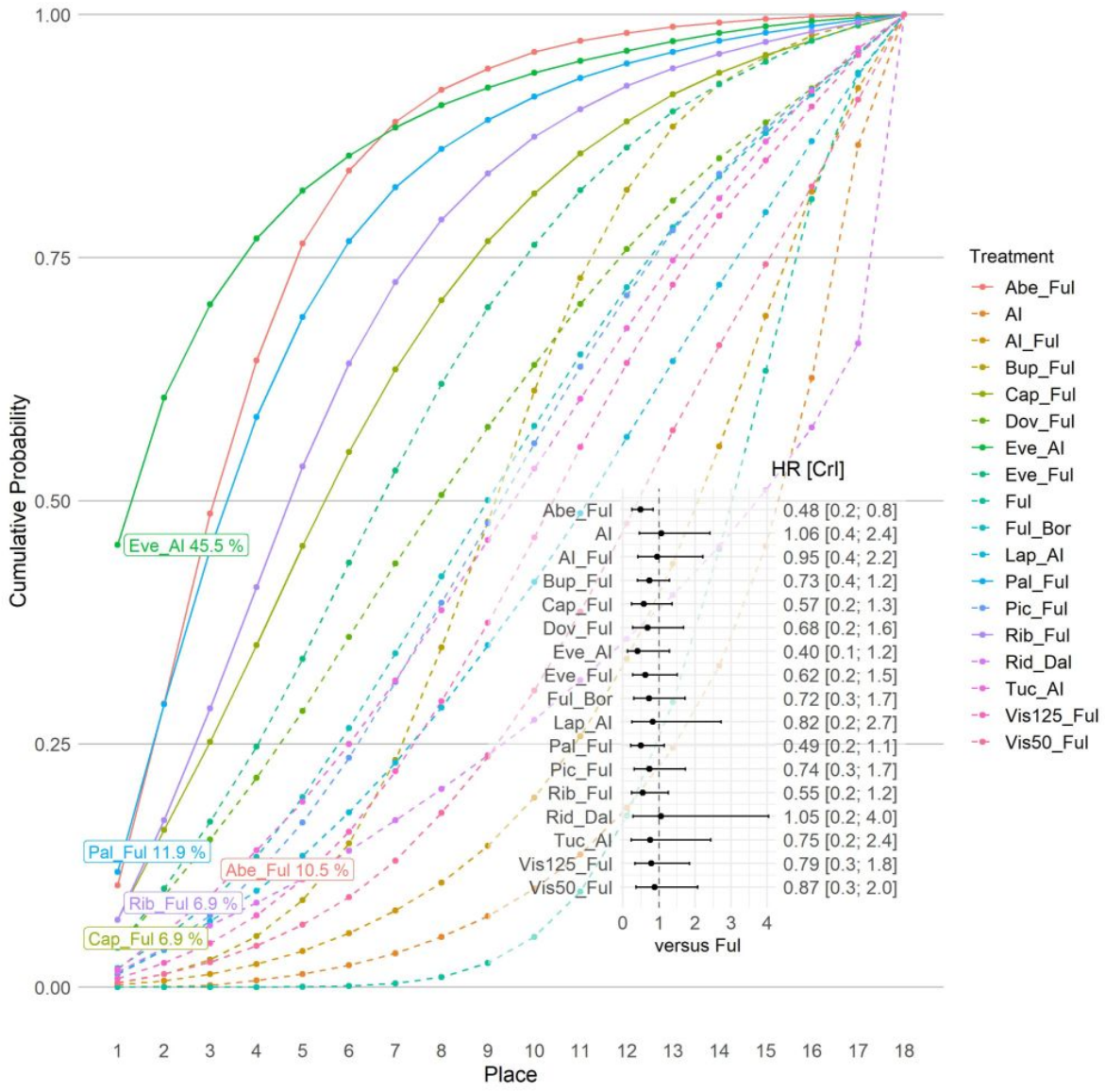


Figure 73: PICO 2 SUCRA and forest plots for PFS; network meta-regression for age; fixed effect model

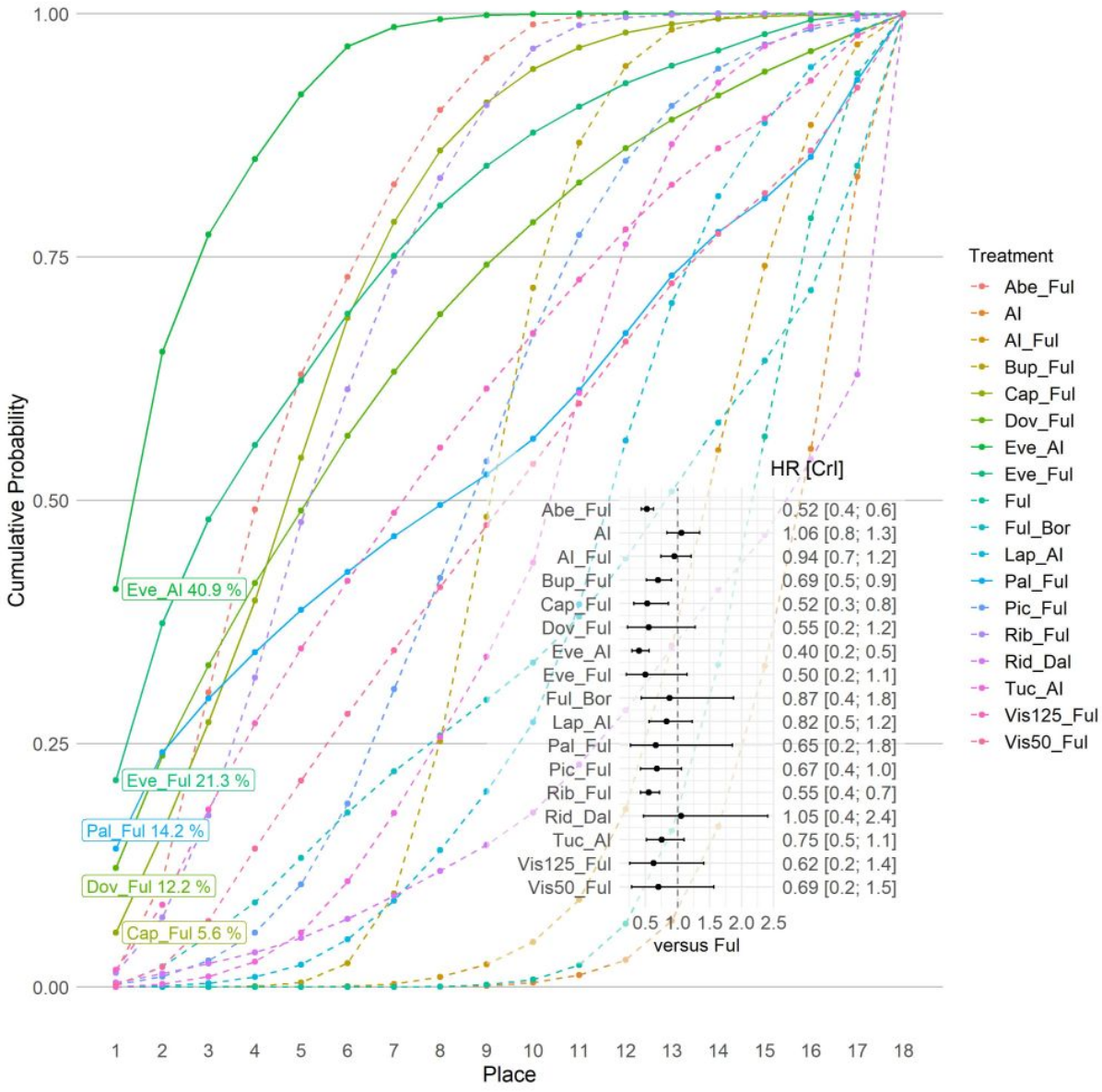


Figure 74: PICO 2 SUCRA and forest plots for PFS; network meta-regression for age; random effects model

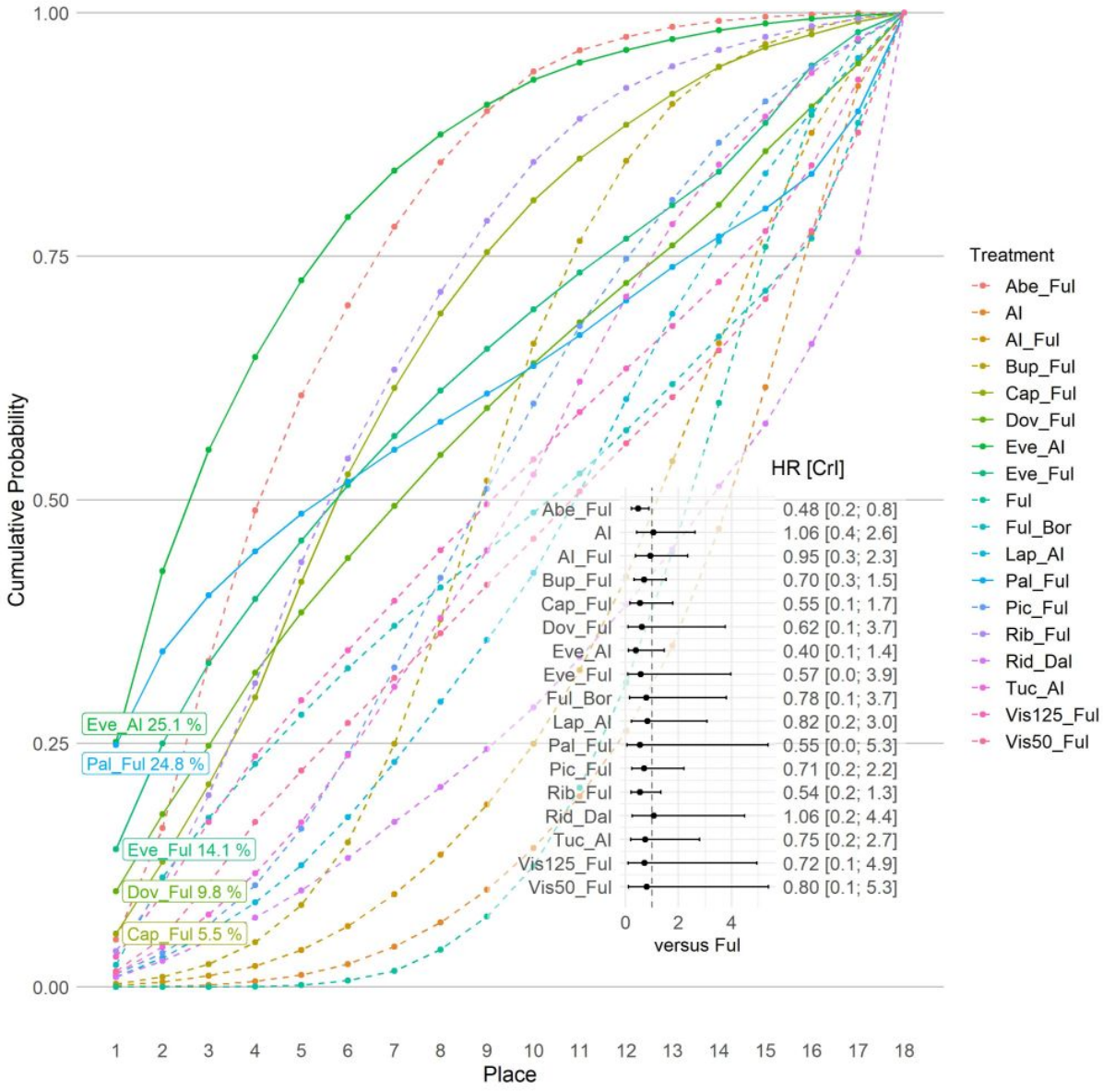


Figure 76: PICO 2 SUCRA and forest plots for OS; random effects model

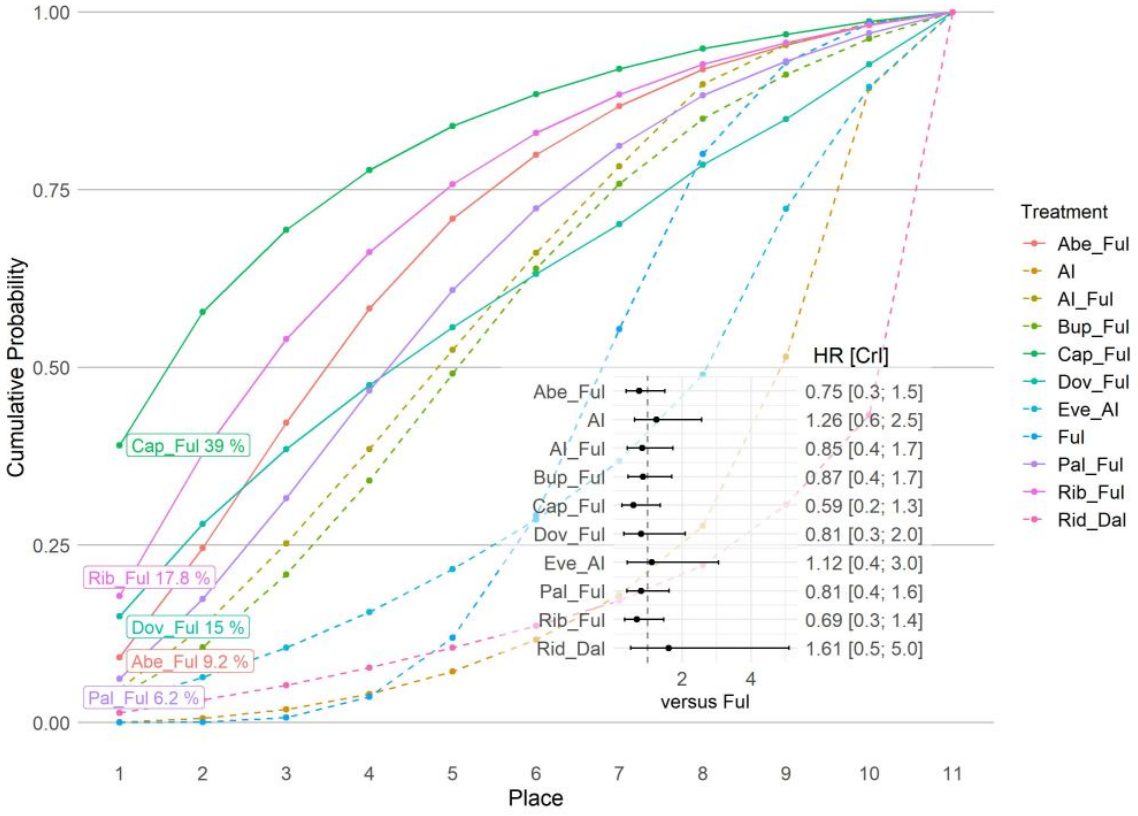


Figure 75: PICO 2 SUCRA and forest plots for OS; network meta-regression for age; fixed effect model

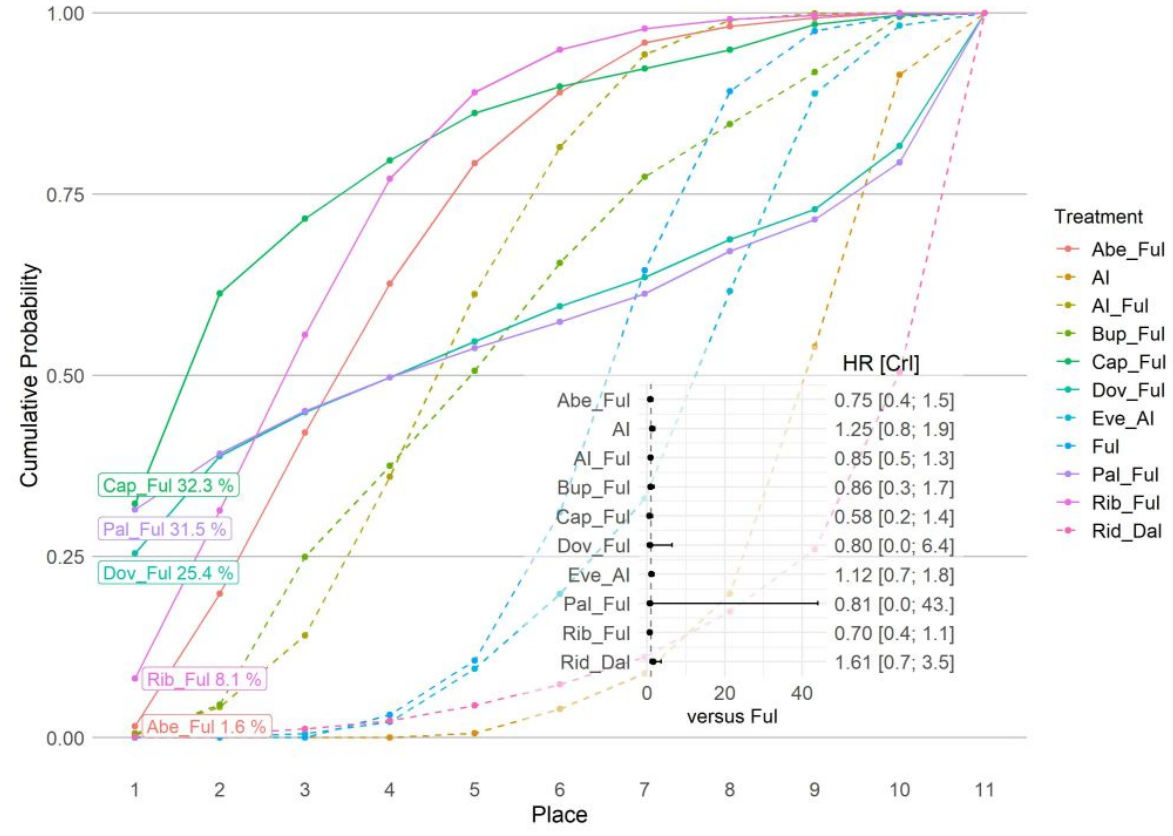


Figure 77: PICO 2 SUCRA and forest plots for OS; network meta-regression for age; random effects model

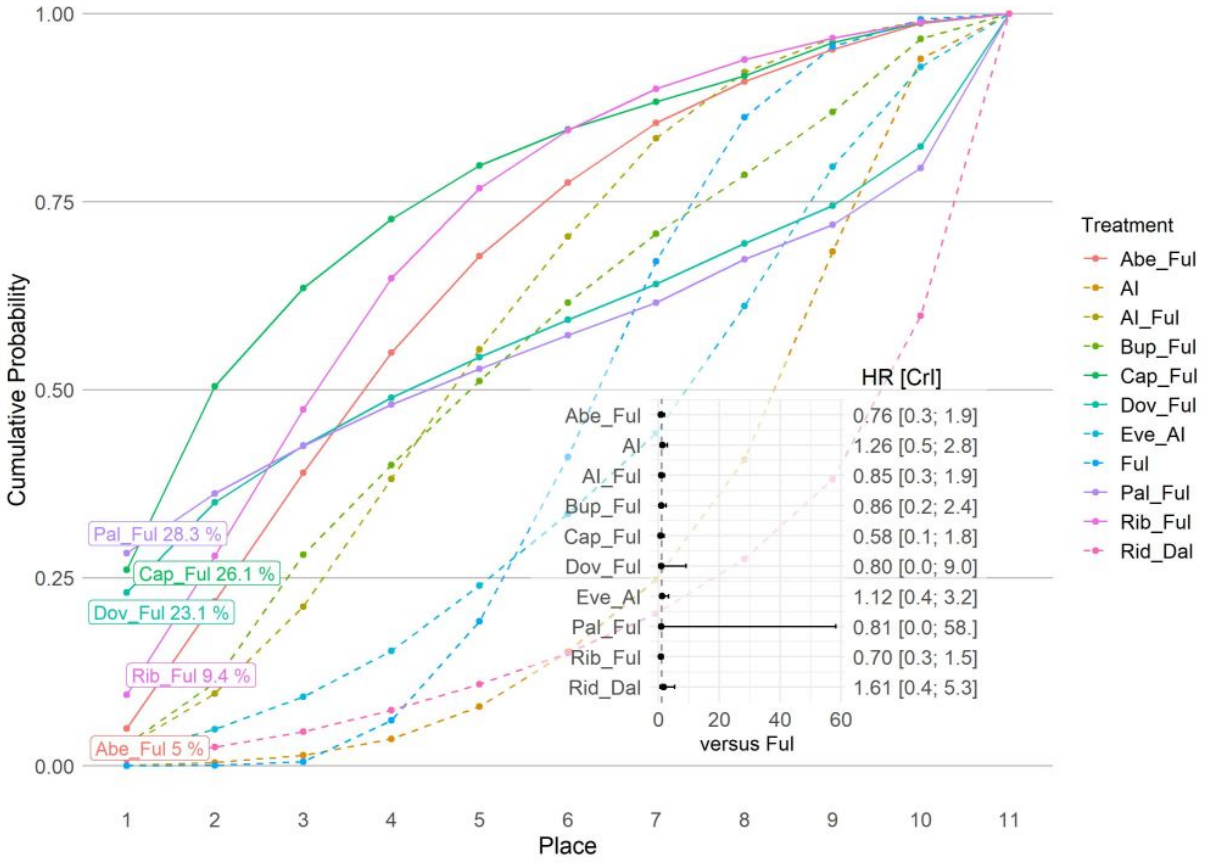


Figure 78: PICO 2 SUCRA and forest plots for QoL; random effects model

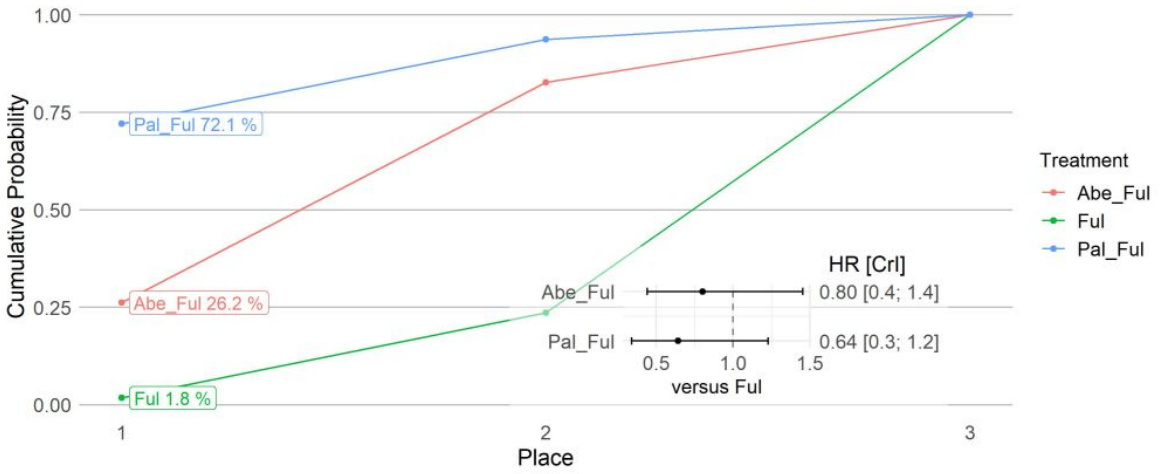


Figure 80: PICO 2 SUCRA and forest plots for QoL; network meta-regression for age; fixed effect model

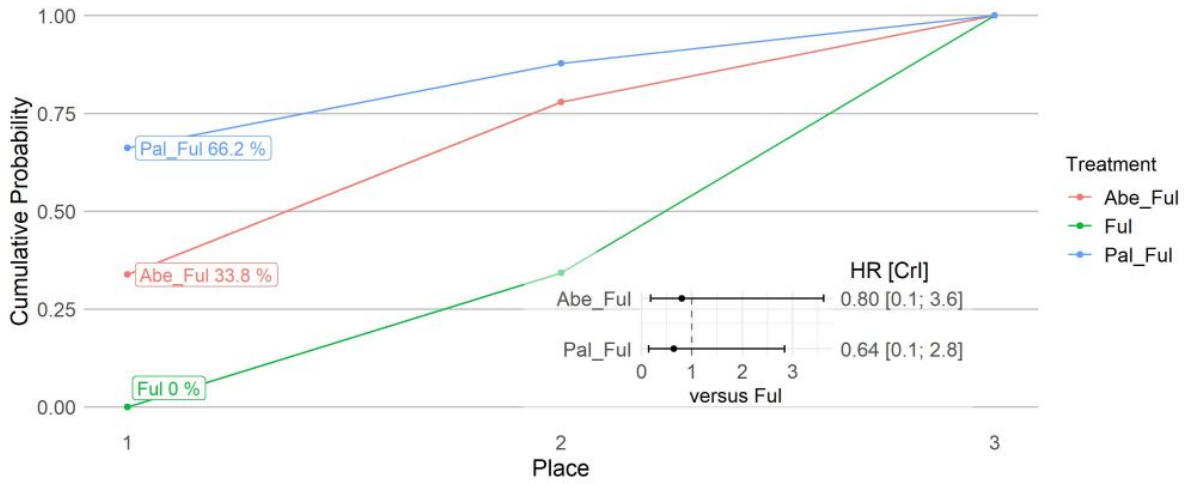


Figure 79: PICO 2 SUCRA and forest plots for QoL; network meta-regression for age; random effects model

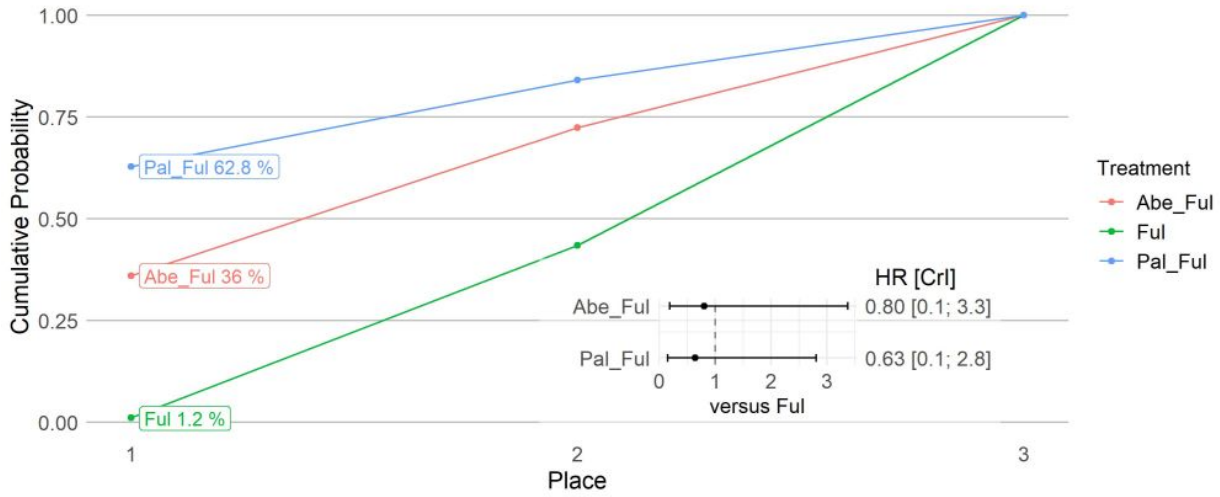


Figure 82: PICO 2 SUCRA and forest plots for AE3+; random effects model

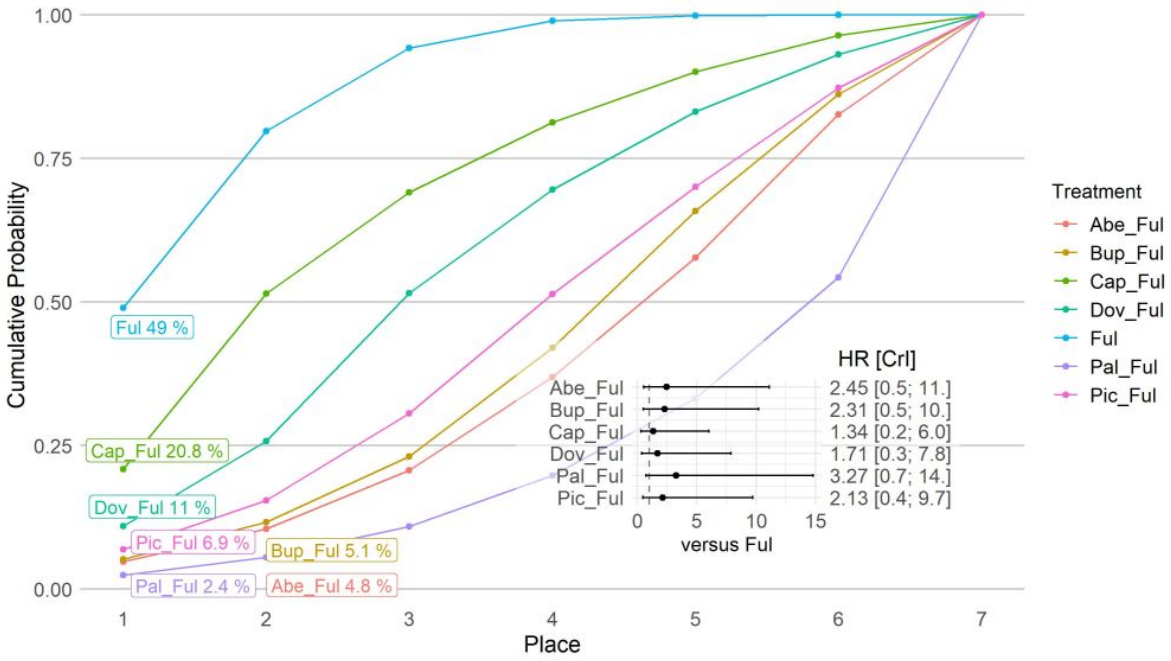


Figure 81: PICO 2 SUCRA and forest plots for AE3+; network meta-regression for age; fixed effect model

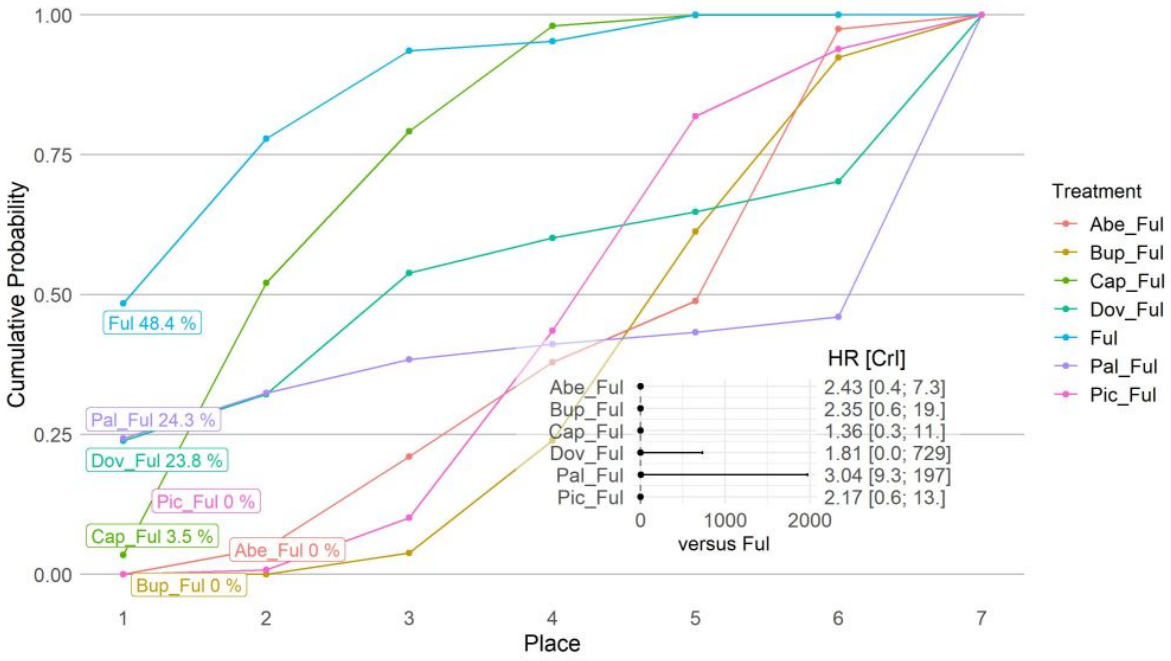


Figure 84: PICO 2 SUCRA and forest plots for AE3+; network meta-regression for age; random effects model

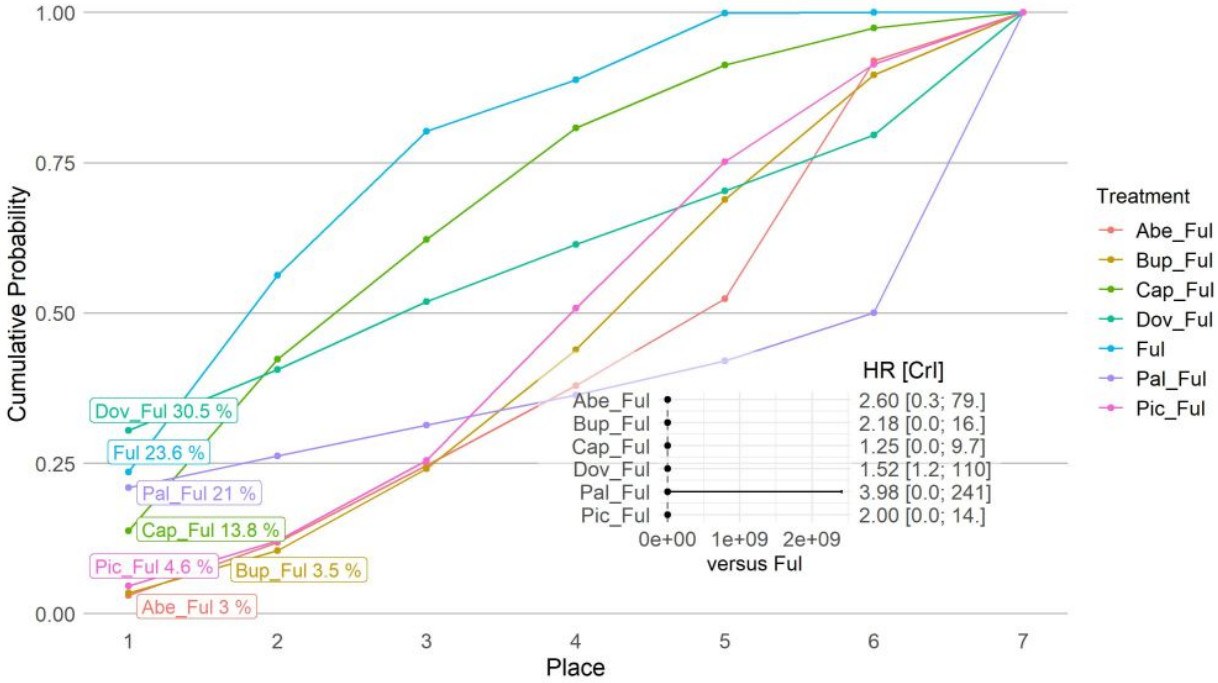


Figure 83: PICO 2 SUCRA and forest plots for discontinuations; random effects model

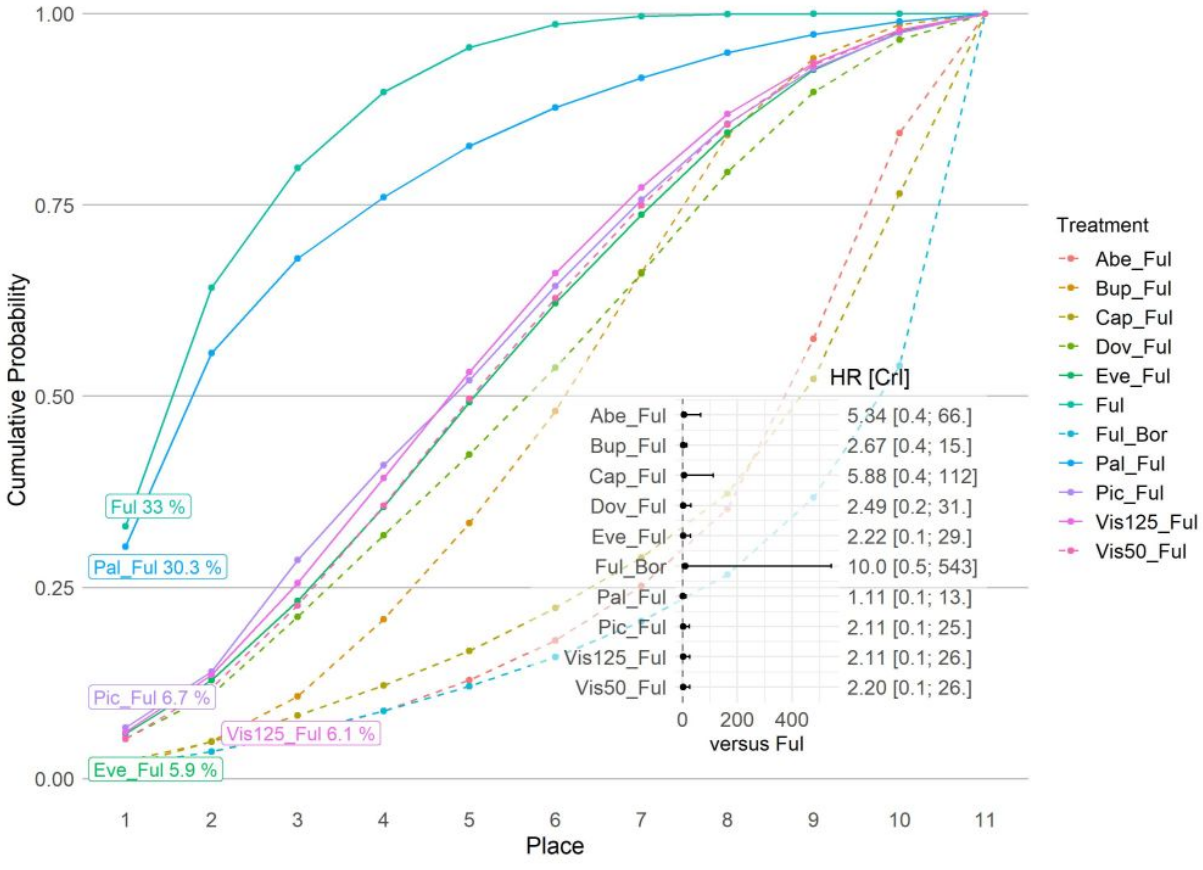


Figure 85: PICO 2 SUCRA and forest plots for discontinuations; network meta-regression for age; fixed effect model

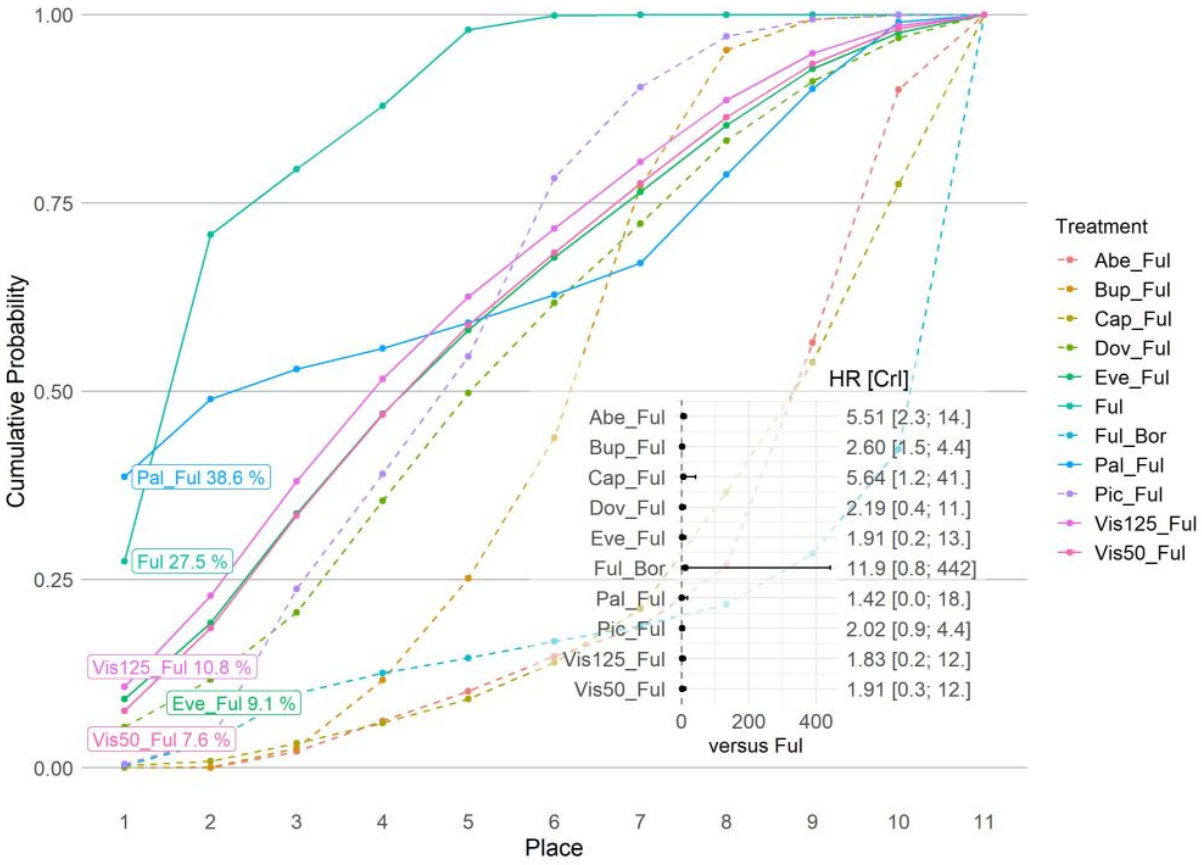
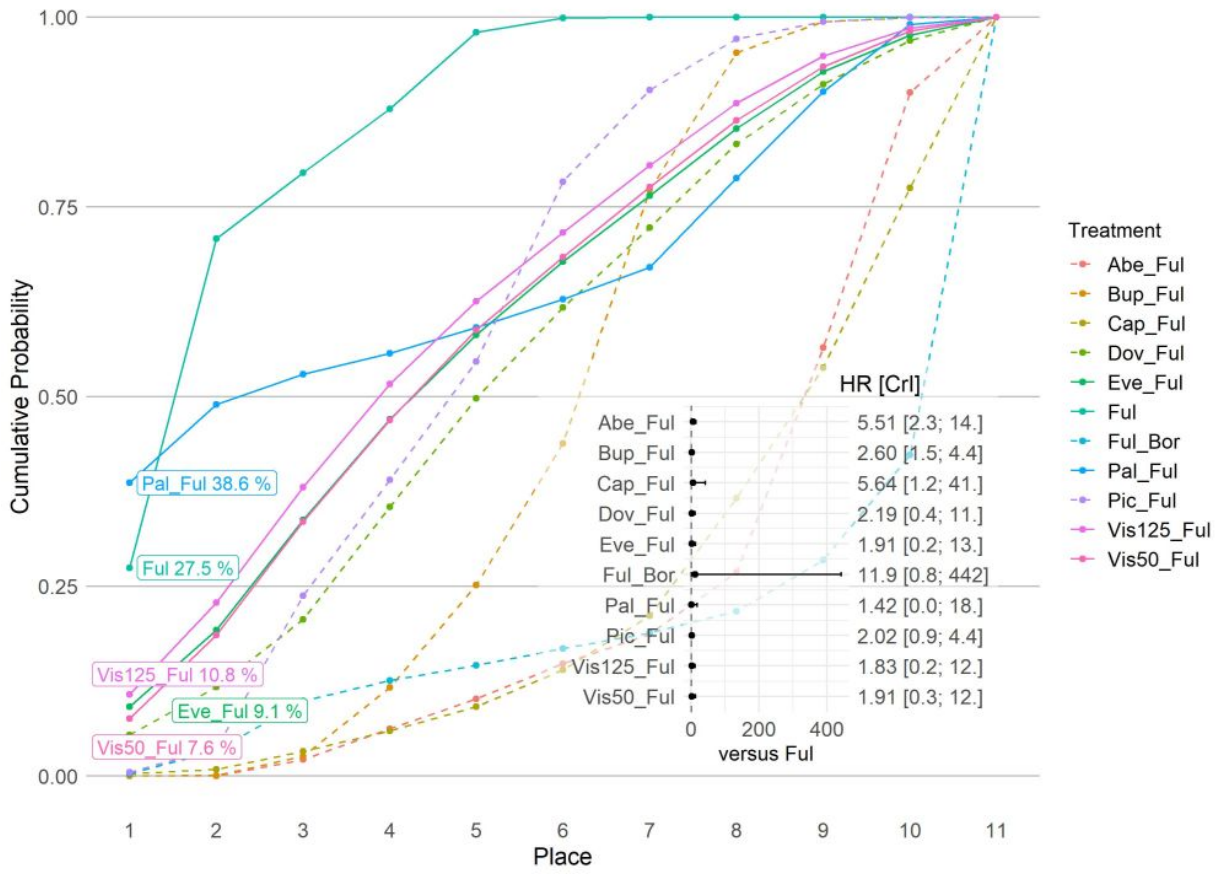


Figure 86: PICO 2 SUCRA and forest plots for discontinuations; network meta-regression for age; fixed effect model



15.5 Supplementary tables and figures cost effectiveness analysis

15.5.1 Resource use

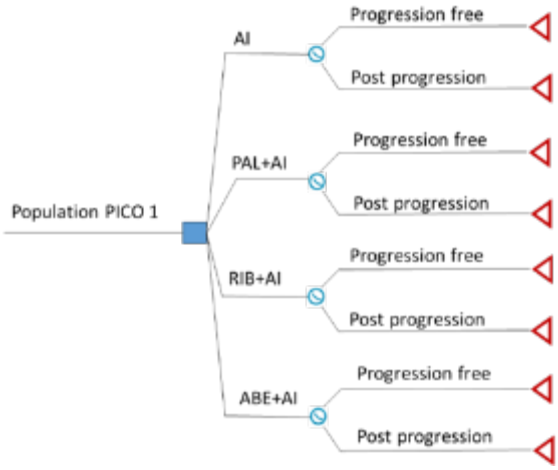
Table 40: AI shares

	LET	ANA	EXE	Source
Monotherapy	36.25%	6.25%	57.50%	Expert opinion
Combination with CDK4/6-Inhibitor	46.25%	3.75%	50.00%	Expert opinion

ANA=anastrozole; CDK=cyclin-dependent kinase; EXE=exemestane; LET=letrozole;

15.5.2 Model structure

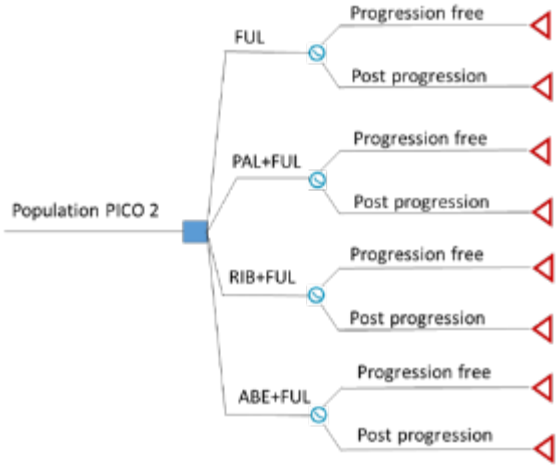
Figure 87: Model structures partitioned survival models for PICO 1



Blue square representing decision node, blue cycle representing start of partitioned survival analysis, red triangles represent end nodes. The partitioned-survival model consists of three mutually exclusive health states, that is, progression free, progressive disease and death in each treatment arm. Individuals start in the progression-free health state; they may progress and exit the progression health state due to death. The hypothetical cohort was followed for an analytic-time horizon of 20 years.

ABE=abemaciclib; AI=aromatase inhibitor; PAL=palbociclib; PICO=population, intervention, comparator, outcome; RIB=ribociclib

Figure 88: Model structures partitioned survival models for PICO 2



Blue square representing decision node, blue cycle representing start of partitioned survival analysis, red triangles represent end nodes. The partitioned-survival model consists of three mutually exclusive health states, that is, progression free, progressive disease and death in each treatment arm. Individuals start in the progression-free health state; they may progress and exit the progression health state due to death. The hypothetical cohort was followed for an analytic-time horizon of 20 years.

ABE=abemaciclib; FUL=fulvestrant; PAL=palbociclib; PICO=population, intervention, comparator, outcome; RIB=ribociclib

15.5.3 Input parameter values

Table 41: Input parameter clinical data base-case analysis (PICO 1, PICO 2)

	Base-case values	**Source**
Mean OS and PFS and HR for OS and PFS		
OS AI [month]	33.3	Clinical trials
HR OS AI alone vs. PAL+AI	1.194	NMA
HR OS AI alone vs. RIB+AI	1.339	NMA
HR OS AI alone vs. ABE+AI	1.339	assumption
PFS AI [month]	15.794	Clinical trials
HR PFS AI alone vs. PAL+AI	1.874	NMA
HR PFS AI alone vs. RIB+AI	1.759	NMA
HR PFS AI alone vs. ABE+AI	2.088	NMA
OS FUL [month]	28.892	Clinical trials
HR OS FUL alone vs. PAL+FUL	1.234	NMA
HR OS FUL alone vs. RIB+FUL	1.431	NMA
HR OS FUL alone vs. ABE+FUL	1.321	NMA
PFS FUL [month]	5.8773	Clinical trials
HR PFS FUL alone vs. PAL+FUL	2.014	NMA
HR PFS FUL alone vs. RIB+FUL	1.817	NMA
HR PFS FUL alone vs. ABE+FUL	1.963	NMA

Table 42: Input parameter values and distribution types for the sensitivity analyses (PICO 1)

Parameter	Type	Base-case value	Low	High
Factors HR for OS and PFS (derived from NMAs of this report)				
De-/increase in HR OS/PFS AI alone vs. PAL+AI	Lognormal	1	0.73	1.38
De-/increase in HR OS/PFS AI alone vs. RIB+AI	Lognormal	1	0.69	1.44
De-/increase in HR OS/PFS AI alone vs. ABE+AI	Lognormal	1	0.69	1.44
De-/increase in OS/PFS AI	Gamma	1	0.63	1.45
Utilities				
PFS AI[52]	Beta	0.712	0.69	0.73
PFS AI+CDK4/6 inhibitors[52]	Beta	0.736	0.72	0.75
PP[164]	Beta	0.48	0.46	0.50
% patients with dose reductions when taking CDK4/6 inhibitors in combination with AI / with FUL				
De-/increase % patients dose reduction PAL	Uniform	1	0.8	1.2
De-/increase % patients dose reduction RIB	Uniform	1	0.8	1.2
De-/increase % patients dose reduction ABE	Uniform	1	0.8	1.2
FU costs[164 173]				
FU costs (monthly; CHF)	Lognormal	6,105	2,493	14,947
De-/increase in FU costs (AI+CDK4/6 inhibitors)	Uniform	1	0.77	1.23

ABE=abemaciclib; AI=aromatase inhibitor; CDK=cyclin-dependent kinase; CHF=Swiss francs; FU=follow up; HR=hazard ratio; OS=overall survival; PAL=palbociclib; PFS=progression free survival; PP=post progression; RIB=ribociclib

Table 43: Input parameter values and distribution types for the sensitivity analyses (PICO 2)

	Type	Base-case value	Low	High
Factors HR for OS and PFS				
De-/increase in HR OS/PFS FUL alone vs. PAL+FUL	Lognormal	1	0.79	1.27
De-/increase in HR OS/PFS FUL alone vs. RIB+FUL	Lognormal	1	0.69	1.45
De-/increase in HR OS/PFS FUL alone vs. ABE+FUL	Lognormal	1	0.8	1.25
De-/increase in OS/PFS FUL	Gamma	1	0.63	1.45
Utilities				
PFS FUL[52]	Beta	0.71	0.66	075
PFS FUL+CDK4/6 inhibitors[52]	Beta	0.73	0.68	0.77
PP [164]	Beta	0.48	0.46	0.50
% patients with dose reductions when taking CDK4/6 inhibitors in combination with AI / with FUL				
De-/increase % patients dose reduction PAL	Uniform	1	0.8	1.2
De-/increase % patients dose reduction RIB	Uniform	1	0.8	1.2
De-/increase % patients dose reduction ABE	Uniform	1	0.8	1.2
FU costs[164 173]				
FU costs (monthly; CHF)	Lognormal	6,139	2,472	14,650
De-/increase in FU Costs (FUL+CDK4/6 inhibitors)	Uniform	1	0.77	1.23

ABE=abemaciclib; CDK=cyclin-dependent kinase; CHF=Swiss francs; FU=follow up; FUL=fulvestrant; HR=hazard ratio; OS=overall survival; PAL=palbociclib; PFS=progression free survival; PP=post progression; RIB=ribociclib

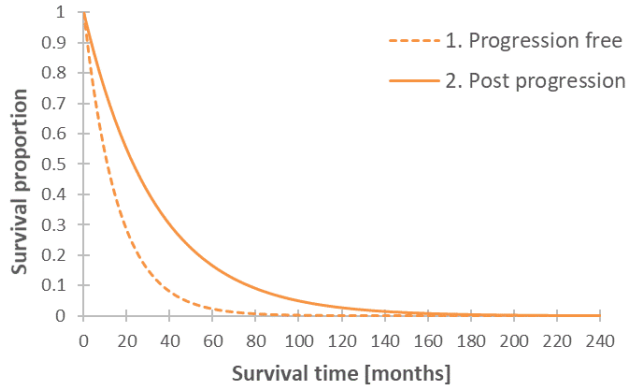
15.5.4 Base-case analysis (PICO 1)

Table 44: Discounted drug, adverse-event, monitoring, follow-up and total costs base-case analysis on average per treated individual for remaining life time (PICO 1)

Strategy	Total costs [CHF]	Drug costs [CHF]	Costs AE [CHF]	Costs AE monitoring [CHF]	Cost disease monitoring [CHF]	Costs FU PP [CHF]
AI	101,998.9	1,375.4	658.8	1,646.9	3,322.6	94,995.2
PAL+AI	176,159.1	105,162.6	3,024.5	9,542.3	6,028.3	52,401.3
RIB+AI	182,323.8	80,676.0	2,254.7	7,789.2	5,682.4	85,921.5
ABE+AI	198,295.9	121,259.1	2,642.3	9,214.0	6,663.5	58,517.0

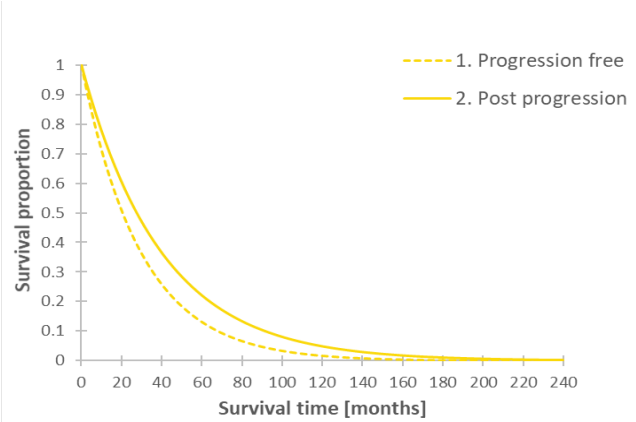
ABE=abemaciclib; AE=adverse events; AI=aromatase inhibitor; CHF=Swiss Francs, FU=follow-up; PAL=palbociclib; PP=post progression; RIB=ribociclib

Figure 89 Modelled survival curve of patients treated with AI monotherapy (PICO 1)



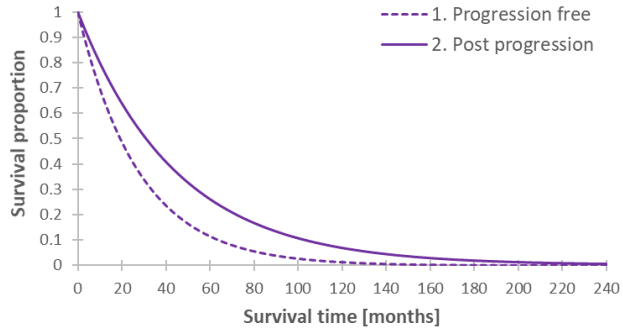
– Area below dotted line represents individuals in progression free, area between solid line and dotted line represents individuals in post progression

Figure 90 Modelled survival curve of patients treated with PAL+AI (PICO 1)



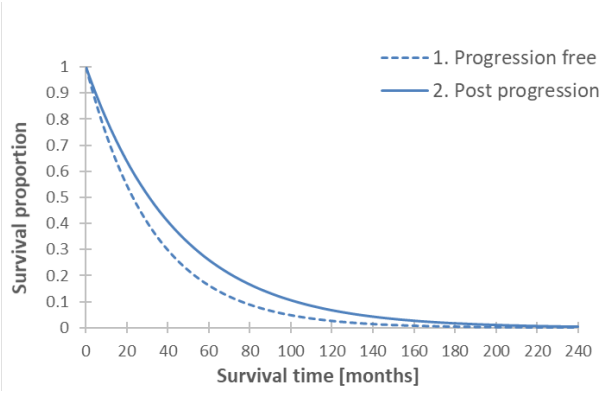
– Area below dotted line represents individuals in progression free, area between solid line and dotted line represents individuals in post progression

Figure 91 Modelled survival curve of patients treated with RIB+AI (PICO 1)



– Area below dotted line represents individuals in progression free, area between solid line and dotted line represents individuals in post progression

Figure 92 Modelled survival curve of patients treated with ABE+AI (PICO 1)



– Area below dotted line represents individuals in progression free, area between solid line and dotted line represents individuals in post progression

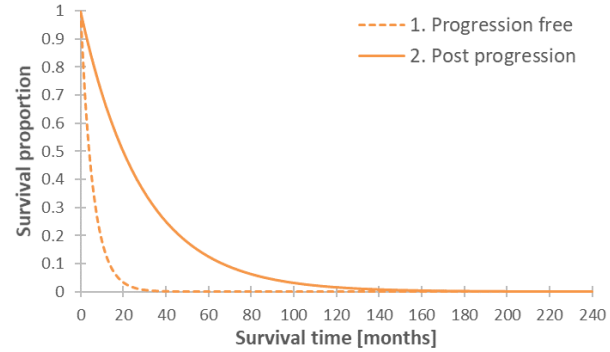
15.5.5 Base-case analysis (PICO 2)

Table 45: Discounted drug, adverse-event, monitoring, follow-up and total costs base-case analysis on average per individual for remaining life time (PICO 2)

Strategy	Total costs [CHF]	Drug costs [CHF]	Costs AE [CHF]	Costs AE monitoring [CHF]	Cost disease monitoring [CHF]	Costs FU PP [CHF]
FUL	136,885	4,958	251	1,136	1,266	129,274
PAL+FUL	190,087	52,069	997	4,769	2,514	129,737
ABE+FUL	204,311	52,648	1,237	3,701	2,452	144,274
RIB+FUL	214,633	42,680	903	3,606	2,274	165,169

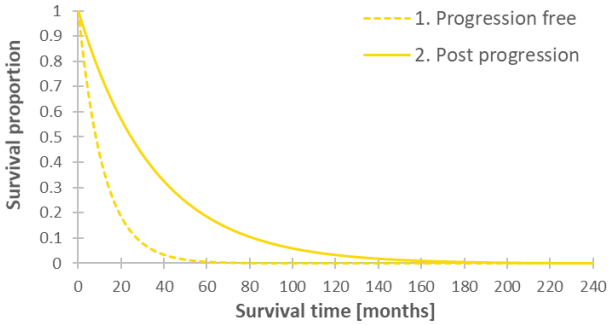
ABE=abemaciclib; AE=adverse events; FU=follow-up; FUL=fulvestrant; PAL=palbociclib; PP=post progression; RIB=ribociclib

Figure 93 Modelled survival curves of patients treated with FUL monotherapy (PICO 2)



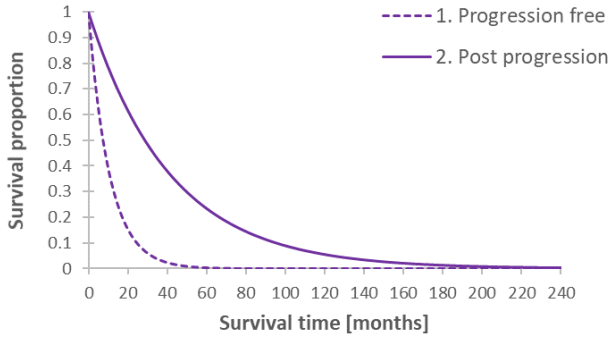
– Area below dotted line represents individuals in progression free, area between solid line and dotted line represents individuals in post progression

Figure 94 Modelled survival curves of patients treated with PAL+FUL (PICO 2)



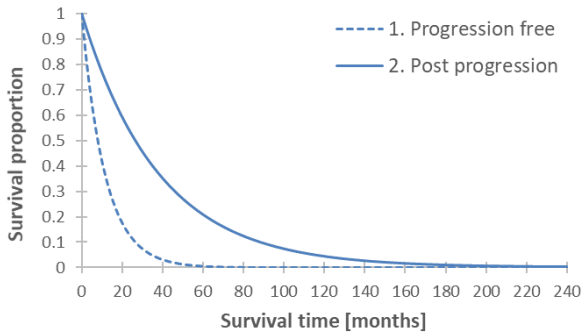
– Area below dotted line represents individuals in progression free, area between solid line and dotted line represents individuals in post progression

Figure 95 Modelled survival curves of patients treated with RIB+FUL (PICO 2)



– Area below dotted line represents individuals in progression free, area between solid line and dotted line represents individuals in post progression

Figure 96 Modelled survival curves of patients treated with ABE+FUL (PICO 2)

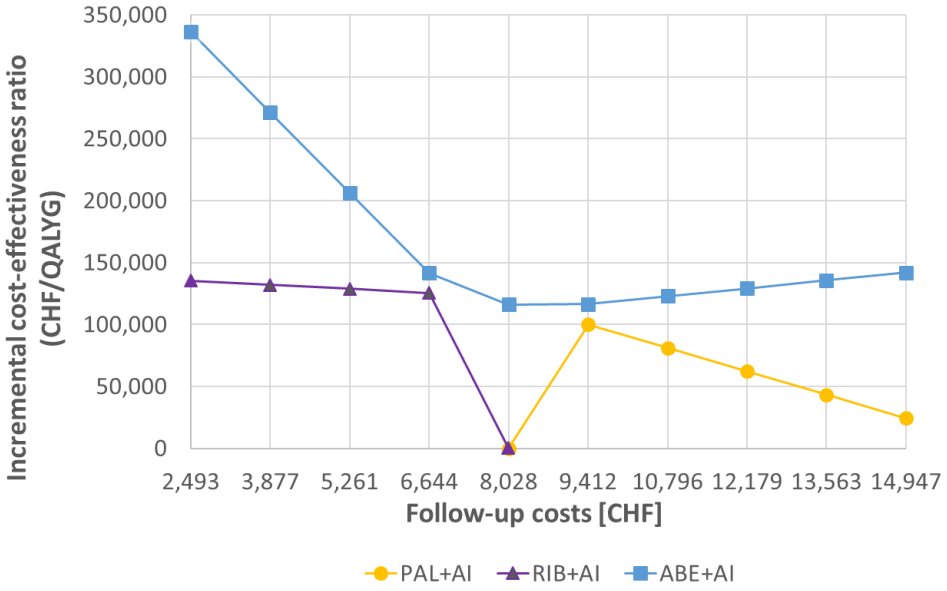


– Area below dotted line represents individuals in progression free, area between solid line and dotted line represents individuals in post progression

15.5.6 Sensitivity and scenario analyses AI-related regimens (PICO 1)

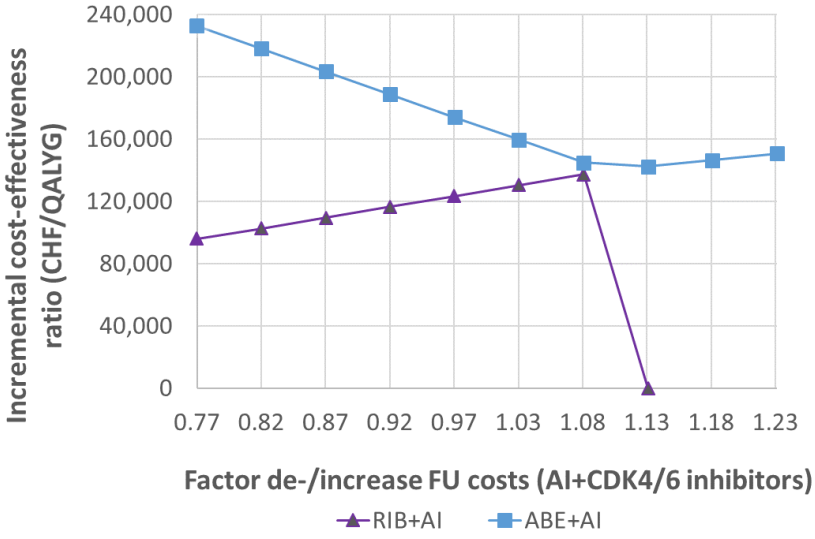
NOTE: Strategies not shown in the graph or with an ICER represented as zero were dominated. If with varying parameter values, a dominated strategy became non-dominated, this is represented by a line moving from zero to the first calculated ICER value. If a non-dominated strategy became dominated, this was represented by a line toward an ICER represented as zero.

Figure 97: Sensitivity analysis on follow-up costs (PICO 1)



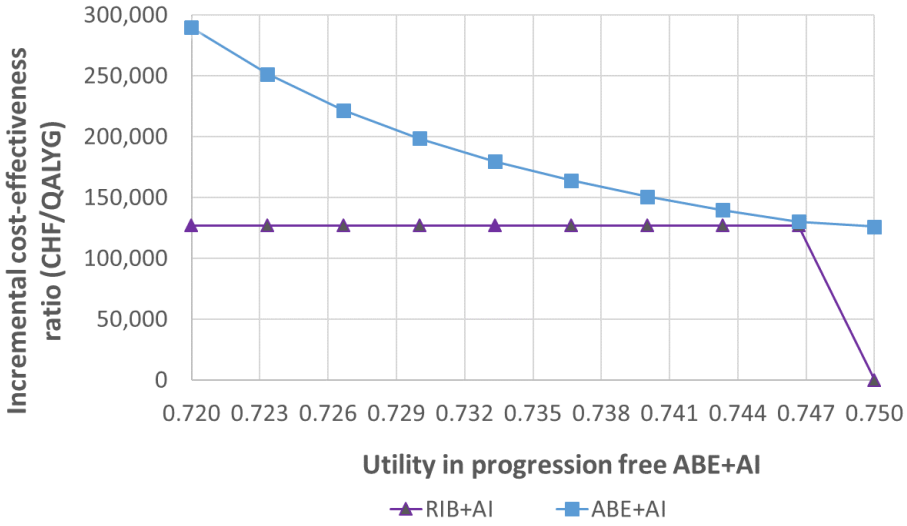
ABE=abemaciclib; AI=aromatase inhibitor; CHF=Swiss francs; QALYG=quality-adjusted life years gained; RIB=ribociclib;

Figure 98: Sensitivity analysis on de-/increase of FU costs for AI+CDK4/6 inhibitors (PICO 1)



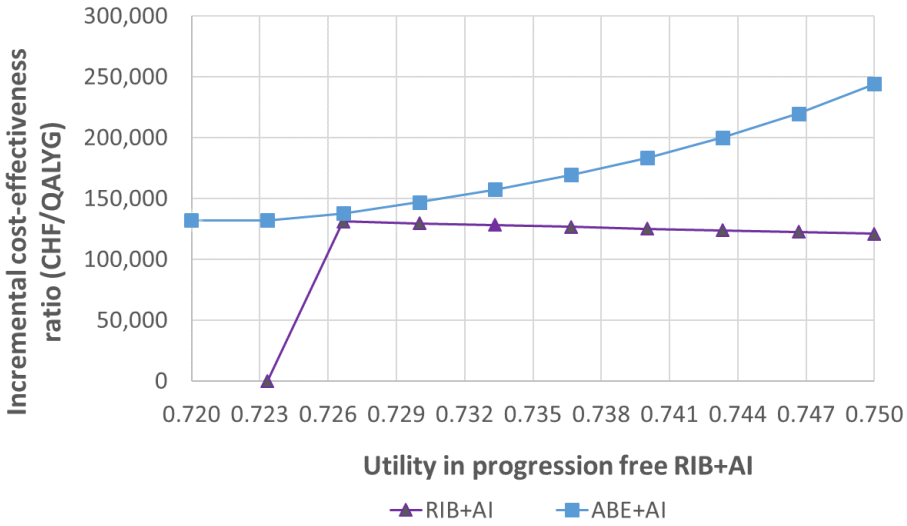
ABE=abemaciclib; AI=aromatase inhibitor; CDK=cyclin-dependent kinase; CHF=Swiss francs; FU=follow up; QALYG=quality-adjusted life years gained; RIB=ribociclib,

Figure 99: Sensitivity analysis on utility weights in progression free for ABE+AI (PICO 1)



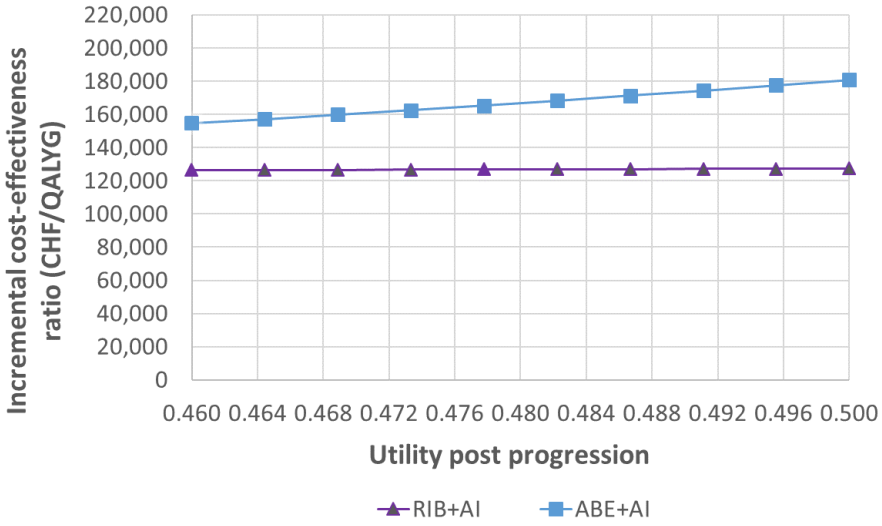
ABE=abemaciclib; AI=aromatase inhibitor; CDK=cyclin-dependent kinase; CHF=Swiss francs; QALYG=quality-adjusted life years gained; RIB=ribociclib;

Figure 100 Sensitivity analysis on utility weights in progression free for RIB+AI (PICO 1)



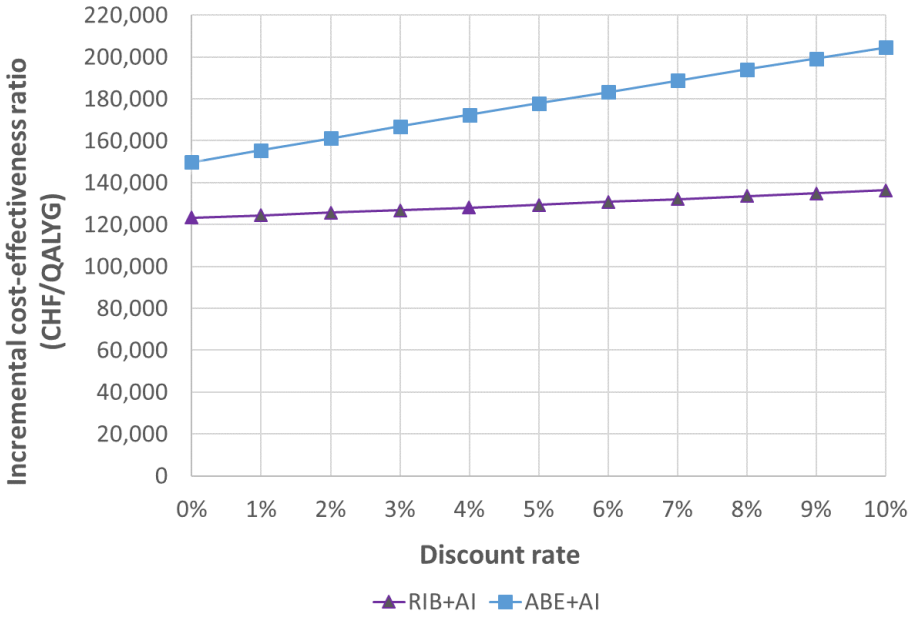
ABE=abemaciclib; AI=aromatase inhibitor; CDK=cyclin-dependent kinase; CHF=Swiss francs; QALYG=quality-adjusted life years gained; RIB=ribociclib

Figure 101 Sensitivity analysis on utility weights in post progression (PICO 1)



ABE=abemaciclib; AI=aromatase inhibitor; CDK=cyclin-dependent kinase; CHF=Swiss francs; QALYG=quality-adjusted life years gained; RIB=ribociclib

Figure 102: Scenario analysis on discount rate (PICO 1)



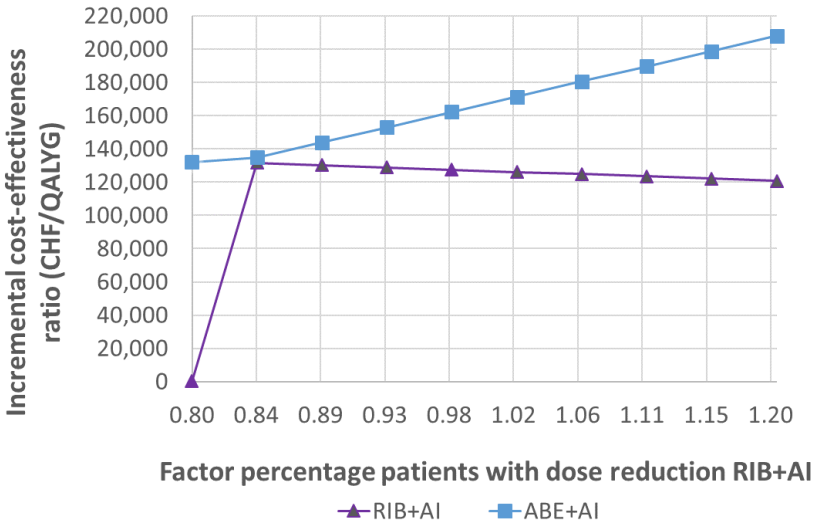
ABE=abemaciclib; AI=aromatase inhibitor; CDK=cyclin-dependent kinase; CHF=Swiss francs; QALYG=quality-adjusted life years gained; RIB=ribociclib

Table 46: Health economic results of PICO 1 at 6% discount rate

Strategy	Disc. total cost [CHF]	Incremental* disc. total cost [CHF]	Disc. quality-adjusted life expectancy [QALY]	Incremental* disc. quality-adjusted life expectancy [QALY]	Incremental* cost- effectiveness ratio [CHF/QALYG]
AI	92,162		1.43		-
PAL+AI	161,503		1.88		D
RIB+AI	164,900	72,738	1.99	0.56	130,758
ABE+AI	180,312	15,412	2.07	0.08	183,278

ABE=abemaciclib; AI=aromatase inhibitor; CHF=Swiss francs; D=dominated; disc.=discounted; PAL=palbociclib; QALY=quality-adjusted life years; QALYG=quality-adjusted life years gained; RIB=ribociclib
* compared to the next less costly and non-dominated strategy

Figure 103: Scenario analysis on dose reduction RIB+AI (PICO 1)



ABE=abemaciclib; AI=aromatase inhibitor; CHF=Swiss francs; QALYG=quality-adjusted life years gained; RIB=ribociclib

Table 47: Scenario analysis HR OS (PFS) AI alone vs. AI+CDK4/6 inhibitors 1.326 (1.912) health economic results (PICO 1)

Strategy	Disc. total cost [CHF]	Incremental* disc. total cost [CHF]	Disc. quality-adjusted life expectancy [QALY]	Incremental* disc. quality-adjusted life expectancy [QALYG]	Incremental* cost- effectiveness ratio [CHF/QALYG]
AI	101,999		1.52		0
ABE+AI	199,901		2.19		D
PAL+AI	197,046		2.19		D
RIB+AI	174,989	97,903	2.19	0.66	147,400

ABE=abemaciclib; AI=aromatase inhibitor; CDK=cyclin-dependent kinase; CHF=Swiss francs; D=dominated; disc.=discounted; HR=hazard ratio; OS=overall survival; PAL=palbociclib; PFS=progression free survival; QALY=quality-adjusted life years; QALYG=quality-adjusted life years gained; RIB=ribociclib
* compared to the next less costly and non-dominated strategy

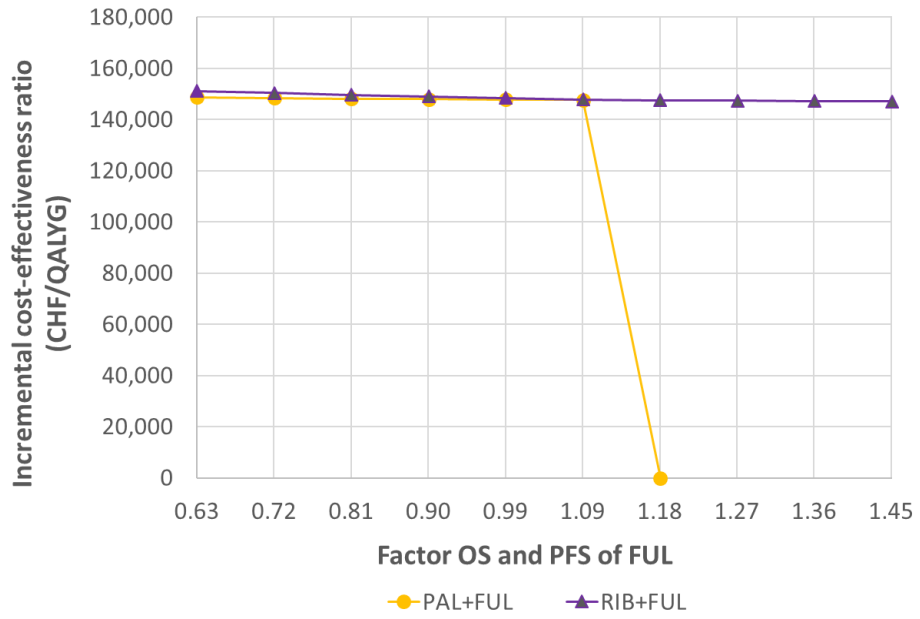
Table 48: Scenario analysis HR OS (PFS) AI alone vs. AI+CDK4/6 inhibitors 1.326 (1.912) discounted drug, adverse-event, monitoring, follow-up and total costs (PICO 1)

Strategy	Total costs [CHF]	Drug costs [CHF]	Costs AE [CHF]	Costs AE monitoring [CHF]	Cost disease monitoring [CHF]	Costs FU PP [CHF]
AI	101,999	1,375	659	1,647	3,323	94,995
RIB+AI	174,989	87,086	2,437	8,347	6,142	70,977
PAL+AI	197,046	107,144	3,071	9,712	6,142	70,977
ABE+AI	199,901	111,767	2,435	8,580	6,142	70,977

ABE=abemaciclib; AE=adverse events; AI=aromatase inhibitor; CDK=cyclin-dependent kinase; CHF=Swiss francs;FU=follow-up; CHF=Swiss Francs; HR=hazard ratio; OS=overall survival; PAL=palbociclib; PP=post progression; PFS=progression free survival; RIB=ribociclib

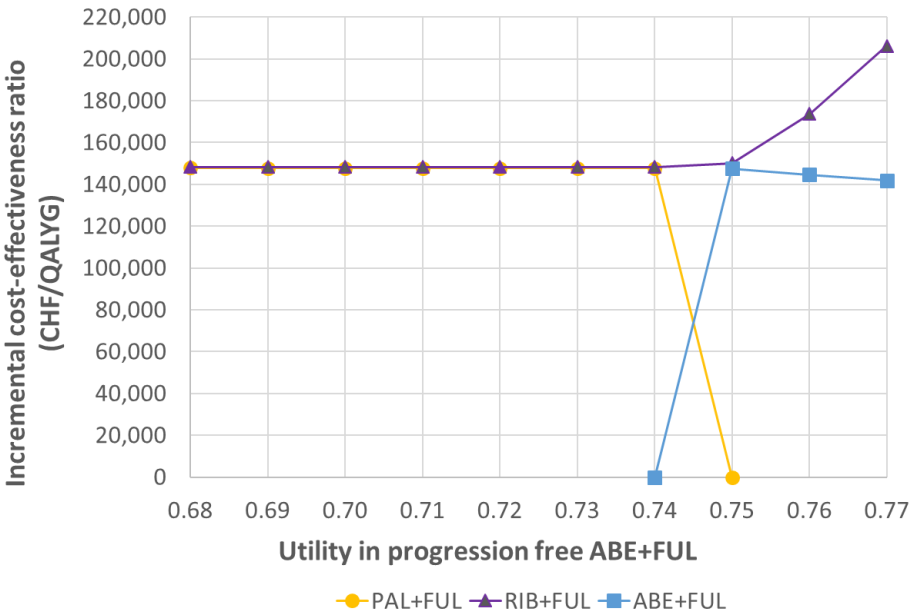
15.5.7 Sensitivity and scenario analyses FUL-related regimens (PICO 2)

Figure 104 Sensitivity analysis on OS and PFS of FUL (PICO 2)



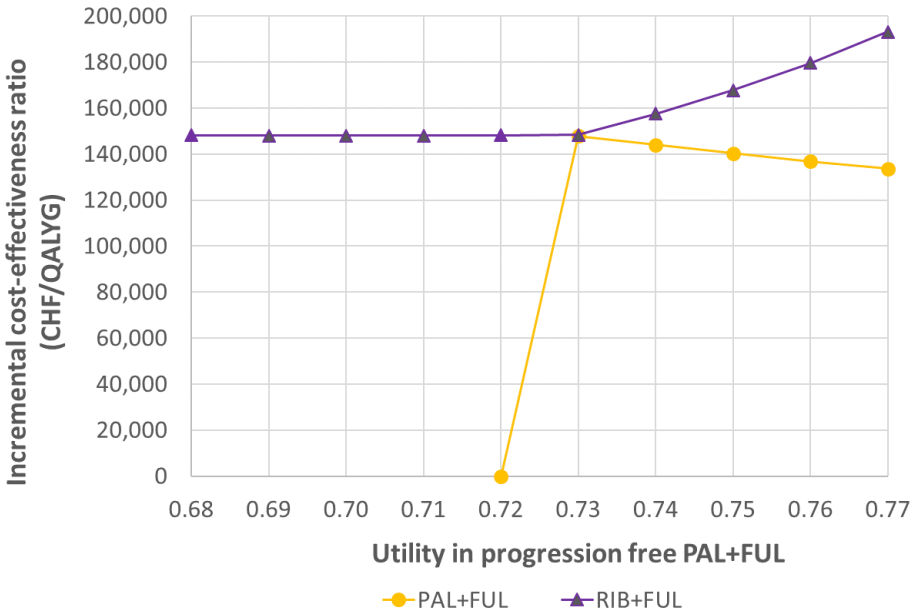
CHF=Swiss francs; FUL=fulvestrant; OS=overall survival; PAL=palbociclib; PFS=progression free survival; QALYG=quality-adjusted life years gained; RIB=ribociclib

Figure 105: Sensitivity analysis on utility weights in progression-free state for ABE+FUL (PICO 2)



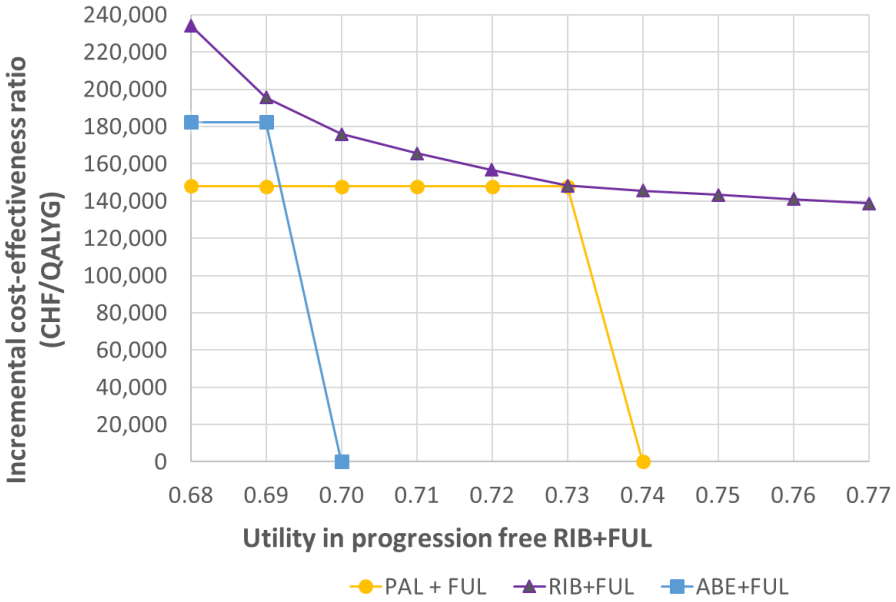
ABE=abemaciclib; CHF=Swiss francs; FUL=fulvestrant; OS=overall survival; QALYG=quality-adjusted life years gained; RIB=ribociclib;

Figure 106 Sensitivity analysis on utility weights in progression-free state for PAL+FUL (PICO 2)



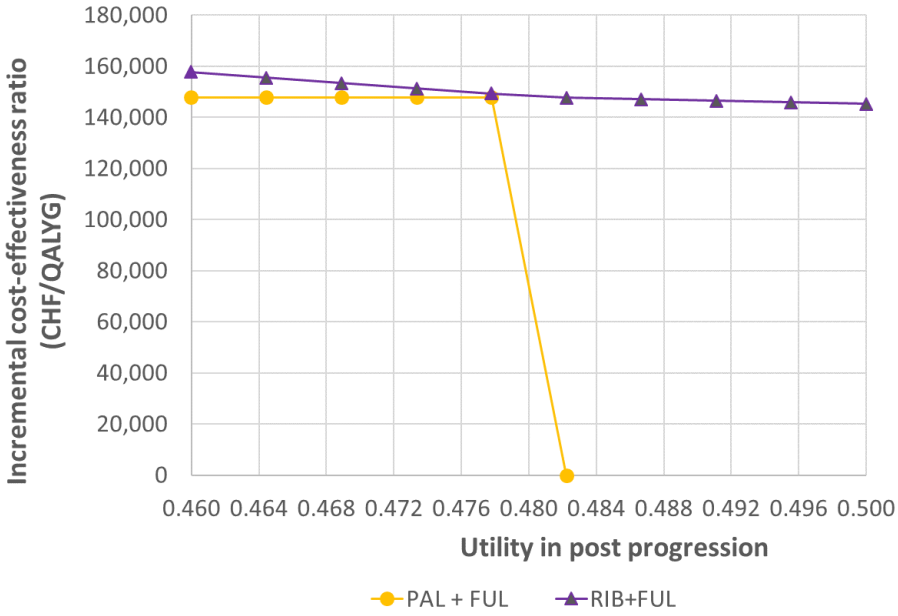
CHF=Swiss francs; FUL=fulvestrant; OS=overall survival; PAL=palbociclib; QALYG=quality-adjusted life years gained; RIB=ribociclib

Figure 107: Sensitivity analysis on utility weights in progression-free state for RIB+FUL (PICO 2)



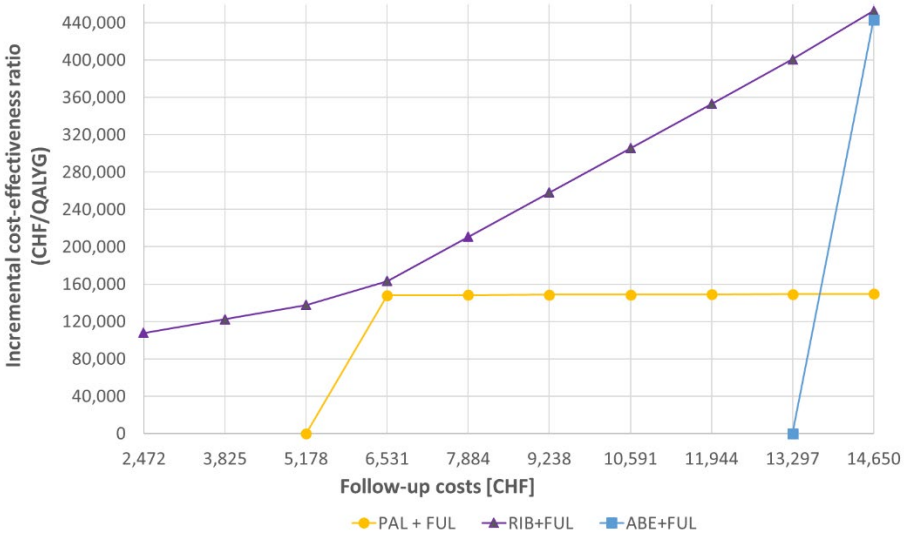
ABE=abemaciclib; CHF=Swiss francs; FUL=fulvestrant; OS=overall survival; QALYG=quality-adjusted life years gained; RIB=ribociclib;

Figure 108 Sensitivity analysis on utility weights in post progression (PICO 2)



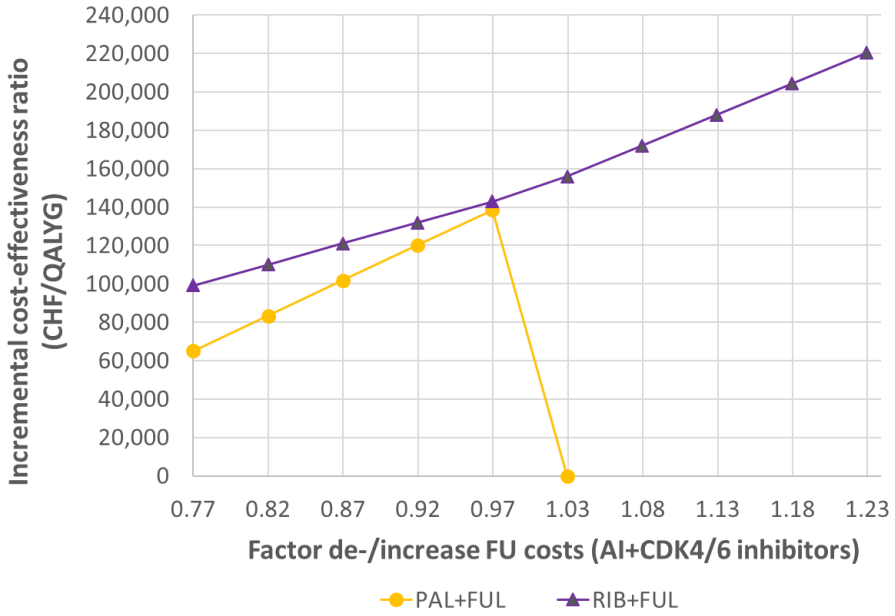
CHF=Swiss francs; FUL=fulvestrant; OS=overall survival; PAL=palbociclib; QALYG=quality-adjusted life years gained; RIB=ribociclib

Figure 109: Sensitivity analysis on follow-up costs (PICO 2)



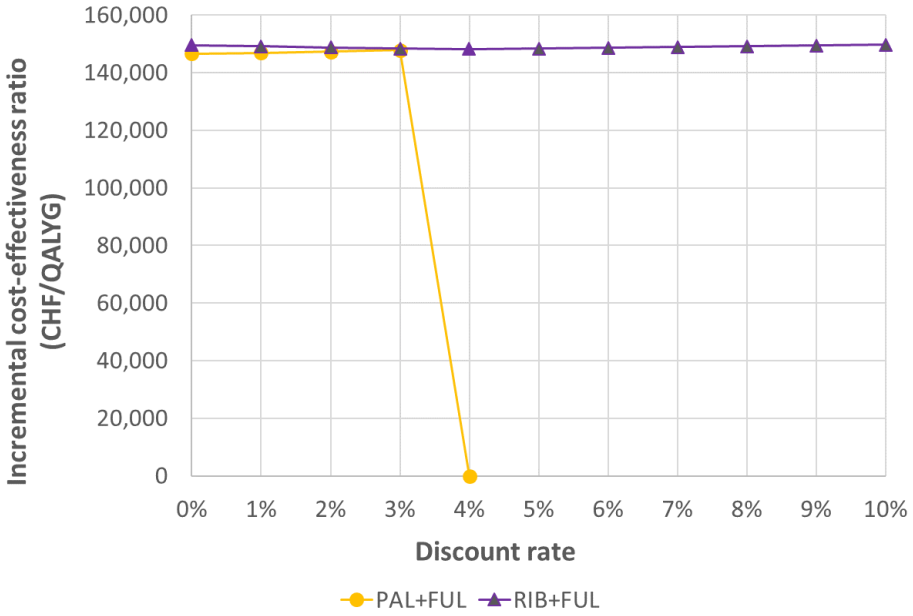
ABE=abemaciclib; CHF=Swiss francs; FUL=fulvestrant; QALYG=quality-adjusted life years gained; RIB=ribociclib;

Figure 110: Sensitivity analysis de-/increase FU costs for AI+CDK4/6 inhibitors (PICO 2)



ABE=abemaciclib; CDK=cyclin-dependent kinase; CHF=Swiss francs; FU=follow up; FUL=fulvestrant; QALYG=quality-adjusted life years gained; RIB=ribociclib

Figure 111: Scenario analysis on discount rate (PICO 2)



CHF=Swiss francs; FUL=fulvestrant; QALYG=quality-adjusted life years gained; RIB=ribociclib

Table 49: Health economic results of PICO 2 at 6% discount rate

Strategy	Disc. total cost [CHF]	Incremental* disc. total cost [CHF]	Disc. quality-adjusted life expectancy [QALY]	Incremental* disc. quality-adjusted life expectancy [QALYG]	Incremental* cost- effectiveness ratio [CHF/QALYG]
FUL	127,301		1.12		-
PAL+FUL	175,906		1.45		D
ABE+FUL	188,269		1.51		D
RIB+FUL	196,343	69,042	1.59	0.46	148,618

ABE=abemaciclib; CHF=Swiss francs; D=dominated; disc.=discounted; FUL=fulvestrant; PAL=palbociclib; QALY=quality-adjusted life years; QALAG=quality-adjusted life years gained; RIB=ribociclib
* compared to the next less costly and non-dominated strategy

Table 50: Scenario analysis HR OS (PFS) FUL alone vs. FUL+CDK4/6 inhibitors 1.316 (1.947) health economic results (PICO 2)

Strategy	Disc. total cost [CHF]	Incremental* disc. total cost [CHF]	Disc. quality-adjusted life expectancy [QALY]	Incremental* disc. quality-adjusted life expectancy [QALYG]	Incremental* cost-effectiveness ratio [CHF/QALYG]
FUL	136,885		1.19		0
RIB+FUL	196,831	59,947	1.62	0.43	138,989
PAL+FUL	202,531		1.62		D
ABE+FUL	203,659		1.62		D

ABE=abemaciclib; CDK=cyclin-dependent kinase; CHF=Swiss francs; D=dominated; disc.=discounted; FUL=fulvestrant; HR=hazard ration; OS=overall survival; PAL=palbociclib; PFS=progression free survival; QALY=quality-adjusted life years; QALYG=quality-adjusted life years gained; RIB=ribociclib
* compared to the next less costly and non-dominated strategy

Table 51: Scenario analysis HR OS (PFS) FUL alone vs. FUL+CDK4/6 inhibitors 1.316 (1.947) discounted drug, adverse-event, monitoring, follow-up and total costs (PICO 2)

Strategy	Total costs [CHF]	Drug costs [CHF]	Costs AE [CHF]	Costs AE monitoring [CHF]	Cost disease monitoring [CHF]	Costs FU PP [CHF]
FUL	136,885	4,958	251	1,136	1,266	129,274
PAL+FUL	196,832	45,544	965	3,804	2,432	144,085
ABE+FUL	202,531	50,405	965	4,644	2,432	144,085
RIB+FUL	203,659	52,236	1,229	3,677	2,432	144,085

ABE=abemaciclib; AE=adverse events; CDK=cyclin-dependent kinase; FU=follow-up; FUL=fulvestrant; HR=hazard ration; OS=overall survival; PAL=palbociclib; PP=post progression; PFS=progression free survival; RIB=ribociclib

15.6 Supplementary tables budget impact analysis

Table 52 Parameters for population estimates (budget impact analysis)

	Absolute Number/%	Sources
BC prevalence in women (Switzerland 10-year prevalence projection 2020)	48023	[182]
BC incidence in women (Switzerland, yearly average 2013 – 2017)	6239	Swiss Federal Statistical Office*
BC mortality in women (Switzerland, yearly average 2013 – 2017)	1369	Swiss Federal Statistical Office*
Proportion of HR+/HER2-cases in BC incidence (USA, Age-Adjusted Rate per 100,000 Women, 2013-2017)	68%	SEER 21†
HR+/HER2- LA/MBC incidence in Switzerland - estimate based on several sources	1158	Data on MBC and HR+/HER2- incidences and prevalences in USA: †[183] [184], data on BC incidence per stage of diagnosis in the Netherlands:[185]
Of those PICO 1	811	‖
Of those PICO 2	347	‖

BC=breast cancer; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; LA = locally advanced; MBC = metastatic breast cancer; PICO= Patients, Interventions, Comparators, Outcomes; SEER= Surveillance, Epidemiology, and End Results; USA=United States of America
*https://www.bfs.admin.ch/bfs/de/home/statistiken/gesundheit/gesundheitszustand/krankheiten/krebs.assetdetail.14816211.html, accessed 16.11.2020
† "Cancer Stat Facts: Female Breast Cancer Subtypes", https://seer.cancer.gov/statfacts/html/breast-subtypes.html and https://seer.cancer.gov/explorer/, both accessed 16.11.2020
‖ expert opinion

Table 53: Results budget impact analysis PICO 1 referring to an incident cohort (first year of treatment) – sensitivity analysis expert 1 estimates

Treatment	direct costs per patient in the 1st year of treatment, CHF	current scenario*			Revised scenario 1*			Revised scenario 2*			Revised scenario 3*		
		% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF
PAL+AI	48,058	38%	304	14,609,974	0%			52%	419	20,151,688	42%	338	16,233,304
RIB+AI	42,368	17%	134	5,667,322	44%	357	15,112,858	0%			18%	149	6,297,024
ABE+AI	49,732	6%	49	2,419,026	16%	130	6,450,737	8%	67	3,336,588	0%		
AI	14,066	30%	243	3,420,899	30%	243	3,420,899	30%	243	3,420,899	30%	243	3,420,899
others	-	10%	81		10%	81		10%	81		10%	81	
total		100%	811	26,117,221‖	100%	811	24,984,494‖	100%	811	26,909,175‖	100%	811	25,951,228‖
Difference revised vs. current scenario, incident cohort							-1,132,727			791,954			-165,993

ABE=abemaciclib; AI=aromatase inhibitor; CHF = Swiss Francs; PAL=palbociclib; PICO=population, intervention, comparator, outcome; RIB=ribociclib
* see Section 8.1.4.6, †rough estimate see Table 52 in the Appendix, ‖excludes costs of other therapy regimes (row “others”), # source: expert 1 estimates

Table 54: Results budget impact analysis PICO 1 referring to an incident cohort (first year of treatment) – sensitivity analysis expert 2 estimates

Treatment	direct costs per patient in the 1st year of treatment, CHF	current scenario*			Revised scenario 1*			Revised scenario 2*			Revised scenario 3*		
		% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF
PAL+AI	48,058	50%	405	19,479,965	0%			69%	559	26,868,918	56%	450	21,644,406
RIB+AI	42,368	22%	178	7,556,429	59%	476	20,150,477	0%			24%	198	8,396,032
ABE+AI	49,732	8%	65	3,225,368	21%	173	8,600,982	11%	89	4,448,784	0%		
AI	14,066	15%	122	1,710,450	15%	122	1,710,450	15%	122	1,710,450	15%	122	1,710,450
others	-	5%	41		5%	41		5%	41		5%	41	
total		100%	811	31,972,212‖	100%	811	30,461,909‖	100%	811	33,028,151‖	100%	811	31,750,888‖
Difference revised vs. current scenario, incident cohort							-1,510,303			1,055,939			-221325

ABE=abemaciclib; AI=aromatase inhibitor; CHF = Swiss Francs; PAL=palbociclib; PICO=population, intervention, comparator, outcome; RIB=ribociclib
* see Section 8.1.4.6, †rough estimate see Table 52 in the Appendix, ‖excludes costs of other therapy regimes (row “others”), # source: expert 2 estimates

Table 55: Results budget impact analysis PICO 2 referring to an incident cohort (first year of treatment) – sensitivity analysis expert 1 estimates

Treatment	direct costs per patient in the 1st year of treatment, CHF	current scenario*			Revised scenario 1*			Revised scenario 2*			Revised scenario 3*		
		% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF
PAL+FUL	56,323	28%	98	5,503,693	0			39%	135	7,591,300	31%	109	6,115,214
RIB+FUL	54,618	12%	43	2,348,299	33%	115	6,262,130	0			14%	48	2,609,221
ABE+FUL	57,806	5%	16	903,780	12%	42	2,410,079	6%	22	1,246,592	0		
FUL	35,522	15%	52	1,851,228	15%	52	1,851,228	15%	52	1,851,228	15%	52	1,851,228
others	-	40%	139		40%	139		40%	139		40%	139	
total		100%	347	10,606,999‖	100%	347	10,523,437‖	100%	347	10,689,121‖	100%	347	10,575,663‖
Difference revised vs. current scenario, incident cohort							-83,562			82,122			-31,336

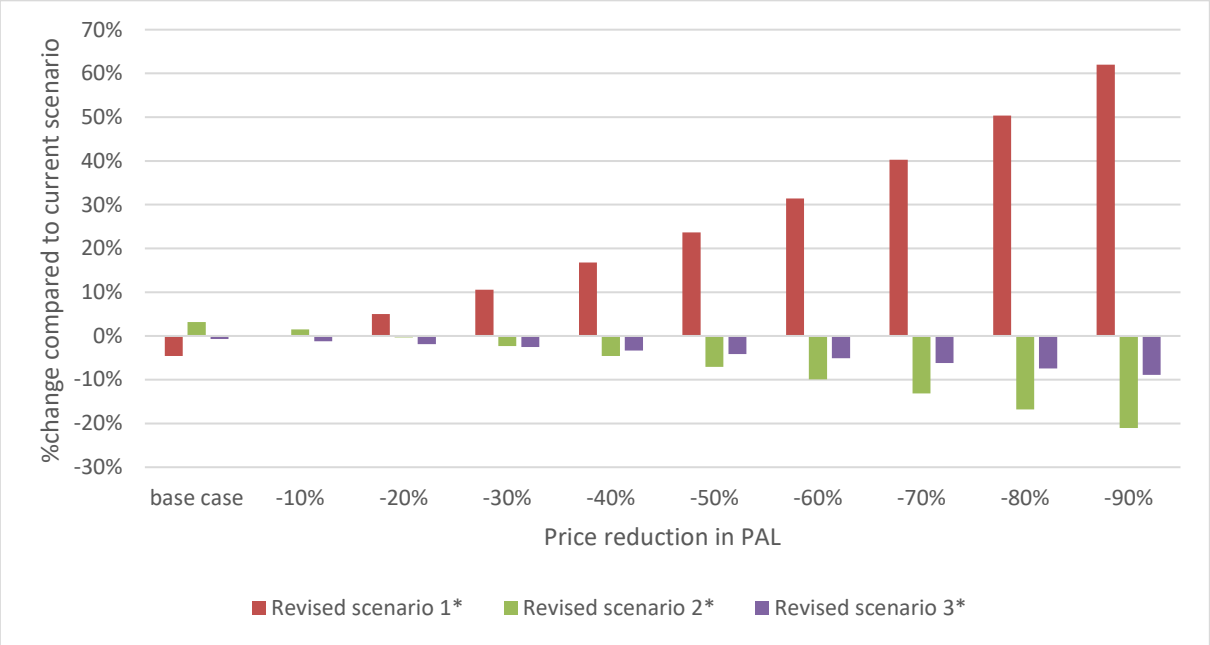
ABE=abemaciclib; AI=aromatase inhibitor; CHF = Swiss Francs; PAL=palbociclib; PICO=population, intervention, comparator, outcome; RIB=ribociclib
* see Section 8.1.4.6, †rough estimate see Table **52** in the Appendix, ‖excludes costs of other therapy regimes (row "others"), # source: expert 1 estimates

Table 56: Results budget impact analysis PICO 2 referring to an incident cohort (first year of treatment) – sensitivity analysis expert 2 estimates

Treatment	direct costs per patient in the 1st year of treatment, CHF	current scenario*			Revised scenario 1*			Revised scenario 2*			Revised scenario 3*		
		% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF	% patients#	Number, incident cohort†	direct costs 1st year of treatment, CHF
PAL+FUL	56,323	44%	152	8,561,300	0			60%	210	11,808,689	49%	169	9,512,555
RIB+FUL	54,618	19%	67	3,652,909	51%	178	9,741,091	0			21%	74	4,058,788
ABE+FUL	57,806	7%	24	1,405,879	19%	65	3,749,011	10%	34	1,939,144	0		
FUL	35,522	5%	17	617,076	5%	17	617,076	5%	17	617,076	5%	17	617,076
others	-	25%	87		25%	87		25%	87		25%	87	
total		100%	347	14,237,164‖	100%	347	14,107,179‖	100%	347	14,364,909‖	100%	347	14,188,419‖
Difference revised vs. current scenario, incident cohort							-129,985			127,745			-48,745

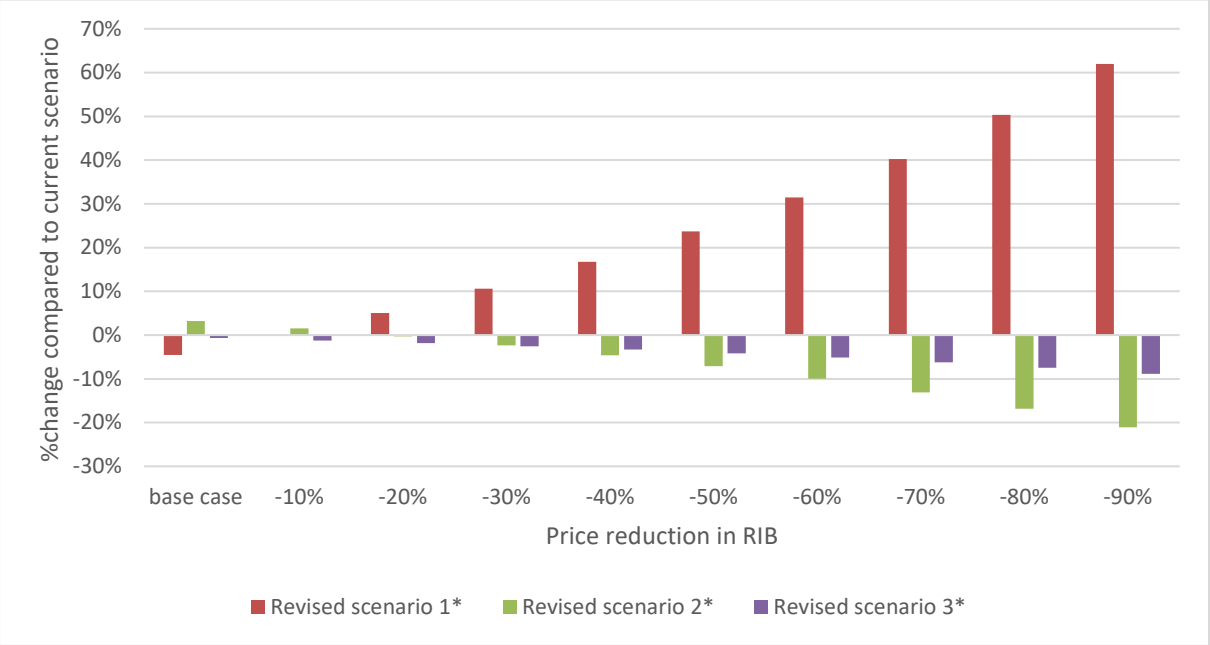
ABE=abemaciclib; AI=aromatase inhibitor; CHF = Swiss Francs; PAL=palbociclib; PICO=population, intervention, comparator, outcome; RIB=ribociclib
* see Section 8.1.4.6, †rough estimate see Table **52** in the Appendix, ‖excludes costs of other therapy regimes (row "others"), # source: expert 2 estimates

Figure 112: Results budget impact analysis PICO 1 referring to an incident cohort (first year of treatment) - sensitivity analysis of a price reduction in PAL: %change compared to current scenario in total direct costs† in 1st year of treatment



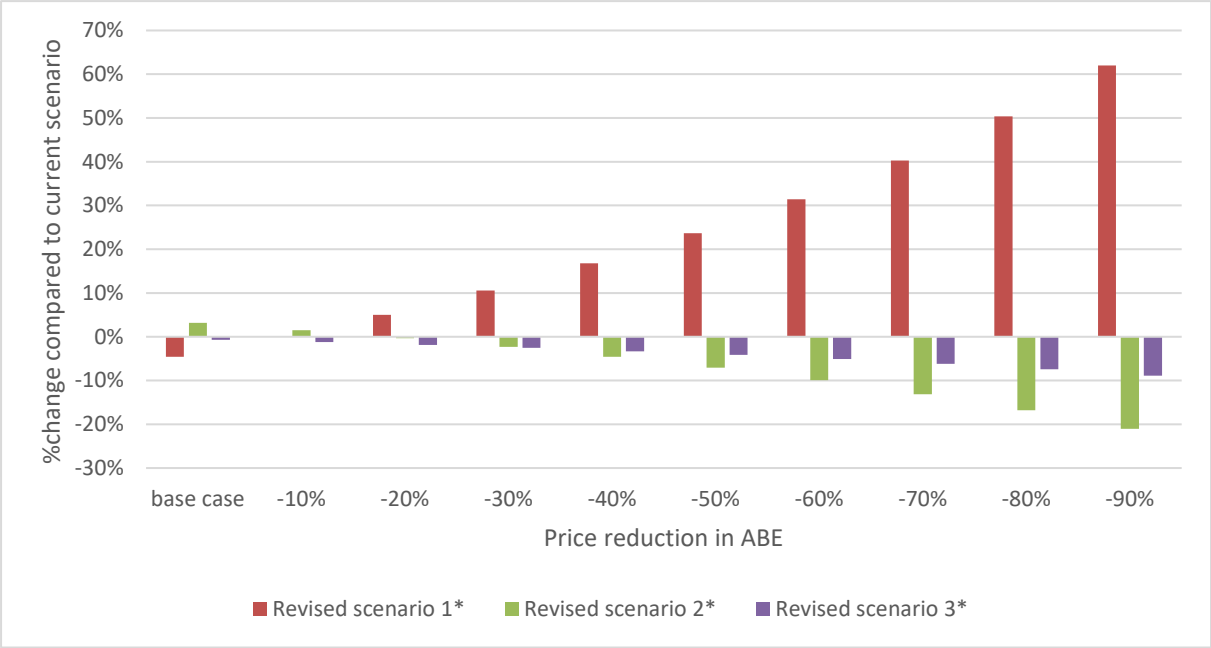
* see Section 8.1.4.6, † excludes costs of non CDK4/6 or AI therapy regimes

Figure 113: Results budget impact analysis PICO 1 referring to an incident cohort (first year of treatment) - sensitivity analysis of a price reduction in RIB: %change compared to current scenario in total direct costs† in 1st year of treatment



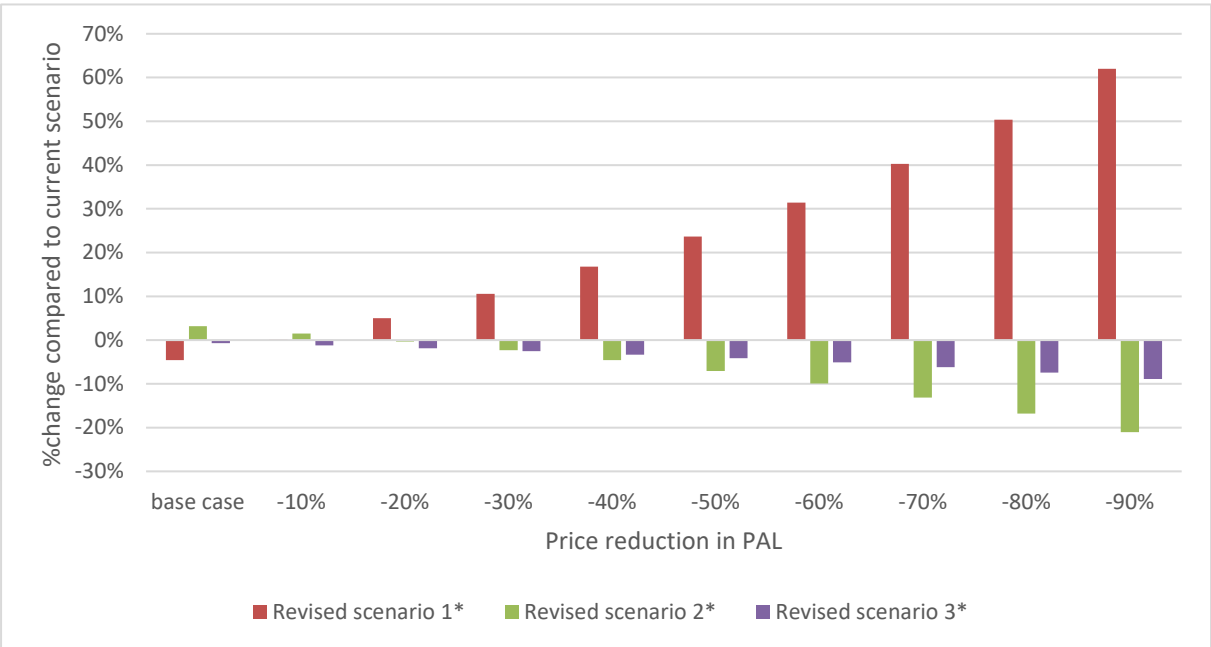
* see Section 8.1.4.6, † excludes costs of non CDK4/6 or AI therapy regimes

Figure 114: Results budget impact analysis PICO 1 referring to an incident cohort (first year of treatment) - sensitivity analysis of a price reduction in ABE: %change compared to current scenario in total direct costs† in 1st year of treatment



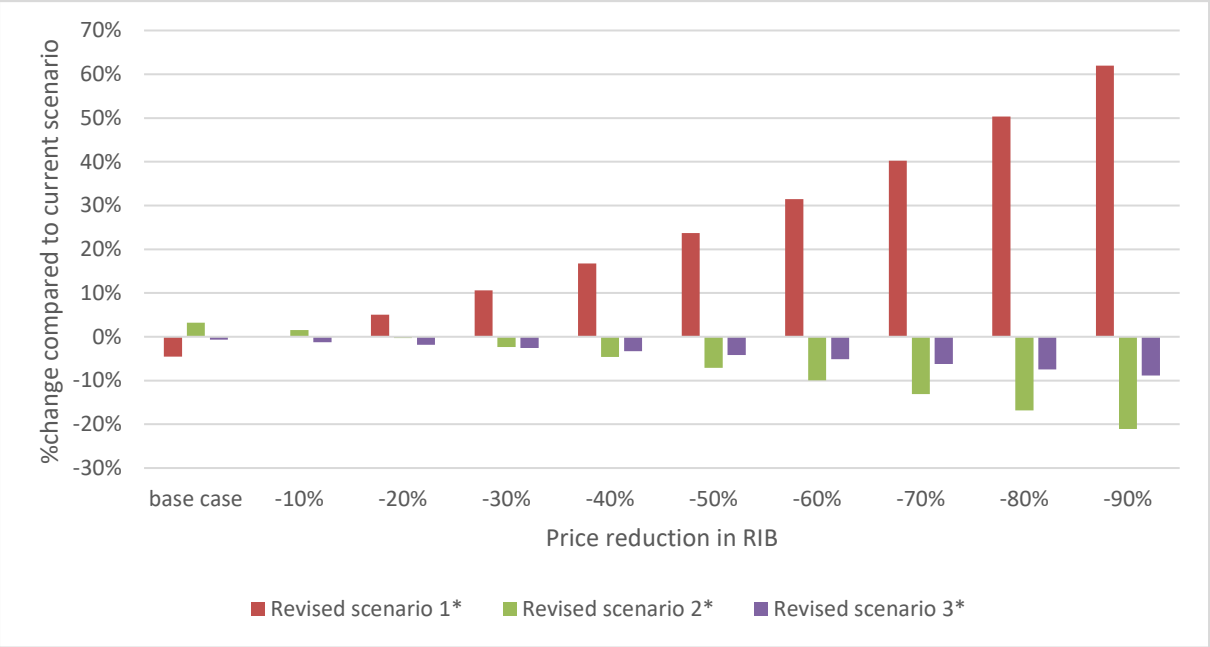
* see Section 8.1.4.6, † excludes costs of non CDK4/6 or AI therapy regimes

Figure 115: Results budget impact analysis PICO 2 referring to an incident cohort (first year of treatment) - sensitivity analysis of a price reduction in PAL: %change compared to current scenario in total direct costs† in 1st year of treatment



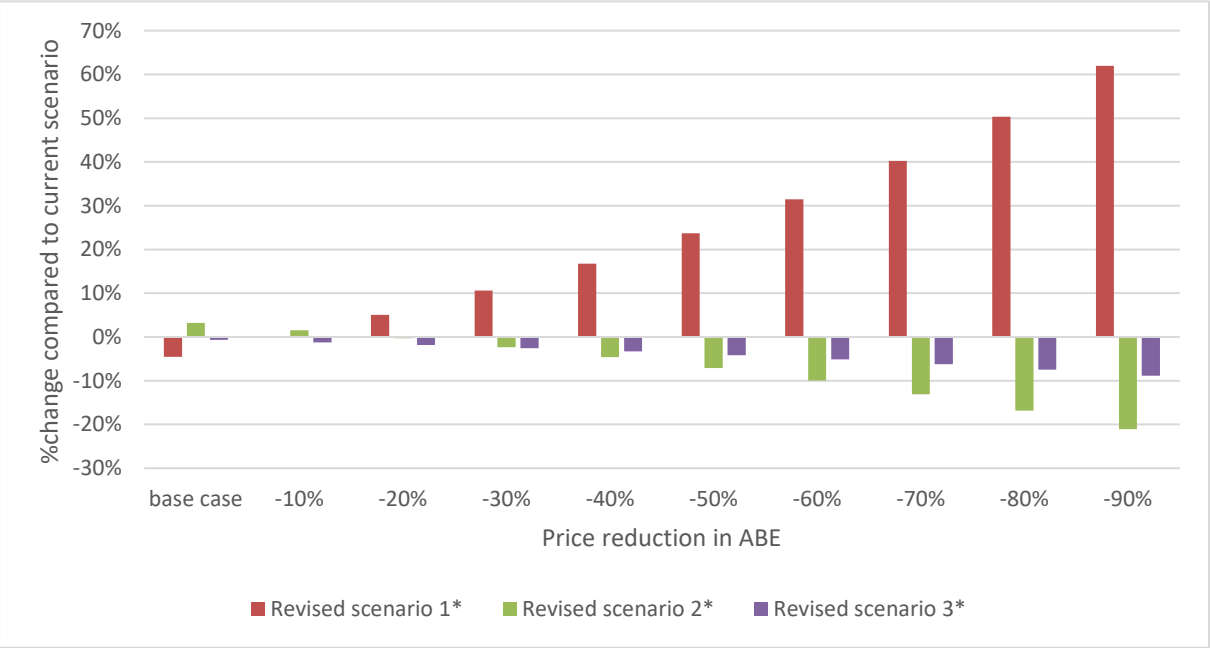
* see Section 8.1.4.6, † excludes costs of non CDK4/6 or FUL therapy regimes

Figure 116: Results budget impact analysis PICO 2 referring to an incident cohort (first year of treatment) - sensitivity analysis of a price reduction in RIB: %change compared to current scenario in total direct costs† in 1st year of treatment



* see Section 8.1.4.6, † excludes costs of non CDK4/6 or FUL therapy regimes

Figure 117: Results budget impact analysis PICO 2 referring to an incident cohort (first year of treatment) - sensitivity analysis of a price reduction in ABE: %change compared to current scenario in total direct costs† in 1st year of treatment



* see Section 8.1.4.6, † excludes costs of non CDK4/6 or FUL therapy regimes

15.7 Search strings for RCTs (NMAs for efficacy and safety)

15.7.1 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)

15.7.2 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 ((double1’724’031 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

15.7.3 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

15.7.4 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)

15.7.5 Search results for RCTs

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

Table 57: Search results for RCTs

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)**

15.8 Search strings for non-randomised studies (extended safety assessment, economic, ethical, social, legal and organisational issues)

15.8.1 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)

15.8.2 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
#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

15.8.3 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

15.8.4 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

15.8.5 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

15.8.6 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"))

15.8.7 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))

15.8.8 Search results for NRSs

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

Table 58: Search results for NRSs

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

15.9 Search strings for non-randomised studies on PAL (update search)

15.9.1 MEDLINE

Search conducted on 29 April 2020. (Including Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily from 2016 to 28 April 2020)

Search Strategy:

1	exp Breast Neoplasms/	(340909)
2	((breast* or mamma*) adj3 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or neoplasm*)).mp.	(477749)
3	1 or 2	(477760)
4	palbociclib.mp.	(1384)
5	Ibrance.mp.	(32)

6	"pd 0332991".mp.	(114)
7	pd 332991.mp.	(4)
8	pd0332991.mp.	(107)
9	pd332991.mp.	(3)
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	(1447)
13	3 and 12	(878)
14	exp animals/ not humans.sh.	(5175658)
15	13 not 14	(863)
16	limit 15 to (english or french or german)	(851)
17	limit 16 to ed=20191104-20200429	(106)
18	remove duplicates from 17	(53)

15.9.2 EMBASE

Search conducted on 29 April 2020.

Search strategy:

No.	Query	Results
#23.	#20 NOT #21 AND [7-11-2019]/sd NOT [30-4-2020]/sd	135
#22.	#20 NOT #21	762
#21.	#20 AND 'Conference Abstract'/it	549
#20.	#18 AND 'human'/de AND ([english]/lim OR [german]/lim OR [french]/lim)	1,311
#19.	#18 AND 'human'/de	1,324
#18.	#7 AND #17	1,422
#17.	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	3,406
#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	154
#12.	'pd 332991':ti,ab,de,tn	16
#11.	'pd 0332991':ti,ab,de,tn	650
#10.	ibrance:ti,ab,de,tn	138
#9.	palbociclib:ti,ab,de,tn	3,391
#8.	'palbociclib'/exp	3,310
#7.	#1 OR #6	154,494
#6.	#4 AND #5	152,095
#5.	advanc*:ti,ab OR metasta*:ti,ab	1,707,082
#4.	#2 OR #3	612,95
#3.	((breast* OR mamma*) NEAR/2 (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR 'adeno c*' OR neoplasm*)):ti,ab,de	606,808
#2.	'breast cancer'/exp	467,991
#1.	'metastatic breast cancer'/exp	19,181

15.9.3 The Cochrane Library

Search conducted on 4 May 2020.

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 adeno-ca* 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 with Cochrane Library publication date in The last 6 months (Word variations have been searched)

34 hits

15.9.4 Search results for NRSs on PAL (update search)

Table 59: Search results for NRSs on PAL (update search)

Database	Number of hits
MEDLINE	53
EMBASE	135
The Cochrane Library	34
Total deduplicated	124

15.10 Search strings for non-randomised studies on RIB or ABE

15.10.1 MEDLINE

Search conducted on 29 April 2020. (Including Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily from 2016 to 28 April 2020)

Search Strategy:

1 exp Breast Neoplasms/ (340909)

2 ((breast* or mamma*) adj3 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or neoplasm*)).mp. (477749)

3 1 or 2 (477760)

4 Ribociclib.mp. (518)

5 "7 cyclopentyl n, n dimethyl 2 [[5 (1 piperazinyl) 2 pyridinyl] amino] 7h pyrrolo [2, 3 d] pyrimidine 6 carboxamide".mp. (0)

6 "7 cyclopentyl n, n dimethyl 2 [[5 (piperazin 1 yl) pyridin 2 yl] amino]

	7h pyrrolo [2, 3 d] pyrimidine 6 carboxamide".mp.	(0)
7	kisqali.mp.	(16)
8	"lee 011*".mp.	(1)
9	lee 11*.mp.	(1)
10	lee011*.mp.	(78)
11	lee11*.mp.	(1)
12	Abemaciclib.mp.	(391)
13	bemaciclib.mp.	(0)
14	ly 2835219.mp.	(1)
15	ly2835219.mp.	(48)
16	"n [5 [(4 ethyl 1 piperazinyl) methyl] 2 pyridinyl] 5 fluoro 4 (4 fluoro 1 isopropyl 2 methyl 1h benzimidazol 6 yl) 2 pyrimidinamine".mp.	(0)
17	"n [5 [(4 ethyl 1 piperazinyl) methyl] 2 pyridinyl] 5 fluoro 4 [4 fluoro 2 methyl 1 (1 methylethyl) 1h benzimidazol 6 yl] 2 pyrimidinamine".mp.	(0)
18	"n [5 [(4 ethylpiperazin 1 yl) methyl] pyridin 2 yl] 5 fluoro 4 [4 fluoro 2 methyl 1 (1 methylethyl) 1h benzimidazol 6 yl] pyrimidin 2 amine".mp.	(0)
19	"n [5 [(4 ethylpiperazin 1 yl) methyl] pyridin 2 yl] 5 fluoro 4 [4 fluoro 2 methyl 1 (propan 2 yl) 1h benzimidazol 6 yl] pyrimidin 2 amine".mp.	(0)
20	verzenio*.mp.	(10)
21	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	(690)
22	3 and 21	(480)
23	exp animals/ not humans.sh.	(5175658)
24	22 not 23	(475)

25	limit 24 to (english or french or german)	(469)
26	remove duplicates from 25	(291)

15.10.2 EMBASE

Search conducted on 29 April 2020.

Search strategy:

No.	Query	Results
#29.	#27 NOT #28	645
#28.	#27 AND 'conference abstract'/it	424
#27.	#25 AND 'human'/de AND ([english]/lim OR [german]/lim OR [french]/lim)	1,069
#26.	#25 AND 'human'/de	1,076
#25.	#4 AND #24	1,160
#24.	#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	1,699
#23.	verzenio*:ti,ab,de,kw	4
#22.	'n [5 [(4 ethylpiperazin 1 yl) methyl] pyridin 2 yl] 5 fluoro 4 [4 fluoro 2 methyl 1 (propan 2 yl) 1h benzimidazol 6 yl] pyrimidin 2 amine':ti,ab,de,kw	
#21.	'n [5 [(4 ethylpiperazin 1 yl) methyl] pyridin 2 yl] 5 fluoro 4 [4 fluoro 2 methyl 1 (1 methylethyl) 1h benzimidazol 6 yl] pyrimidin 2 amine':ti,ab,de,kw	
#20.	'n [5 [(4 ethyl 1 piperazinyl) methyl] 2 pyridinyl] 5 fluoro 4 [4 fluoro 2 methyl 1 (1 methylethyl) 1h benzimidazol 6 yl] 2 pyrimidinamine':ti,ab,de,kw	

#19.	'n [5 [(4 ethyl 1 piperazinyl) methyl] 2 pyridinyl] 5 fluoro 4 (4 fluoro 1 isopropyl 2 methyl 1h benzimidazol 6 yl) 2 pyrimidinamine':ti,ab,de,kw	
#18.	ly2835219:ti,ab,de,kw	72
#17.	'ly 2835219':ti,ab,de,kw	
#16.	bemaciclib*:ti,ab,de,kw	
#15.	abemaciclib*:ti,ab,de,kw	946
#14.	'abemaciclib'/exp	916
#13.	lee11*:ti,ab,de,kw	1
#12.	lee011*:ti,ab,de,kw	136
#11.	'lee 11*':ti,ab,de,kw	4
#10.	'lee 011*':ti,ab,de,kw	4
#9.	kisqali:ti,ab,de,kw	15
#8.	'7 cyclopentyl n, n dimethyl 2 [[5 (piperazin 1 yl) pyridin 2 yl] amino] 7h pyrrolo [2, 3 d] pyrimidine 6 carboxamide':ti,ab,de,kw	
#7.	'7 cyclopentyl n, n dimethyl 2 [[5 (1 piperazinyl) 2 pyridinyl] amino] 7h pyrrolo [2, 3 d] pyrimidine 6 carboxamide':ti,ab,de,kw	
#6.	ribociclib*:ti,ab,de,kw	1,209
#5.	'ribociclib'/exp	1,138
#4.	#1 OR #2 OR #3	612,95
#3.	((breast* OR mamma*) NEAR/2 (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR 'adeno c*' OR neoplasm*)):ti,ab,de	606,808
#2.	'breast cancer'/exp	467,991
#1.	'metastatic breast cancer'/exp	19,181

15.10.3 The Cochrane Library

Search conducted on 4 May 2020.

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 adeno-ca* OR neoplasm*)) (Word variations have been searched)
#3	#1 OR #2 (Word variations have been searched)
#4	(Ribociclib) (Word variations have been searched)
#5	("7 cyclopentyl n, n dimethyl 2 [[5 (1 piperazinyl) 2 pyridinyl] amino] 7h pyrrolo [2, 3 d] pyrimidine 6 carboxamide") (Word variations have been searched)
#6	("7 cyclopentyl n, n dimethyl 2 [[5 (piperazin 1 yl) pyridin 2 yl] amino] 7h pyrrolo [2, 3 d] pyrimidine 6 carboxamide") (Word variations have been searched)
#7	(kisqali) (Word variations have been searched)
#8	("lee 011*") (Word variations have been searched)
#9	("lee 11*") (Word variations have been searched)
#10	(lee011*) (Word variations have been searched)
#11	(lee11*) (Word variations have been searched)
#12	(Abemaciclib) (Word variations have been searched)
#13	(bemaciclib) (Word variations have been searched)
#14	("ly 2835219") (Word variations have been searched)
#15	(ly2835219) (Word variations have been searched)
#16	("n [5 [(4 ethyl 1 piperazinyl) methyl] 2 pyridinyl] 5 fluoro 4 (4 fluoro 1 isopropyl 2 methyl 1h benzimidazol 6 yl) 2 pyrimidinamine") (Word variations have been searched)
#17	("n [5 [(4 ethyl 1 piperazinyl) methyl] 2 pyridinyl] 5 fluoro 4 [4 fluoro 2 methyl 1 (1 methylethyl) 1h benzimidazol 6 yl] 2 pyrimidinamine") (Word variations have been searched)
#18	("n [5 [(4 ethylpiperazin 1 yl) methyl] pyridin 2 yl] 5 fluoro 4 [4 fluoro 2 methyl 1 (1 methylethyl) 1h benzimidazol 6 yl] pyrimidin 2 amine") (Word variations have been searched)

#19 ("n [5 [(4 ethylpiperazin 1 yl) methyl] pyridin 2 yl] 5 fluoro 4 [4 fluoro 2 methyl 1 (propan 2 yl) 1h benzimidazol 6 yl] pyrimidin 2 amine") (Word variations have been searched)

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

#21 #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 (Word variations have been searched)

#22 #3 AND #21 (Word variations have been searched)

250 Hits

15.10.4 Search results for NRSs on RIB or ABE

Table 60: Search results for NRSs on RIB or ABE

Database	Number of hits
MEDLINE	291
EMBASE	645
The Cochrane Library	250
Total deduplicated	809