UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM EPIDEMIOLOGIA

TESE DE DOUTORADO

INIBIDORES DA VIA HER2 ("*HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2*") NO TRATAMENTO DO CÂNCER DE MAMA INICIAL E LOCALMENTE AVANÇADO: UMA METANÁLISE EM REDE

Aluno: MÁRCIO DEBIASI

Orientador: Prof. Dr. CARÍSI ANNE POLANCZYK

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A apresentação desta tese é exigência do Programa de Pós-graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul, para obtenção do título de Doutor.

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DEDICATÓRIA ou MENSAGEM

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ABREVIATURAS E SIGLAS

AHRQ: *Agency of Health Care Research and Quality*

AJCC: *American Joint Commettee on Cancer*

ASCO: *American Society of Cinical Oncology*

BC: *Breast cancer*

BRCA1: breast cancer 1 gene

BRCA2: breast cancer 2 gene

CAP: *College of American Pathologists*

CHF: *congestive heart failure*

CI: *credibility interval* (como indicado no texto dos artigos, sendo este um trabalho baseado em estatística Bayesiana, a medida de dispersão utilizada é o intervalo de credibilidade; e não o intervalo de confiança)

CNPq: Conselho Nacional de Desenvolvimento Científico e Tecnológico

CPR: *Complete Pathological Response*

DFS: *disease-free survival*

DNA: ácido desoxirribonucleico

EBC: *Early Breast cancer*

ECR: ensaio clínico randomizado

EGFR: *Epidermal Growth Factor Receptor*

ESMO: *European Society for Medical Oncology*

FISH: fluorescence in situ hybridization

GSK: GlaxoSmithKline

HER2: *human epidermal growth fator receptor 2*

IHQ: imunohistoquímica

INCA: Instituto Nacional do Câncer José Alencar Gomes da Silva

LABC: *Locally Advanced Breast Cancer*

METABRIC: *Molecular Taxonomy of Breast Cancer International Consortium*

MLG: Modelo Linear Generalizado

MTC: Mixed Treatment Comparisson

NICE: *National Institute for Health Care Excellence*

OMS: Organização Mundial da Saúde

OS: *overall survival*

RCT: *randomized clinical trial*

RE: receptor de estrógeno

RP: receptor de progesterona

RPC: resposta patológica complete

SABCS: *San Antonio Breast Cancer Symposium*

SG: sobrevida global

SLD: sobrevida livre de doença

RESUMO

Introdução

O câncer de mama constitui problema de saúde pública em todo o mundo, sendo esta a neoplasia maligna mais comum da mulher. Aproximadamente 15 a 25% destes tumores são classificados como HER2-positivos – um subgrupo que apresenta comportamento biológico mais agressivo e pior prognóstico. O tratamento adjuvante e neoadjuvante desses tumores com quimioterapia associada a inibidores da via HER2 é eficaz em aumentar a chance de cura das pacientes, porém ainda não se sabe qual é o melhor regime de tratamento para esta situação clínica em virtude da dificuldade em estabelecer modelos matemáticos capazes de lidar com a grande variedade de opções existentes. Esta tese teve por objetivo revisar a literatura acerca do tema e conduzir uma metanálise em rede a fim de elaborar uma inferência mais detalhada quanto às opções terapêuticas para esta situação clínica.

Métodos

Foi conduzida revisão sistemática da literatura a partir das principais bases de dados (MEDLINE, EMBASE e *Cochrane Central Register of Controlled trials*) e dos anais de congressos pertinentes ao tema. Detalhes da estratégia de busca encontram-se descritos na sessão 9.2 desta tese. Foram incluídos todos os ECRs que compararam quimioterapia associada a pelo menos um inibidor da via HER2 com quimioterapia isolada ou qualquer outro regime de quimioterapia associada à terapia anti-HER2. Dois revisores independentes revisaram a lista de títulos e extraíram os dados. Um terceiro revisor contrapôs as listas e os dados, resolvendo casos de discrepâncias. Medidas de efeito entre tratamentos foram sumarizadas em cada ECR como HR para desfechos mensurados como "tempo-até-evento" – sobrevida global (SG) e sobrevida

livre de doença (SLD) – e como RR para eventos dicotômicos – resposta patológica completa (RPC) e cardiotoxicidade. Foi conduzida metanálise em rede baseada no modelo Bayesiano combinando evidência direta e indireta a fim de se estabelecer medidas de efeito comparativas entre todos os braços de tratamentos incluídos nas redes, apresentando as estimativas pontuais e os intervalos de credibilidade (IC) para todas as comparações possíveis. A partir desses dados, os tratamentos foram ranqueados para cada desfecho utilizando a área sob a curva de ranqueamento cumulativo (SUCRA). Os estudos incluídos em cada rede diferiram entre si em virtude da disponibilidade de desfechos. Inconsistências entre as evidências diretas e indiretas foram avaliadas pelo método "*split node*" (em redes complexas) e pelo método de Bucher (em redes simples).

Resultados

A revisão sistemática da literatura identificou 1553 referências únicas, das quais 70 foram incluídas na metanalise, totalizando 33 ECRs. A rede de SG incluiu 12 ECRs (27.277 pacientes) e demonstrou que o duplo bloqueio da via HER2 com trastuzumab e lapatinibe associado à quimioterapia é o melhor regime de tratamento (HR 0.78; IC95% 0.61-0.99, quando comparado ao esquema padrão-ouro de quimioterapia associada à trastuzumabe por 12 meses). A rede de SLD incluiu 14 ECRs (30.219 pacientes) e corroborou os achados descritos acima referentes à eficácia do duplo-bloqueio, adicionando os promissores resultados da utilização sequencial de 12 meses de neratinibe após quimioterapia e 12 meses de trastuzumabe (esquema para o qual ainda não foram publicados resultados de SG). Em relação à RPC, 17 ECRs foram incluídos, totalizando 4.383 pacientes. Aqui também o duplo-bloqueio se mostrou superior aos demais esquemas. Taxano

associado à trastuzumabe com lapatinibe ou pertuzumabe foram superiores aos demais esquemas e comparáveis entre si, com uma superioridade marginal, porém não significativa, a favor do pertuzumabe (RR 1.10; IC 95% 0.70-1.60). Para todos os desfechos que avaliaram a efetividade do tratamento, os regimes contendo quimioterapia isolada ou com um inibidor da via HER2 que não o trastuzumabe foram as piores opções. Já a cardiotoxicidade foi avaliada em uma rede composta por 21 ECR que em conjunto totalizaram 29.555 pacientes. O duplo bloqueio com trastuzumabe e pertuzumabe se mostrou mais cardiotóxico, mas cabe a ressalva de que quedas sintomáticas e irreversíveis da fração de ejeção constituem evento raro neste cenário clínico (<1%).

Conclusões

Os achados desta tese vêm a corroborar o conceito do duplo-bloqueio da via HER2 como melhor opção terapêutica em termos de eficácia no tratamento de tumores HER2 positivos e reiteram a associação de quimioterapia com trastuzumabe como pedra angular deste tratamento. Evidência de benefício em termos de ganho de sobrevida global foi identificada com uma destas estratégias (quimioterapia associada à trastuzumabe e lapatinibe). Outras alternativas de duplo-bloqueio – tais como quimioterapia associada à trastuzumabe com pertuzumabe ou com neratinibe sequencial – se mostraram promissoras em relação aos outros desfechos de eficácia avaliados nesta tese (SLD e RPC), mas seus resultados de sobrevida global ainda são esperados para uma melhor caracterização da rede. O uso concomitante do trastuzumabe com o pertuzumabe aumenta a cardiotoxicidade, mas este agravo é de pequena magnitude clínica. Já a associação com lapatinibe é bastante segura do

ponto de vista cardiológico, mas aumenta a incidência de diarreia (desfecho este não avaliado nesta tese em virtude da heterogeneidade dos reportes).

ABSTRACT

Introduction

Breast cancer is the most common malignancy among women worldwide. Roughly 15 to 25% of breast cancers are classified as HER2-positive, a subgroup of tumors with a more aggressive clinical phenotype and worse prognosis due to unregulated cell growth and abnormal survival mediated by the overexpression of the HER2 protein. Treating these tumors in the adjuvant and neoadjuvant settings with chemotherapy and anti-HER2 targeted therapy is efficacious with positive impact in overall survival (OS). However, the best regimen to treat these patients has not yet been defined due to the lack of meta-analysis usign appropriate mathematical models capable of dealing with the variety of trials and treatment options that are seen in this scenario. The present theses aims to review the literature on this issue and carry out a network meta-analysis in order to provide more detailed inference on this topic.

Methods

MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials as well as the main congress proceedings on this theme were searched in a systematic review. Details regarding the search strategy can be found at the 9.2 section of this theses. All phase II or III randomized controlled trials (RCTs) that compared chemotherapy plus any anti-HER2 therapy with chemotherapy alone or any other different combination of chemotherapy and anti-HER2 therapy in the adjuvant or neoadjuvant settings were included. Two independent reviewers examined the lists of trials and extracted data. A third reviewer adjudicated cases of discordance between the first two reviewers. Time-to-event outcomes, such as overall survival (OS) and disease-free survival (DFS), were pooled as hazard ratios, while relative risks were used to

pool effect sizes for complete pathological response (CPR) and cardiotoxicity. The Bayesian framework was used to conduct this network meta-analysis in order to combine direct and indirect evidence. Due to different availability of outcomes among the included studies, distinct networks were built for each outcome. Results were summarized as point estimates and their 95% credibility intervals (CI). Treatments were ranked for each outcome using the area under the cumulative ranking curve (SUCRA). This analysis yields a probability interval for each arm indicating the likelihood of a given schedule being the best. In order to check for inconsistencies between direct and indirect evidence within a closed loop, we used the "split node method" (for complex networks) or the Bucher method (for simple networks).

Results

Systemic review of the literature retrieved 1.553 unique references, of which 70 were included accounting for 33 RCTs. The OS network included 12 RCTs (27,277 patients) and showed that the dual blockage of the HER2 pathway with trastuzumab plus lapatinib associated with chemotherapy is the best schedule for this outcome (HR 0.78; 95%CI 0.61-0.99, when compared to the gold-standard regimen of chemotherapy associated with trastuzumab for 12 months). DFS network was composed by 14 RCTs (30,219 patients) and reinforced the previous findings regarding the efficacy of the dual blockage. However, it added the promise results of 12 months of neratinib sequential to chemotherapy plus 12 months of trastuzumab (OS results for this study have not yet been published). Probability of achieving CPR was evaluated based on 17 RCTs (4,383 patients). The dual blockage also proved to be superior for this outcome. Taxane associated with trastuzumab and lapatinib or

pertuzumab were better than the other regimens and showed comparable efficacy between them, with marginal, though not significant, superiority in favor of pertuzumab (RR 1.10; 95%CI 0.70-1.60). In all the networks that evaluated efficacy, regimens containing only chemotherapy with no anti-HER2 therapy or with any other anti-HER2 therapy other than trastuzumab were the worst options. Cardiotoxicity was assessed in a network with 21 RCTs (29,555 patients). This analysis showed that the dual blockage with trastuzumab and pertuzumab had more cardiotoxicity events, but it is important to state that irreversible symptomatic CHF is a rare event in this clinical scenario (<1%).

Conclusion

The findings of these networks endorses the concepts that the dual blockage of the HER2 pathway is the best therapeutic option in terms of efficacy for HER2-positive breast cancer and that trastuzumab plus chemotherapy is the backbone of this treatment. It was identified beneffit in terms of OS with one of these schedules (chemotherapy associated with trastuzumab and lapatinib). Other alternatives of dual blockage, such as chemotherapy associated with trastuzumab and pertuzumab or sequential neratinib, are promising alternatives considering their results on DFS and CPR, but their results on OS are still waited. Concomitant use of trastuzumab and pertuzumab increases cardiotoxicity. However, it must be emphasized that clinical meaningfull outcomes such as permanent symptomatic CHF are very uncomon. On the other hand, the simultaneous use of lapatinib is safe from the cardiological point of view, but it increases the incidence of diarrhea (an outcome that was not evaluated in this theses due to high heterogeneity on the reports).

1. APRESENTAÇÃO

Este trabalho consiste na tese de doutorado intitulada "Inibidores da via HER2 ("Human Epidermal Growth factor Receptor 2) no tratamento do Câncer de Mama inicial e localmente avançado: uma metanálise em rede", apresentada ao Programa de Pós-Graduação em Epidemiologia da Universidade Federal do Rio Grande do Sul, em 15 de fevereiro de 2016. O trabalho é apresentado em três partes, na ordem que segue:

1. Introdução, Revisão da Literatura e Objetivos
2. Artigo(s)
3. Conclusões e Considerações Finais.

Documentos de apoio estão apresentados nos anexos.

2. INTRODUÇÃO

O câncer de mama é a neoplasia maligna mais frequente em mulheres em todo o mundo (Jemal, 2011; Siegel, 2012). Com prevalência estimada ao longo da vida da mulher de 12%, representa importante problema de saúde pública em todo o mundo (Jemal, 2011). Segundo dados da Organização Mundial da Saúde (OMS), foram registrados 1,68 milhão de novos diagnósticos e 522.000 mortes por câncer de mama em 2012 (OMS,2013). Em termos de prevalência, a situação no Brasil assemelha-se bastante ao cenário internacional, com esta neoplasia figurando como o câncer mais frequente na mulher nas regiões Sul, Sudeste, Centro-oeste e Nordeste. Ao todo, estima-se que a incidência de câncer de mama será ao redor de 58.000 novos casos em 2016 (INCA, 2015).

A evolução do conhecimento em relação às mutações envolvidas na biologia tumoral permitiu a identificação de perfis moleculares com direto impacto prognóstico, baseados nos padrões de expressão genética (Perou, 2000). Essa subdivisão do câncer de mama em subtipos moleculares foi incorporada à prática clínica de modo que, atualmente, é recomendação unânime da ASCO *(American Society of Clinical Oncology)* e do CAP (*College of American Pathologists*) que todos os casos de câncer de mama devam ser classificados segundo seu perfil molecular. Essa segmentação subdivide os tumores de mama em luminais A e B, HER2 e basalóides. Cabe salientar que os tumores classificados como “luminais B” ainda se subdividem em HER2 positivos e negativos.

Os métodos utilizados para proceder essa caracterização molecular das neoplasias mamárias incluem os testes genéticos do genoma tumoral e a avaliação por imunohistoquímica (IHQ) do status dos receptores hormonais (estrogênio e progesterona), do receptor HER2 e de marcadores de proliferação celular, tais como Ki-67 (Goldhirsch, 2013b). A presente tese tem por foco de interesse todos os tumores que apresentam amplificação do gene HER2 ou superexpressão da sua proteína na membrana plasmática, incluindo, portanto, os tumores classificados como "HER2" e "luminais B HER2-positivos". Sabe-se que estes correspondem a aproximadamente 15-20% dos casos de câncer de mama (Ross, 2009).

Os tumores que apresentam esta alteração molecular demonstram fenótipo clínico mais agressivo e têm pior prognóstico quando comparados com cânceres de mama luminais HER2-negativos. Isto se deve ao crescimento celular desregulado e à sobrevida celular anormal mediada pela hiperexpressão da proteína HER2 nas células neoplásicas (Owens, 2004; Slamon, 1987; Slamon, 1989; Wolff, 2007; Yarden, 2001; Yaziji, 2004). Entretanto, o desenvolvimento de inibidores da via HER2 mudou a história natural desses tumores. Hoje, quando tratados de forma adequada, estas neoplasias apresentam prognóstico semelhante às suas contrapartes HER2-negativas.

Do ponto de vista molecular, os inibidores da via HER2 podem classificados em anticorpos monoclonais (trastuzumabe e pertuzumabe), inibidores de tirosina-quinase (afatinib, lapatinib e neratinib) e conjugados droga-anticorpo (TDM-1). Destes, o primeiro a ser desenvolvido foi o trastuzumabe. Ainda na década de 1990, foi

aprovado para o uso no cenário metastático e, desde 2005, figura como tratamento mandatório no contexto adjuvante e neoadjuvante (Baselga, 1996; Cobleigh, 1999; Piccart-Gebhart, 2005; Romond, 2005; Smith, 2007; Rimawi, 2015b). Sua utilização aumenta a sobrevida global de pacientes com tumores avançados (HR 0,79; IC95% 0,65-0,96) e iniciais (HR 0,66; IC95% 0,57-0,77) (Moja, 2012; Zhu, 2013). Todavia, a despeito da indubitável eficácia do trastuzumabe no tratamento dos tumores HER2-positivos, muitos tumores exibem resistência intrínseca ou adquirida à terapia-alvo anti-HER2. Desde então, os cientistas vêm pesquisando formas de contrapor os mecanismos de resistência, seja combinando trastuzumabe com diferentes esquemas de quimioterapia, seja bloqueando a via de sinalização HER2 com mais de um inibidor (bloqueio duplo). No cenário paliativo, existem exemplos bem-sucedidos dessas estratégias, tais como o aumento de sobrevida global com o uso combinado de quimioterapia mais bloqueio duplo com trastuzumabe e pertuzumabe em primeira linha (HR 0.68, IC95% 0.56-0.84, $p<0.0001$) e o uso do TDM-1 em segunda linha (Swain, 2015, Verma, 2012).

Nos cenários adjuvante e neoadjuvante, existem inúmeros ensaios clínicos randomizados que comprovam de forma contundente a eficácia dos inibidores da via HER2 em aumentar a chance de cura das pacientes. Esta grande variedade de experimentos gera uma embricada rede de evidências que inclui a comparação de trastuzumabe com diferentes esquemas de quimioterapia, bem como diferentes estratégias de bloqueio duplo. Frente a esse problema, faz-se necessário lançar mão de métodos de sumarização de evidências para se chegar a uma inferência válida em relação a escolha do regime de tratamento sistêmico que deverá ser oferecido às

pacientes. Infelizmente, o método clássico de sumarização de evidência baseado nas metanálises "*pairwise*" não é capaz de abarcar a complexidade dessa rede de estudos. Em contrapartida, o emprego de metodologias mais abrangentes, como, por exemplo, o modelo de metanalise em rede baseado em MTC ("*Mixed Treatment Comparison*") consegue lidar com esses distintos braços de tratamento em um modelo matemático único. Dessa forma, é possível que a aplicação desse modelo nos permita refinar a inferência existente de modo a beneficiar as pacientes, otimizando os desfechos.

3. REVISÃO DE LITERATURA

3.1. CÂNCER DE MAMA: EPIDEMIOLOGIA

O câncer de mama é a neoplasia maligna mais frequente em mulheres em todo o mundo (Jemal, 2011; Siegel, 2012). Com prevalência estimada ao longo da vida de 12% para mulheres que se encontram sob risco usual, representa 23% do total de diagnósticos de câncer em mulheres e 14% das mortes por câncer em mulheres nos EUA (Jemal, 2011). Segundo dados da Organização Mundial da Saúde (OMS), foram registrados 1,68 milhão de novos diagnósticos e 522.000 mortes por câncer de mama em 2012 (OMS,2013). Em virtude do acima exposto, esta condição destaca-se como importante problema de saúde pública, representando a principal causa de morte por câncer nos países em desenvolvimento e a segunda principal causa nas regiões desenvolvidas, superada somente por câncer de pulmão (OMS, 2013). Dentre os diversos subtipos moleculares dessa doença, cabe destacar que cerca de 15-25% desses casos são classificados como HER2-positivos (*Human Epidermal growth fator Receptor 2*) – ou seja, as células tumorais apresentam mutação no gene HER2 ou superexpressão dessa proteína em suas membranas plasmáticas (Ross, 2009). Tumores que apresentam esta alteração molecular demonstram fenótipo clínico mais agressivo e têm pior prognóstico quando comparados com cânceres de mama luminais HER2-negativos. Isto se deve ao crescimento celular desregulado e sobrevida celular anormal mediada pela hiperexpressão desse receptor HER2 nas células neoplásicas (Owens, 2004; Slamon, 1987; Slamon, 1989; Wolff, 2007; Yarden, 2001; Yaziji, 2004).

A situação no Brasil assemelha-se bastante ao cenário internacional. Dados publicados pelo Instituto Nacional do Câncer (INCA) demonstram que essa neoplasia, excluindo-se tumores de pele não-melanoma, representa o câncer mais frequente em mulheres nas regiões Sul, Sudeste, Centro-oeste e Nordeste, estimando-se a ocorrência de 57.960 novos casos para 2016 (INCA, 2015). Existem poucos estudos sobre o perfil molecular dos casos nacionais, mas dados provenientes de uma coorte retrospectiva conduzida por Liedke e colaboradores identificaram uma prevalência 13% para tumores HER2-positivos (Liedke, 2013).

3.2. CÂNCER DE MAMA: ETIOPATOGENIA E BIOLOGIA MOLECULAR

O câncer de mama, como todas as neoplasias malignas, é uma doença genética que pode ser melhor entendida pelas alterações no DNA que levaram ao desenvolvimento do tumor. Desde o sequenciamento do genoma humano, tem-se buscado compará-lo com o das células tumorais, a fim de se encontrar as mutações responsáveis pelo processo de carcinogênese e, com isso, promover a prevenção e cura dessa doença. O câncer de mama é uma neoplasia heterogênea provocada fundamentalmente pela acumulação progressiva de aberrações genéticas, tais como mutações ponto, amplificações cromossômicas, deleções, rearranjos, translocações e duplicações (Woods, 2007). Alterações genéticas hereditárias decorrentes de mutações na linhagem germinativa são responsáveis por cerca de 5-10% dos casos, definindo-se estas situações como “câncer de mama hereditário” (Slattery, 1993; CGHFBC, 2001). Em contrapartida, por volta de 70% dos tumores da mama decorrem de

alterações genéticas somáticas que surgem de maneira esporádica e aleatória como consequencia da interação do genoma com o meio, sendo estes tumores designados como "esporádicos" (Vinayak, 2011). Já os outros 20-25% dos casos são classificados como "familiares", pois se identifica um padrão de distribuição fenotípica com características de tumor hereditário mas não se consegue determinar uma mutação deletéria específica como agente causal na família (Couch, 2014; Slattery, 1993).

Os principais fatores de risco para o câncer de mama são o sexo feminino e a idade (Jemal, 2011). Além destes, a história familiar destaca-se como importante fator de risco (CGHFBC, 2001). As formas familiares da doença representam aproximadamente 30% dos casos, porém a maior parte dos genes que determinam essas formas ainda estão para serem identificados (Couch, 2014; Slattery, 1993). As síndromes genéticas de câncer de mama ocorrem na maior parte das vezes pela transmissão de mutações germinativas em genes de alta penetrância, determinando heranças autossômicas dominantes com penetrância incompleta, nas quais o fenótipo (definido como o desenvolvimento de câncer) manifesta-se em indivíduos com mutações herdadas em heterozigose, mas não em 100% dos casos.

Dentre os genes conhecidos atualmente, destacam-se o *BRCA1* e o *BRCA2* (Bell, 2010). Esses genes codificam proteínas que participam dos sistemas de reparo do DNA celular, sendo genericamente nomeados como "genes supressores tumorais". Nestes casos, a tumorigênese decorre da perda de função destes, o que usualmente necessita a inativação dos seus dois alelos. Isto significa dizer que, em pacientes com

uma mutação germinativa deletéria herdada em um destes genes, o fenótipo manifesta-se ao longo da vida quando ocorre a inativação do alelo "normal". Estima-se que a penetrância média para câncer de mama para o gene BRCA1 seja de aproximadamente 60% e para o BRCA2 de 40% (Chen, 2007). Mutações nos genes *BRCA1* e *BRCA2* representam aproximadamente metade das formas hereditárias do câncer de mama. Assim, mesmo sendo raras na população em geral, essas mutações têm grande impacto na saúde pública, uma vez que seus carreadores apresentam importante aumento no risco de desenvolver câncer de mama em relação à população em geral, resultando em uma probabilidade de manifestar o fenótipo que pode chegar a 85% ao longo da vida (Vinayak, 2011). Apesar da transcendência clínica do tema, esses tumores caracterizam-se por apresentarem perfil molecular diferente dos tumores HER2-positivos, fugindo, portanto, do escopo do interesse desta revisão. Além do BRCA1 e 2, existem outros genes que também se associam com aumento de risco para câncer de mama, são eles: *CHEK2*, *TP53*, *PTEN*, *BRIP1*, *PALB2*, *ATM*, *CDH1*, *STK11*, entre outros (Hemminki, 1998; Olivier, 2003; Velculescu, 2008).

Estabelencendo contraponto com os tumores hereditários, a forma esporádica do câncer de mama representa a grande maioria dos casos, sendo causada por um acúmulo de numerosas alterações genéticas somáticas que culminam com a transformação de uma célula normal em célula tumoral. Dados de pesquisa básica mostram que um típico tumor maligno apresenta entre 50 e 80 mutações somáticas (Wood, 2007). Boa parte dessas mutações ocorre devido a uma replicação errônea do DNA; enquanto outras podem ocorrer como resultado de exposição a carcinógenos endógenos e exógenos. A maioria delas são consideradas "*passenger mutations*", isto

é, biologicamente neutras e que não contribuem para a oncogênese. Elas se contrapõem às "*driver mutations*", as quais conferem vantagens no crescimento celular e no desenvolvimento da neoplasia (Vinayak, 2011). Os genes mais frequentemente mutados e que pertencem a essa última categoria são: *TP53*, *CDH1*, *PI3K*, *ciclina D*, *PTEN* e *AKT*. Cada um desses genes individuais é mutado em menos de 5% dos tumores de mama, gerando uma grande heterogeneidade de fenótipos, o que explica a grande variabilidade da doença em termos de comportamento biológico e responsividade aos tratamentos (Bell, 2010; Wood, 2007; Perou, 2000).

Nos anos mais recentes, a descoberta das modificações genéticas e do seu impacto nas características clínicopatológicas da doença gerou uma nova classificação do câncer de mama em perfis moleculares, baseado nos padrões de expressão genética (Perou, 2000). Desde então, diversas instituições têm aperfeiçoado a classificação desses grupos e adicionado mais características moleculares. Dentre essas instituições destaca-se o Consórcio Internacional de Taxonomia Molecular do Câncer de Mama (METABRIC), que definiu os principais subgrupos tumorais do câncer de mama que têm importância na prática clínica: tumores luminais A e B (tumores tipicamente positivos para receptores de estrogênio e progesterona); tumores HER2-positivos; e tumores triplo-negativos (CGN, 2012).

Essa subdivisão do câncer de mama em subtipos moleculares foi de tal forma incorporada à prática clínica que hoje é recomendação unânime da ASCO *(American Society of Clinical Oncology)* e do CAP (*College of American Pathologists*) que

todos os casos de câncer de mama devem ser classificados segundo seu perfil molecular. Essa inclusão de conceitos de biologia molecular à classificação taxonômica do tumor auxilia a identificar os pacientes que mais se beneficiam das diferentes intervenções terapêuticas disponíveis para o câncer de mama, conceituando o que hoje se chama de "medicina de precisão". Como exemplo, desde 2011 a Conferência Internacional de Câncer de Mama de Saint Gallen reconhece que o câncer de mama não deve ser tratado como uma única doença, recomendando que esta seja definida a partir do seu subtipo molecular. Para isso, são utilizados testes genéticos e avaliação por imunohistoquímica (IHQ) do status dos receptores hormonais (estrogênio e progesterona), do receptor HER2 e de marcadores de proliferação celular, tais como Ki-67 (Goldhirsch, 2013b).

De especial interesse para esta revisão é a determinação dos receptores hormonais e do *status* HER2. Os receptores hormonais (estrógeno e progesterona) são avaliados por técnica de imunohistoquímica, utilizando-se escores padronizados para sua classificação ("*Allred score*" ou "H-score"). A classificação mais comumente utilizada atualmente constitui publicação conjunta da ASCO *(American Society of Clinical Oncology)* e do CAP (*College of American Pathologists*) (Hammond, 2010). Esta diretriz determina como "positiva" a expressão >1% no H-score para os receptores de estrógeno e progesterona.

Já a determinação dos *status* HER2 do tumor pode ser definida tanto por imunohistoquímica quanto por hibridização *in situ* (Gown, 2008). Existe relação entre a amplificação do gene HER2 e a consequente superexpressão da proteína na

membrana celular, como descrito na figura 1 (Gown, 2008). A IHQ avalia o grau de expressão dos receptores HER2 na membrana plasmática de forma indireta a partir da intensidade da coloração da membrana celular secundária a utilização de um anticorpo anti-HER2 ligado a um composto corante. Seu resultado é dividido em três categorias: positivo (coloração +++/+++), negativo (coloração 0 ou +/+++) e duvidoso (coloração ++/+++). A determinação destas categorias segue critérios específicos, conforme publicado pelo CAP em 2013. Este algorítimo encontra-se descrito na figura 2. Em contrapartida, as técnicas de hibridização *in situ* identificam o número de cópias do gene HER2 e a sua relação com o número de cromossomos 17 (cromossomo onde se localiza do gene HER2) presentes no núcleo da célula (Wolff, 2013). A figura 3 ilustra o resultado final da uma das técnicas de hibridização *in situ* denominada FISH (*Fluorescent In Situ Hybridization*)

FIGURA 1: correlação entre amplificação do gene HER2 e a expressão da proteína na membrana celular (Gown, 2008)

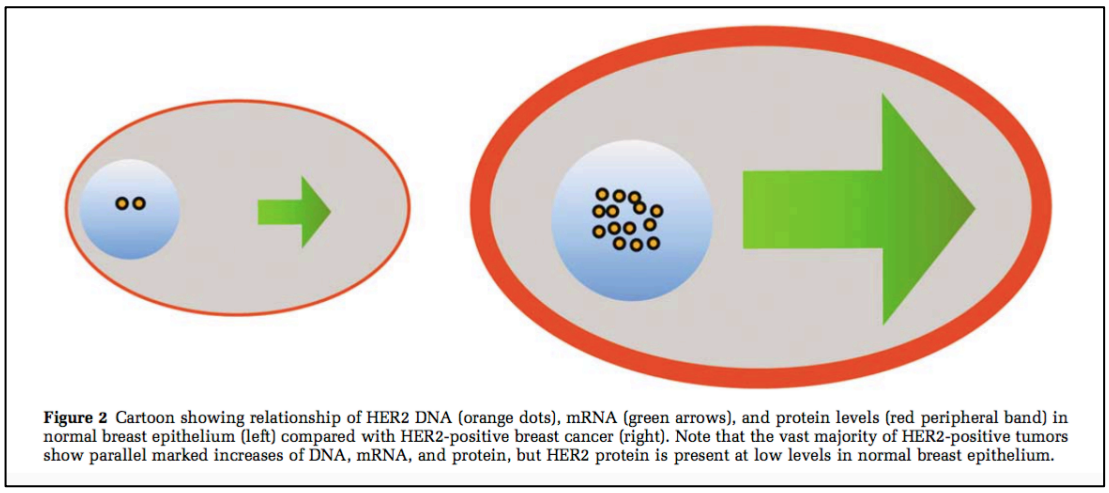


Figure 2 Cartoon showing relationship of HER2 DNA (orange dots), mRNA (green arrows), and protein levels (red peripheral band) in normal breast epithelium (left) compared with HER2-positive breast cancer (right). Note that the vast majority of HER2-positive tumors show parallel marked increases of DNA, mRNA, and protein, but HER2 protein is present at low levels in normal breast epithelium.

A última diretriz da ASCO-CAP é considerar como HER2-positivo todo tumor que apresentar à IHQ coloração completa em mais de 10% das células do componente

invasivo ou, caso se esteja utilizando técnica de hibridização *in situ*, número igual ou superior a seis cópias do gene HER2 ou razão de HER2/cromossomo 17 maior ou igual a dois (Wolff, 2013). A tabela 1 define os principais tipos moleculares no câncer de mama.

FIGURA 2: algorítimo do *College of American Pathologists* para determinação do *status* HER2 conforme imunohistoquímica (Wolff, 2013)

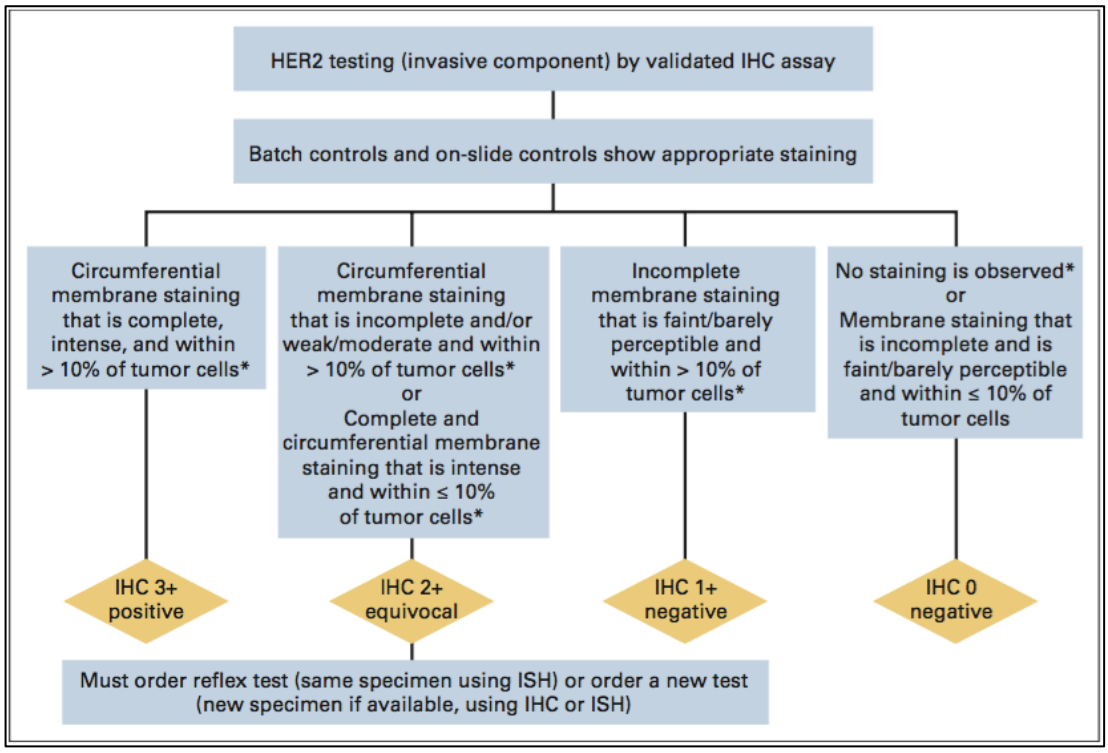
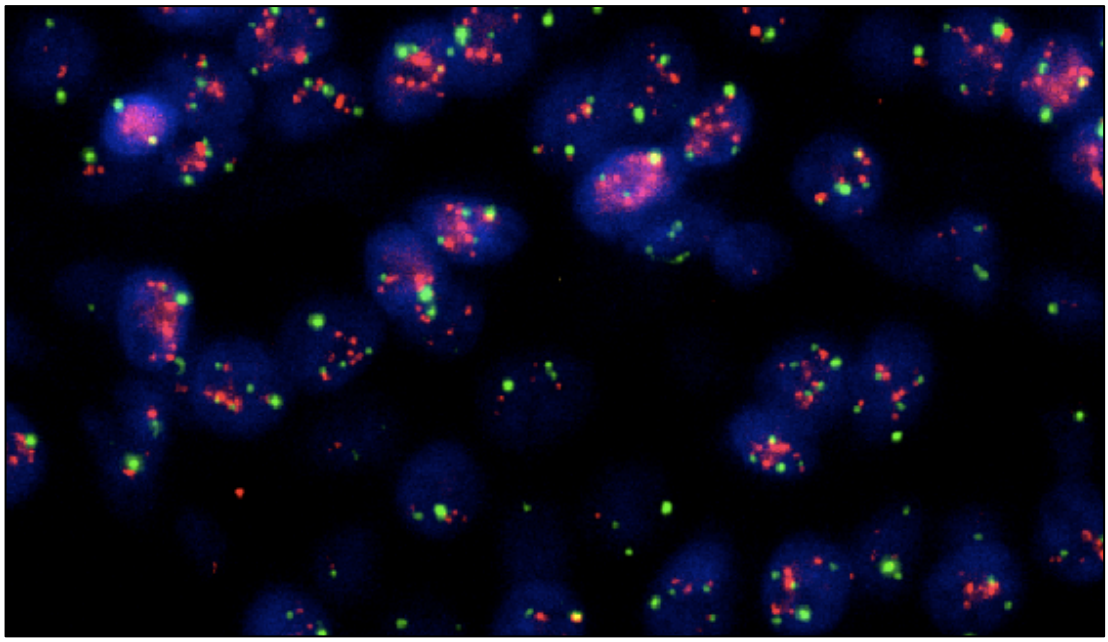


FIGURA 3: imagem de FISH, demonstrando as cópias dos cromossomos 17 (em verde) e as cópias do gene HER2 (em vermelho).*



* Imagem publicamente disponível em http://www.imstarsa.com/products-2/pathfinder/morphoscan/breast-cancer/

TABELA 1: Classificação molecular dos subtipos de câncer de mama (Coates, 2015; Senkus, 2015)

Subtipo Molecular*	**Definição Clínico-patológica****	**Notas**
Luminal A	**"Luminal A símile"** • RE positive • HER2 negativo • RP fortemente expresso* • Ki67 baixo**	* ponto de corte sugerido para determinar alta expressão do RP como > 20% ** sugere-se que os valores de Ki67 sejam valorizados conforme

		padronização do laboratório local

Luminal B	**"Luminal B símile (HER2 negativo)"**
	• RE positivo
	• HER2 negativo
	• Qualquer dos abaixo:
	  o PR fracamente expresso
	  o Ki67 alto
	
	"Luminal B símile (HER2 positivo)"
	• RE positivo
	• HER2 positivo
	• Qualquer RP
	• Qualquer Ki67	

HER2 superexpresso	**"HER2 superexpresso não-luminal"** • HER2 positivo • RP e RP negativos	
Basalóide	**"Triplo negativo"** • HER2 negativo • RP e RE negativos	Estima-se que exista aproximadamente 80% de concordância entre a identificação de um

		tumor “triplo negativo” à IHQ e a ocorrência de fenótipo basalóide

RE: receptor de estrógeno, RP: receptor de progesterona

* determinada por avaliação genômica do tumor

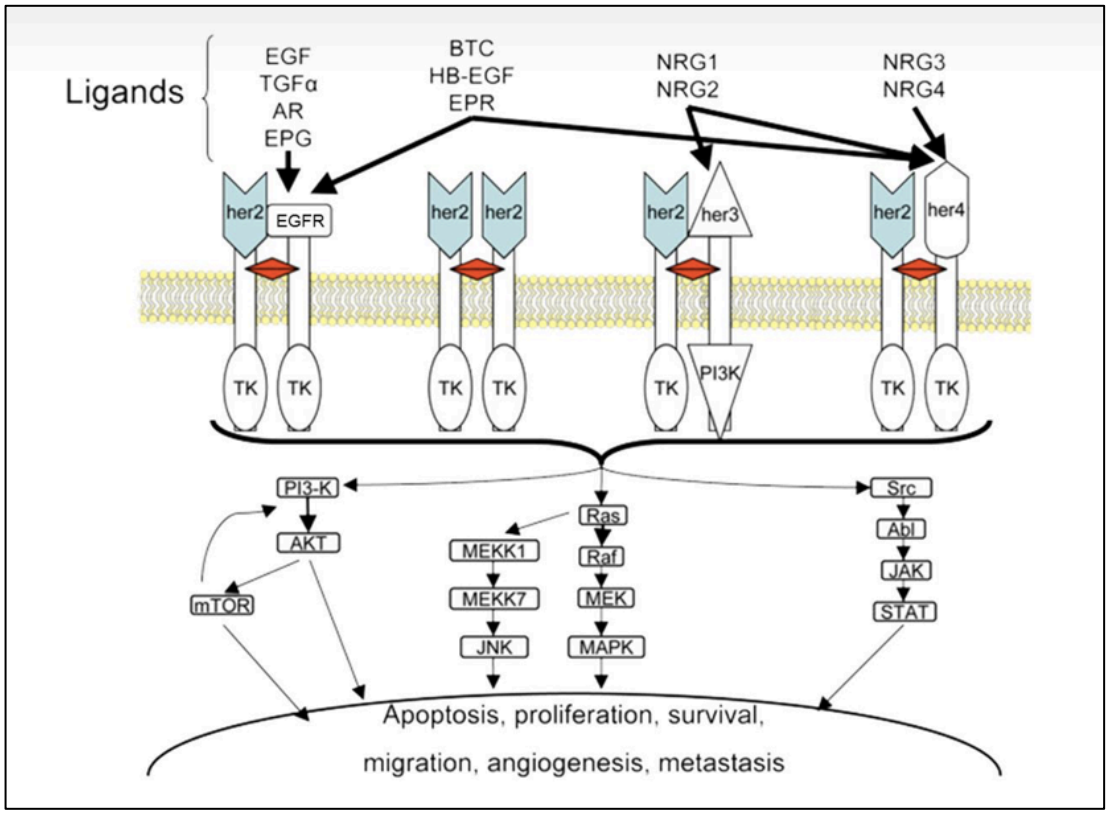
** estimada a partir de características substitutas clínico-patológicas

3.3. CÂNCER DE MAMA: RECEPTORES DA FAMÍLIA HER

Os receptores da família ErbB (também denominados HER – “*Human Epidermal growth fator Receptor*”) são proteínas transmembrana cujos domínios intracelulares são ligados à tirosina quinase. A cascata de reações ocasionada pela ativação desses receptores é reconhecida como parte no processo de proliferação celular e carcinogênese desde os anos 1980, quando foi descoberto que o vírus do tumor eritoblástico aviário codifica uma forma aberrante dessa proteína (Yarden, 2001). Expresso em quase todos os tecidos humanos e fundamental para o desenvolvimento de diversos órgãos e sistemas, a superativação desses receptores está relacionada a um mau prognóstico em diversos tipos de cânceres, uma vez que, quando ativados, estes receptores estimulam, através de complexas vias de sinalização celular, o crescimento celular, a inibição da apoptose, a migração celular, a invasividade e a angiogênese, entre outros processos que estão associados a progressão de tumores malignos (Freitas, 2008).

Essa familia é composta pelos receptores HER1, HER2, HER3 e HER4 cuja síntese e processamento dos transcritos e das proteínas são extremamente reguladas pelas células. Os polipeptídeos que compões esses receptores são codificados por diferentes genes. No cromossoma 7, encontra-se o gene responsável pela síntese do EGFR/HER1; no cromossoma 17, o HER2; no cromossoma 12, o HER3; e, finalmente, no cromossoma 12, o HER4 (Freitas, 2008). A ativação desses receptores desempenha seu papel biológico a partir de um mecanismo denominado transdução de sinal, o qual ocorre da seguinte forma: quando um ou mais fatores de crescimento externos liga-se a um dos receptores HER (EGFR, HER3 ou HER4), esse dimeriza-se com outros receptores iguais (homodimerização) ou com outros membros da família (heterodimerização), ocasionando a fosforilação do sítio específico de tirosina da porção intra-celular do receptor, o que leva a ativação enzimática de diversas proteínas em sequência, gerando, em última instância, as alterações da fisiologia celular já descritas acima. O receptor HER2 não possui um ligante conhecido, porém atua como "parceiro" preferido de dimerização dos outros receptores, uma vez que os heterodímeros com HER2 são mais estáveis e sua sinalização mais potente (Ross, 2009). Além disso, o HER2 pode, quando superexpresso, homodimerizar-se e disparar a cascata intracelular independente da presença de fator de crescimento externo. Esse mecanismo é sumarizado na figura 4.

FIGURA 4: sumário da via de sinalização dos receptores da via HER (Morrow, 2009)



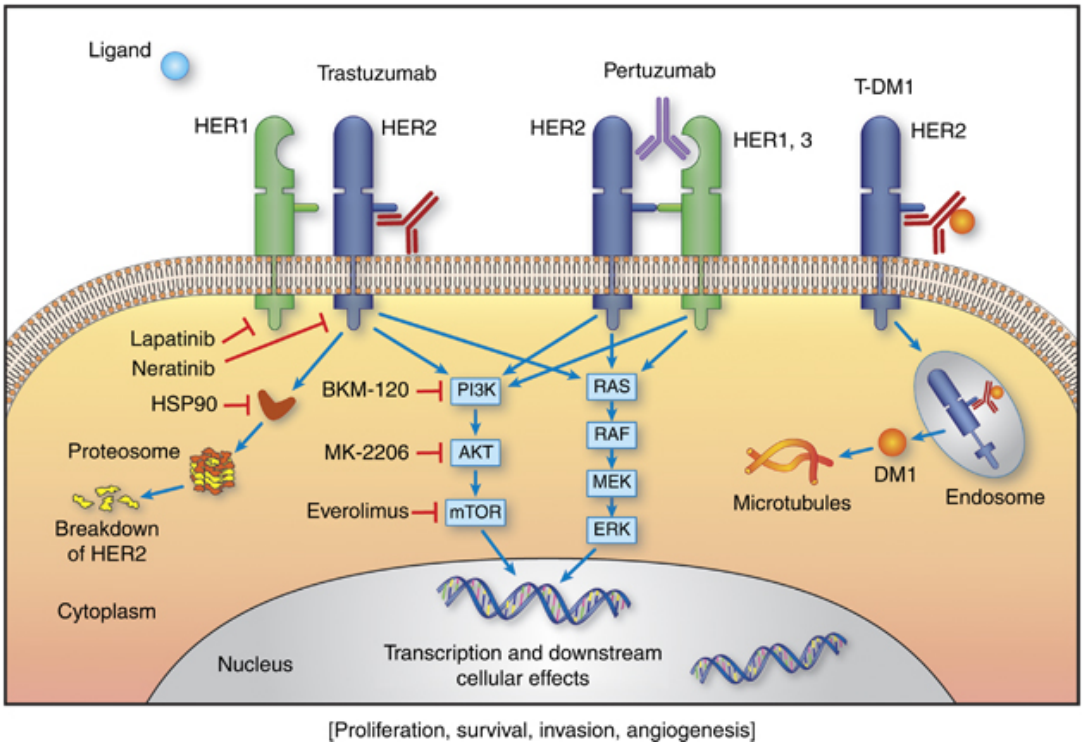
No câncer de mama, a amplificação/hiperexpressão do receptor HER2 ocorre em 15-25% das pacientes com neoplasia invasiva (Slamon, 1987; Slamon, 1987; Wolff, 2013). Desde os anos 1980, inúmeros estudos têm detectado que anormalidades na expressão de HER2 ao nível genético, transcripcional ou proteico estão associados a um pior prognóstico nos pacientes com câncer de mama, tanto linfonodo-positivo quanto linfonodo-negativo. Neste sentido, o trabalho mais importante em identificar que a hiperexpressão/amplificação de HER2 era um fator de pior prognóstico foi

publicado em 1987 por Slamon e colaboradores (Slamon, 1987). Este estudo demonstrou que HER2 era um fator de mau prognóstico em tumores de mama em análise multivariável, independente de receptor hormonal, idade e *status* linfonodal. Como previamente descrito nesta tese, existem duas técnicas validadas para a detectação da superexpressão da via HER2: exame imunohistoquímico – o qual consiste em detectar a quantidade de receptores expressos na membrana citoplasmática através da coloração de blocos de parafina com anticorpos específicos – e técnicas de hibridização in situ (FISH) – que detectam a presença e quantificam a sequência de DNA responsável pela codificação do receptor nos cromossomas da célula. Ambos os métodos estão fortemente correlacionados e encontram-se respaldados pela literatura e órgãos regulamentadores. A partir de meados dos anos 2000, a testagem da expressão ou amplificação do receptor HER2 tornou-se o padrão-ouro mandatório, devendo ser utilizada em todos os casos de tumores primários da mama com componente invasor (Ross, 2009; Wolff, 2013). Esta caracterização é de suma importância em virtude de terem sido desenvolvidos medicamentos, genericamente denominados de "inibidores da via HER2", que mudaram a história natural da doença. Estas medicações aumentam em aproximadamente 36% a chance de cura de pacientes com tumores iniciais de mama. Já naquelas com tumores disseminados, o sequenciamento otimizado dessas drogas aumenta a sobrevida mediana de um patamar inicial de aproximadamente 19 meses com o uso exclusivo da quimioterapia para 56.5 meses (Moja, 2012; Swain, 2015).

3.4. INIBIDORES DA VIA HER2

Atualmente, existem pelo menos seis inibidores da via HER conhecidos e já aprovados para uso clínico no câncer de mama ou em fases avançadas de investigação em humanos: afatinibe, lapatinibe, neratinibe, pertuzumabe, TDMA-1 e trastuzumab. A seguir, esses medicamentos serão brevemente descritos, incluindo seus mecanismos de ação. A figura 5 resume os sítios de ação dessas drogas.

FIGURA 5: inibidores da via HER2 (Esteva, 2014)



3.4.1. Afatinibe

O afatinibe é um inibidor irreversível da família HER que atua bloqueando a cascata de sinalização intracelular de todos os homo e heterodímeros de HER1, HER2 e

HER 4 (Li, 2008; Solca, 2012). Essa droga se mostrou ativa no tratamento de mulheres com câncer de mama metastático que recorreram após a terapia com trastuzumabe em estudo de fase II (Lin NU, 2012).

3.4.2. Lapatinibe

O lapatinibe é um medicamento de uso oral que atua como inibidor reversível do sítio tirosino-kinase intracelular do receptores HER 1 (EGFR) e HER2 (Konecny GE,2006). Já demonstrou ser droga ativa no tratamento do câncer de mama, estando aprovado para o uso em mulheres com câncer de mama avançado HER2 positivo que falham a terapia com trastuzumab (Cameron, 2008; Di Leo, 2008; Geyer, 2006; Konecny, 2006).

No contexto neoadjuvante, a adição do lapatinibe aumenta a taxa de resposta patológica completa, mas essa diferença não impacta em aumento de sobrevida global (Azambuja, 2014a; Baselga, 2010; Baselga, 2012; Piccart-Gebhart, 2013; Piccart-Gebhart, 2014). Em mulheres com indicação de trastuzumabe adjuvante, mas que por qualquer razão não tenham recebido o tratamento, adicionar lapatinibe isolado após a quimioterapia não demonstrou beneficio em termos de redução de mortalidade ou de recorrência local, regional ou a distância quando comparado com placebo (Goss PE, 2013).

3.4.3. Neratinibe

O neratinibe é um inibidor irreversível do domínio intracelular da tirosina-kinase dos receptores HER1, HER2 e HER3 (Gradishar, 2012). Sua eficácia clinica já foi evidenciada em pacientes com câncer de mama HER2+ metastáticos pré tratados com trastuzumabe (Burstein, 2009; Rabindran, 2004). O estudo ExteNET está em andamento, mas já demonstrou aumento de sobrevida livre de doença com o uso do neratinibe extendido (ou seja, após 1 ano de quimioterapia mais trastuzumabe adjuvantes) em pacientes com câncer de mama inicial HER2-positivo (Chan, 2015).

3.4.4. Pertuzumabe

O pertuzumabe é um anticorpo humano monoclonal IgG1 que se liga ao domínio II do HER2 e bloqueia a dimerização dependente de ligante do HER2 com os demais membros da família HER (Agus DB, 2002).

Esta medicação, quando utilizada em combinação com trastuzumbe e docetaxel, está aprovada para uso em primeira linha em tumores de mama HER2 positivos metastáticos, sendo esta combinação considerada a primeira escolha terapêutica para esta indicação. Ela também está aprovada no contexto neoadjuvante no tratamento de tumores de mama HER2 positivos localmente avançados, inflamatórios, ou em estadios clínicos iniciais de alto risco (definidos como: pacientes com linfonodos axilares negativos mas com tumores maiores que 2 cm ou presença de linfonodos axilares positivos) (Baselga, 2012; Swain, 2013).

A aprovação por parte do FDA da combinação de pertuzumabe mais trastuzumabe e docetaxel previamente descrita foi sustentada pela publicação de um estudo de fase III chamado CLEOPATRA, no qual pacientes com tumores recorrentes, irressecáveis ou metastáticos foram randomizadas em primeira linha paliativa para o grupo experimental (quimioterapia com docetaxel mais bloqueio duplo da via HER2 com trastuzumabe e pertuzumabe) ou para o grupo controle (quimioterapia com docetaxel mais bloqueio simples da via HER2 com trastuzumabe). Na última atualização dos dados publicada em 2015, o grupo que recebeu quimioterapia mais bloqueio duplo apresentou aumento de sobrevida global de 49.3 meses para 56.5 (HR 0.68, IC95% 0.56-0.84, p<0.0001) (Swain, 2015). Apesar de a adição de pertuzumabe ter aumentado a incidência de efeitos adversos grau 3, não houve piora significativa na função cardíaca das pacientes, o que era uma preocupação em relação ao bloqueio duplo da via com dois anticorpos monoclonais.

Já a aprovação para o uso de pertuzumabe associado ao trastuzumabe e docetaxel no cenário neoadjuvante de câncer de mama em tumores localmente avançados ou em estadios iniciais de alto risco foi baseada em estudo fase II que demonstrou aumento na taxa de resposta patológica completa de 17,8% (Gianni, 2012a).

3.4.5. TDM-1

Trastuzumabe entansina (T-DM1) é um conjugado anticorpo-droga que combina um agente potente de microtúbulos (DM1) com trastuzumab numa molécula única

usando um ligante tioeter (Barginear, 2012; Junttila, 2011; Phillips, 2008). Uma vez que a fracção trastuzumab da molécula reconhece e se liga ao HER2, ele é internalizado e a porção de DM1 é lançada dentro da célula (Barginear, 2012; Junttila, 2011; Phillips, 2008). A eficácia deste medicamento já foi estabelecida no contexto metastático: em um ensaio clínico randomizado de fase III, trastuzumabe entansina melhorou a sobrevida livre de progressão (SLP), quando comparado com um regime combinado de capecitabina com lapatinibe em pacientes com câncer da mama avançado que tinham sido previamente tratados com trastuzumab (Verma, 2012). Sua atividade clínica está sendo testada no cenário adjuvante pelo estudo ATEMPT (https://clinicaltrials.gov/ct2/show/NCT01853748), porém seus resultados ainda não foram reportados.

3.4.6. Trastuzumabe

O trastuzumabe é um anticorpo humano IgG1 contra o dominio IV do receptor HER2 (Cartere, 1992). Seu mecanismo de ação ainda não foi completamente elucidado, mas sabe-se que este medicamento, a partir da sua ligação ao domínio extracelular do receptor, atua inibindo a via de sinalização intracelular, suprime a angiogênese para o tumor e aumenta a resposta imune contra as células neoplásicas (Juntila, 2009; Molina, 2001; Scheuer, 2009; Slamon, 2001). Sabe-se que o trastuzumabe interage com os agentes citotóxicos, aumentando a sua capacidade de induzir morte em células tumorais. Sua interação se dá de forma aditiva com a doxorrubicina, a epirrubicina e o paclitaxel; e de forma sinergística com a carboplatina, a ciclofosfamida, o docetaxel e a vinorelbina (Lopez 1999; Pegram 1999; Pegram

2004; Pietras 1998). Desde o desenvolvimento do trastuzumabe, ainda se investiga qual é a sua melhor combinação com agentes citotóxicos.

Este medicamento foi o primeiro anticorpo monoclonal aprovado pelo FDA para o tratamento de tumores sólidos baseado em inúmeros estudos que demonstraram que a inibição da via HER2 mudava a história natural dos tumores que hiperexpressam esse receptor no contexto de tumores de mama metastáticos (Baselga, 1996; Cobleigh, 1999). Em estudo de fase III, o trastuzumabe em combinação com quimioterapia citotóxica aumentou a taxa de resposta de 25% para 57,3% comparado com quimioterapia baseada em taxanos sozinha (Slamon, 1998). Dados provenientes de uma metanálise de sete estudos randomizados demonstram que a adição de trastuzumabe ao tratamento padrão aumenta a sobrevida global de pacientes com câncer de mama metastático HER2-positivos: HR 0,79; IC95% 0,65-0,96 (Zhu, 2013)

Além isso, o trastuzumabe também sagrou-se como tratamento padrão, associado à quimioterapia citotóxica, nos cenários adjuvante e neoadjuvante, demonstrando redução de 50% no risco de recorrência após 1 ano e aumento de sobrevida global (HR 0,66; IC95% 0,57-0,77) (Moja, 2012; Piccart-Gebhart MJ 2005; Romond EH 2005; Smith I 2007). Todavia, sabe-se que este tratamento apresenta cardiotoxicidade do tipo II, que costuma ser reversível com a suspensão do tratamento, sendo raros agravos importantes a longo prazo na função cardíaca das pacientes tratadas com trastuzumabe (Ewer,1999; Zagar, 2015).

3.5. INIBIDORES DA VIA HER2 NO TRATAMENTO DO CÂNCER DE MAMA

O receptor HER2 é um membro de uma família de receptores de tirosina quinase denominada HER ("*Human Epidermal growth fator Receptor*"). A amplificação do gene ou a superexpressão do receptor ocorre em aproximadamente 20% dos casos de câncer de mama, sendo este um fator de mau prognóstico, mas também preditivo de resposta ao uso de inibidores desta via (Slamon, 1987, Slamon 1989, Wolff, 2013). O primeiro inibidor da via HER2 a ser desenvolvido foi o anticorpo monoclonal trastuzumabe. Sua descoberta mudou a história natural da evolução desses tumores, marcando o início da era da Medicina de Precisão na oncologia, paradigma que define a busca de alvos moleculares para customizar o tratamento ideal para o paciente. Já na década de 1990, foi aprovado para o uso no cenário metastático e, desde 2005, figura como tratamento mandatório no contexto adjuvante e neoadjuvante (Baselga, 1996; Cobleigh, 1999; Piccart-Gebhart, 2005; Romond, 2005; Smith, 2007; Rimawi, 2015b). Sua utilização aumenta a sobrevida global de pacientes com tumores avançados (HR 0,79; IC95% 0,65-0,96) e iniciais (HR 0,66; IC95% 0,57-0,77) (Moja, 2012; Zhu, 2013).

A despeito da indubitável eficácia do trastuzumabe no tratamento dos tumores HER2-positivos, muitos tumores exibem resistência intrínseca ou adquirida à terapia-alvo anti-HER2. Uma variedade de diferentes mecanismos de resistência ao trastuzumab já foram propostos (Austin, 2004; Bachman, 2004; Bedolis, 2004; Diermeier, 2005; Gallardo, 2012; Lu, 2001; Nagy, 2005; Samuels, 2004; Scaltriti, 2011; Scott, 1993; Shattuck, 2008; Vadlamudi, 2003; Vu, 2012; Yamauchi, 2011). Apesar da relevância do tema, uma revisão aprofundada deste tópico vai além do escopo de interesse desta tese e, portanto, não será aqui apresentada. Assim, tendo por base o conceito de que a resistência adquirida à terapia-alvo com tratuzumabe é evento que acaba por acontecer na quase totalidade dos indivíduos com doença avançada, a busca pela combinação de diferentes estratégias de bloqueio em diferentes pontos na via de sinalização HER2 é conclusão lógica.

Nesse contexto, a crescente compreensão da biologia e da complexidade da rede de sinalização HER2 e dos potenciais mecanismos de resistência por parte das célular tumorais têm orientado o desenvolvimento de novos inibidores da via HER2, tais como os supracitados, afatinibe, lapatinibe, neratinibe, TDM-1 e pertuzumabe. Diferentes combinações destas drogas visam inibir de forma mais completa os sítios de ligação extracelular do receptor ou bloquear simultaneamente o domínio extracelular do receptor e os pontos críticos de sinalização intracelular. Exemplos bem-sucedidos dessas estratégias são o uso combinado de quimioterapia mais bloqueio duplo da via HER2 com trastuzumabe e pertuzumabe que demonstrou importante aumento de sobrevida global em pacientes tratados em primeira linha paliativa (HR 0.68, IC95% 0.56-0.84, $p<0.0001$) (Swain, 2015). Além disso, o duplo

bloqueio com trastuzumabe e lapatinibe também se mostrou superior ao bloqueio único em termos de sobrevida global em pacientes com tumores já expostos à trastuzumabe (Blackwell, 2010; Blackwell, 2012; Konecny, 2006). Como resultado desta intensa produção científica, o câncer de mama HER2-positivo figura entre as áreas em que a pesquisa clínica e sua interação com a pesquisa básica trouxe mais benefícios para as pacientes, tendo como consequência um grande número de aprovações de novos medicamentos por parte do FDA nos últimos 20 anos (Rimawi,2015).

3.6. METANÁLISE

A partir da década de 1980, os pesquisadores evoluíram de revisões meramente descritivas da literatura para a realização de metanálises, que consistem no emprego de métodos matemáticos específicos para sumarizar em uma medida única o resultado de diferentes trabalhos acerca do mesmo tema, desde que sejam respeitados alguns requisitos de qualidade e homogeneidade em relação a critérios de inclusão, seguimento e desfechos (Borenstein, 2009). Os métodos matemáticos utilizados para calcular a estimativa sumarizada da metanálise variam conforme o desfecho considerado, mas todos têm em comum o fato de gerarem uma estimativa única cujo valor é ponderado conforme o peso de cada estudo no cálculo.

3.6.1. Metanálise "clássica" ("*pairwise*")

No seu senso mais estrito, metanálise é uma técnica estatística para estimar de forma quantitativa o efeito combinado de uma medida aferida em diferentes estudos (Petitti, 2001). Existem diversos tipos de metanálise; esta tese, porém, se concentra nas técnicas para comparação de intervenções terapêuticas. O modelo mais difundido e consagrado na literatura de metanálise, doravante denominado metanálise "clássica" ou "*pairwise*", sintetiza em uma única estimativa a medida de efeito entre dois tratamentos distintos. Esta síntese, que tem por objetivo ser a mais fidedigna aproximação do real efeito entre os tratamentos, pode ser genericamente resumida como uma média da estimativa-ponto da medida de efeito obtida em cada estudo ponderada pelo inverso da variância desta mesma estimativa em cada estudo (Borenstein, 2009). Existem diferentes formas de se proceder esse cálculo, tais como modelos de efeitos randômicos e modelos de efeitos fixos, que não serão aqui abordadas.

A avaliação da heterogeneidade do efeito dentro das comparação é parte integrante de toda metanálise clássica. Apesar de ser mandatória a sua realização, o método pelo qual esta deve ser conduzida ainda representa tema controverso. Tomam parte no processo de avaliação da heterogeneidade o teste Q de Cochrane, o I^2 e a avaliação clínico-metodológica por parte do leitor. Uma explanação pormenorizada acerca destes métodos foge do escopo desta tese, mas o leitor interessado por esse tema pode encontrar mais informações nas seguintes referências, todas elas listadas

ao final desta tese: Althuis, 2014; Baker, 2009; Borenstein, 2009; Engels, 2000; Ioannidis, 2008; Kirsh, 2001; Petitti, 2001;.

A metodologia clássica da metanálise "*pairwise*" baseada em estatística frequentista apenas permite aos investigadores a comparação simultânea de dois braços de tratamento. Neste sentido, pode-se citar como exemplo a metanálise publicada pela Cochrane Collaboration em 2012 que utilizou esse método, para investigar o efeito da adição de trastuzumabe à quimioterapia adjuvante no câncer de mama HER2-positivo. A partir da leitura deste trabalho, é apenas possível inferir que a utilização de trastuzumabe associado à quimioterapia é melhor do que a utilização da quimioterapia isolada (Moja, 2012). Todavia, em virtude da limitação do método, seguem dúvidas em relação a qual é o melhor esquema de quimioterapia em termos de sinergia terapêutica com o trastuzumab, bem como em relação ao tempo de uso do trastuzumab e o momento ideal de sua utilização: adjuvante ou neoadjuvante, concomitante ou não concomitante com antraciclinas.

Além disso, o método tradicional de metanálise não permite incluir em uma única rede as novas estratégias de bloqueio da via HER2 que estão sendo testadas no cenário adjuvante e neoadjuvante, tais como pertuzumab, lapatinibe, neratinibe e TDM-1. Desse modo, conclui-se que a complexidade associada à rede de evidências acerca do tratamento adjuvante e neoadjuvante do câncer de mama não pode ser abarcada em uma metanálise clássica.

3.6.2. Metanálise em rede: "*Mixed Treatment Comparisons*"

O MTC ("*Mixed Treatment Comparisson*") consiste em uma generalização do método clássico de metanálise "*pairwise*" que combina evidência direta e indireta para comparar múltiplos braços de tratamento entre estudos, desde que exista pelo menos um braço de tratamento em comum entre eles. A implementação algébrica do MTC é conduzida via um Modelo Linear Generalizado (MLG) utilizando abordagem de estatística frequentista ou Bayesiana (Lu, 2004a; Lumley, 2002; Hoaglin, 2011). As análises utilizadas nesta tese serão conduzidas a partir da abordagem Bayesiana, uma vez que este método demonstrou-se suficientemente flexível para contemplar a complexidade das redes de estudos formadas nesta revisão, incluindo estudos com múltiplos braços de tratamento.

Os resultados gerados a partir desta modelagem trazem medidas sumarizadas de efeito (risco relativo, razão de chances ou *hazard ratios*) comparando todas as opções terapêuticas envolvidas na análise. A partir deste resultado, é possível estimar um ranqueamento entre os braços, indicando a probabilidade de cada braço pertencer a cada estrato de ranqueamento (do melhor ao pior, dentro de cada desfecho) (Coleman, 2012; Salanti, 2008). Entretanto, cabe aqui a ressalva de que o resultado principal da análise é a tabela comparativa das medidas de efeito entre os braços de tratamento e que o ranqueamento dever ser interpretado à luz dos dados da tabela principal, sendo apenas uma ferramenta útil em auxiliar o leitor a identificar os regimes de tratamento de interesse. O predicado mais importante desta modelagem é o fato de ela organizar as opções terapêuticas em uma tabela comparativa e num

ranqueamento que indicam em intervalos de probabilidade qual é o tratamento que melhor se desempenha para um dado desfecho, o que confere significado clínico intuitivo para o leitor em seu processo de tomada de decisão.

Uma peculiaridade em relação a interpretação de estudos conduzidos sob a perspectiva Bayesiana é o fato de que os resultados se distribuem em intervalos do credibilidade (ou de probabilidade); e não em intervalos de confiança, como na estatística frequentista. Apesar de existirem diferenças matemáticas importantes entre essas definições, sua interpretação é bastante semelhante, de modo que o leitor familiarizado com a interpretação de intervalos de confiança saberá como valorizar os intervalos de credibilidade expostos nesta tese.

A complexidade da programação computacional necessária para a execução dos modelos Bayesianos de comparação múltipla impõe limitação para a disseminação e popularização do método (Jonas, 2013). Entretanto, a despeito desta limitação, a robustez matemática e a aplicabilidade clínica dos resultados derivados destas análises, estão fazendo com que este método seja cada vez mais utilizado e aceito na literatura médica. Exemplo disto são os achados de uma revisão sistemática financiada pela AHRQ ("*Agency of Health Care Research and Quality*") que identificou que a abordagem Bayesiana é mais comumente utilizada do que a frequentista na condução de metanálises de comparação múltipla, representando 33 das 42 publicações identificadas por esta revisão (Coleman, 2012). Entre os 33 MTCs conduzidos a partir da modelagem Bayesiana, quatro avaliavam temas

referentes à área da oncologia clínica (Golfinopoulos, 2007; Golfinopoulos, 2009; Kyrgiou, 2006; Mauri, 2008).

Um aspecto relevante de ser destacado em relação a condução dessas análises é a potencial influência das distribuições de probabilidades iniciais no resultado final (Jonas, 2013). Dado este potencial risco de desvio sistemático dos resultados, o NICE ("*National Institute for Health Care Excellence*") recomenda que os autores utilizem distribuições prévias não-informativas, de modo a garantir a não interferência do autor no resultado final da análise (Dias, 2011).

Outra importante peculiaridade das metanálises em rede que deve ser destacada é a avaliação da inconsistência, também denominada "variação entre comparações" (em contraposição com a definição de heterogeneidade – "variação intra comparação"). O conceito de inconsistência deriva do fato de que, dentro das "alças fechadas" de uma rede (do inglês "*closed loops*"), a inferência em relação à estimativa de um dado efeito é derivada de dois componentes distintos: comparações diretas e comparações indiretas. Entende-se por inconsistência a discordância entre a informação proveniente da inferência direta em relação à indireta acerca da mesma comparação "*pairwise*". (Dias, 2010; Valkenhoef, 2015). Para fins da avaliação da inconsistência nesta tese, será utilizado o método conhecido como "*split node*" para redes complexas (definidas como: presença de pelo menos uma alça fechada composta por mais de 4 braços ou mais de uma alça fechada) e o método de Bucher para redes simples (Bucher, 1997). A lógica que subjaz a aplicação do método "*split node*" é bastante complexa e consiste na comparação do ajuste de um modelo que assume a

existência de consistência em toda a rede em relação ao ajuste de um outro modelo que relaxa esse pressuposto. Para cada comparação "*pairwise*" da rede em que houver a combinação de evidência direta e indireta, o método "*split node*" gera um valor de probabilidade cuja hipótese nula é a não existência de diferença entre os modelos (Valkenhoef, 2015).

3.7. JUSTIFICATIVA

Refinar a inferência que existe acerca da evidência científica que suporta a tomada de decisão em relação ao tratamento adjuvante e neoadjuvante dos tumores de mama HER2 positivos constitui questão primordial no cenário da oncologia atual. Isto se deve ao fato de que existem hoje diversas opções terepêuticas comprovadamente eficazes, porém custosas e não livres de parefeitos, para estes tumores que são frequentes na população e que apresentam comportamento biológico agressivo.

Atualmente, verifica-se uma ampla gama de ensaios clínicos randomizados que combinam diferentes regimes de quimioterapia com diferentes doses de trastuzumabe. Além disso, outros inibidores da via HER2, tais como lapatinibe, pertuzumabe e neratinibe, também tomam parte nesta rede de evidências, demonstrando a eficácia do bloqueio duplo quando comparado a esquemas com inibição simples da via HER2. Dentro de um cenário hipotético ideal, deveriam ser conduzidas comparações diretas entre todas as estratégias, porém é clara a não factibilidade desta hipótese, posto que o número de comparações possíveis aumenta em proporção quadrática com o número de estratégias de tratamento.

A partir dessa premissa, faz-se necessário lançar mão de métodos de sumarização de evidências para se chegar a uma inferência válida em relação a escolha do regime de tratamento sistêmico que deverá ser oferecido às pacientes. Infelizmente, o método clássico de sumarização de evidência baseado nas metanálises "*pairwise*" não é capaz de abarcar a complexidade dessa rede de estudos. Em contrapartida, metodologias mais abrangentes, como, por exemplo, o modelo de metanálise em rede baseado em MTC ("*Mixed Treatment Comparison*") conseguem lidar com esses distintos braços de tratamento em um modelo matemático único, gerando resultados com empregabilidade clínica direta, uma vez que os tratamentos são ranqueados, demonstrando qual tratamento apresenta melhor desempenho para os diferentes desfechos testados. Isso posto, é possível que a aplicação desse modelo nos permita refinar a inferência acerca da evidência existente em relação a esta situação clínica específica, de modo a melhor embasar o processo de tomada de decisão por parte do médico, tendo por foco o benefício do último e mais importante elo desta cadeia: a paciente com câncer de mama.

4. OBJETIVOS

Objetivo Geral

Avaliar a eficácia e a segurança dos inibidores da via HER2 nos cenários adjuvante e neoadjuvante empregando o método de metanálise em rede baseado em estatística Bayesiana MTC ("*Mixed Treatment Comparison*") na rede de evidências composta pelos ensaios clínicos randomizados acerca deste tema.

Objetivos Específicos

Estabelecer redes específicas para cada desfecho de interesse a fim de ranquear os diferentes braços de tratamento e refinar a inferência a respeito da decisão terapêutica nos seguintes desfechos de interesse:

- Sobrevida global
- Sobrevida livre de doença
- Resposta patológica completa
- Cardiotoxicidade
- Toxicidades graus 3 e 4

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6. ARTIGO 1

A ser enviado ao JAMA Oncology

Eficácia e Segurança dos Agentes Anti-HER2 em combinação com quimioterapia adjuvante e neoadjuvante em pacientes com câncer de mama inicial e localmente avançado: uma metanálise em rede

Efficacy and Safety of anti-HER2 Agents in combination with adjuvant or neoadjuvant chemotherapy for early and locally advanced breast câncer: a network Meta-analysis.

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ABSTRACT

Background

Neoadjuvant and adjuvant treatment of HER2-positive breast cancer is a rapidly evolving field in oncology with many treatment strategies being compared in a variety of clinical trials. Since it is not feasible to have adequate pairwise comparison of all these therapeutic options, network meta-analysis offers on opportunity for more detailed inference regarding efficacy and toxicity in this setting.

Methods

Phase II or III randomized clinical trials comparing different strategies of inhibiting the HER2-pathway were included. Treatment effects were pooled as HRs for time-to-event outcomes (OS and DFS) and as RRs for dichotomous outcomes (cardiotoxicity). A network meta-analysis was carried out using the Bayesian framework to rank these schedules considering their efficacy and toxicity.

Results

Systematic review of the literature retrieved 1553 unique references, with 33 studies meeting the eligibility criteria. Different networks were composed by different trials according to the availability of the outcome: OS network (12 trials and 27,277pts); DFS network (14 trials and 30,219pts); cardiotoxicity network (21 trials and 29,555pts). In terms of OS, chemotherapy plus trastuzumab and lapatinib for 12 months proved to be the best option (HR 0.78; 95% credibility interval 0.61-0.99, when compared to chemotherapy plus trastuzumab for 12 months, the standard treatment). DFS network reinforced this finding and showed that extended HER2-blokcade with neratinib is a promising option. Cardiotoxicity data evidences that the combination of lapatinib with trastuzumab is safe, but the safest regimens are those

in which pegylated doxorubicin is used instead of regular anthacyclines (RR 0.17; 95% credibility interval 0.06-0.44, when compared to chemotherapy plus trastuzumab for 12 months).

Conclusions

This review suggests that combining chemotherapy plus lapatinib is probably the best treatment option in the neoadjuvant and adjuvant setting for HER2-positive breast cancer patients. However, the results of the trials evaluating the combination of trastuzumab plus pertuzumab are being expected.

INTRODUCTION

Breast cancer is the most common malignancy among women worldwide: each year there are approximately1.68 million new cases and 522,000 deaths (1). Roughly 15 to 25% of breast cancers are classified as HER2-positive, a subgroup of tumors with a more aggressive clinical phenotype and worse prognosis due to unregulated cell growth and abnormal survival mediated by the overexpression of the HER2 protein (2)(3)(4)(5)(6)(7)(8).

Currently for HER2-positive breast cancer, there are multiple therapies with demonstrated efficacy that inhibit the HER2 pathway at different critical checkpoints. Since the approval of the first HER2-targeted therapy, trastuzumab, in 2005, other anti-HER2 targeted agents have been developed and tested in the clinical setting including lapatinib, pertuzumab, neratinib and most recently TDM1. Of all these options, trastuzumab is the primary HER2 therapy for treatment of HER2-

positive breast cancer in the neoadjvuant and adjvuant setting achieving 4-year overall survival around 90% (9)(10). Despite the fact that trastuzumab is very efficacious for HER2-positive breast cancers, recurrences do occur and present a clinical challenge since many tumors exhibit *de novo* resistance or can quickly acquire resistance to trastuzumab therapy (11)(12)(13)(14)(15)(16)(17). To overcome trastuzumab resistance, trastuzumab has been combined with different chemotherapies and other HER2-targeted agents, known as dual blockade of the HER2 pathway, in clinical trials for neoadjuvant and adjvuant treatment of breast cancer. Unfortunately, it is not feasible to have adequate pairwise comparative data for all these treatment options because the number of possible head-to-head comparisons directly expands in a quadratic proportion with the number of treatment options (18).

Mixed treatment comparison (MTC) is a generalization of classical meta-analysis that combines direct and indirect evidence to compare multiple treatment arms across studies with the proviso that there is at least one linking-arm between them (18)(19)(20). Although the classical pairwise meta-analysis is currently the highest possible level of source evidence due to its robustness and narrow focus on the main outcome, MTC offers the opportunity for a more detailed inference as this method extends beyond the standard and critical meta-analysis constraint of only incorporating information from direct randomized comparisons. Within the current context of personalized medicine, in which physicians must base their decisions on the highest level of available evidence in order to face the challenge of selecting the best regimen to treat their patients, the present review aims to rank the efficacy and

toxicity (in terms of overall survival, disease-free survival and cardiotoxicity) of the regimens used to treat patients with early and locally advanced breast cancer.

METHODS

Search Strategy

We searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials without any restriction of language or year of publication. Different search algorithms were used for each database. Detailed search strategies are described in the appendix 1. In order not to miss recent neoadjuvant and adjuvant trials, we also conducted electronic search at the main international congress proceedings: American Society of Clinical Oncology (ASCO), San Antonio Breast Cancer Symposium (SABCS), European Society for Medical Oncology (ESMO), and St. Gallen International Breast Cancer Conference. Additionally, other relevant trials were sought by reviewing the references lists of the selected trials.

Selection Criteria

The prespecified eligibility criteria for trials entering in this review were as follows: phase II or III randomized controlled trials that compared chemotherapy plus any anti-HER2 therapy with chemotherapy alone or any different combination of chemotherapy plus any anti-HER2 therapy in the adjuvant or neoadjuvant settings. Trials with three or more treatment arms and including patients with node positive

and/or negative disease were considered eligible for this review. Excluding criteria for trials were: investigation of anti-HER2 targeted therapy in the metastatic setting.

Data Extraction

Two independent authors (PF and CA) extracted data regarding year of publication, industry sponsor, sample size, baseline patients' characteristics (median age, hormonal receptor status, node status, etc) and outcomes (hazard ratios for overall survival and disease-free survival and the percentage of patients who developed cardiotoxicity). The Cochrane Collaboration risk of bias tool was used to assess studies' quality (21). A third reviewer (MD) adjudicated cases of discordance between the first two reviewers. When studies have more than one report, the original report was used as a reference for methodological and baseline data, while the relevant outcomes were sought in the most recent and complete publication.

Definition of Outcomes

For the purpose of this review, the primary outcome is overall survival. It was defined regularly among studies as the time from randomization until death, using intention to treat analysis. Disease-free survival was defined as time from randomization to death or any disease-free survival event. The definitions of the disease-free survival events varied among the included trials. Table 1 summarizes these definitions. Reports on cardiotoxicity were very heterogeneous, so that we considered the most widely accepted definition of significant left ventricle ejection

fraction (LVEF) decrease, which is an absolute decline of at least 10% from baseline or any decline to a value lower than 50%.

Statistical Methods

Time-to-event outcomes, such as overall survival and disease-free survival, were pooled as hazard ratios, while relative risk was used to pool effect sizes for cardiotoxicity. The Bayesian framework was used to conduct this network meta-analysis in order to combine direct and indirect evidence. Due to different availability of outcomes among the included studies, distinct networks were built for each outcome. In order to check for inconsistencies between direct and indirect evidence within a closed loop, we used the "split node method" or the Bucher method(22)(23). While the Bucher`s method is used to evaluate simple networks, the "split node method" is used to evaluate complex networks. It considers each pairwise comparison as a node composed of direct and indirect evidence. It splits the evidence for a specific node comparing the fit of a model that assumes consistency throughout the network for that particular node with one that relaxes this assumption based on a null hypothesis that consistency is present(22).

Results were summarized as point estimates and 95% credibility intervals (CI). Treatments were ranked for each outcome using the area under the cumulative ranking curve (SUCRA). This analysis yields a probability interval for each arm indicating the likelihood of a given schedule being the best. Hazard ratios were

modeled using the software WinBUGS (version 1.4.3) while relative risks were modeled using the package GEMTC (version 0.7) of the software R (version 3.2.2).

RESULTS

Our electronic search for possible studies to include in this analysis yielded 1553 unique references, of which 70 met the inclusion and exclusion criteria for this review. Twelve trials were included in the overall survival network; 14 trials in the disease-free survival network; and 21 trials in the cardiotoxicity network. Figure 1 summarizes the PRISMA chart of study selection. Table 2 describes all the trials included in at least one network (overall survival, disease-free survival or cardiotoxicity). The risk of bias evaluation of each trial is described in table 3. Inconsistency was not deemed to be an issue in none of the networks.

Overall Survival Network

A total of 12 trials including 27,277 patients were included in this network. Table 4 and figure 2 show the trials included in this network as well as their treatment arms and the direct comparisons between them. Based on the ordered ranks of treatment schedules for overall survival, it is possible to infer that regimens containing chemotherapy associated with trastuzumab and lapatinib are most probably the best treatment options for this outcome (table 5). On the other hand, arms containing chemotherapy without any anti-HER2 targeted therapy or only lapatinib (with no trastuzumab) are probably the worst options.

All hazard ratios and their 95% credibility intervals (CI) for this network are shown in table 6. This analysis shows that up to six months of trastuzumab is inferior to12 months of trastuzumab (HR 1.35 95% CI: 1.01-1.81) and that schedules containing only taxanes plus trastuzumab are superior to chemotherapy alone (HR 0.68 95% CI: 0.50-0.93). This is particularly relevant since more than 95% of patients included in the "any chemo" arms of this review did receive a chemotherapy regimen that contained an anthracycline. The combination of chemotherapy plus 12 months of trastuzumab and 12 months of lapatinib showed to be superior with significant benefit compared to chemotherapy alone, chemotherapy plus 6 months of trastuzumab, chemotherapy plus 12 months of trastuzumab and had benefit compared to the chemotherapy plus lapatinib arms, but this regimen was not significant in relation to a taxane plus 12 months of trastuzumab or dose-dense doxorubicin, cyclophosphamide and paclitaxel (dd-ACT) plus 12 months of trastuzumab. The use of chemotherapy plus 3 months of trastuzumab and 9 months of lapatinib is also promising compared to chemotherapy alone, chemotherapy with trastuzumab for $\leq$6 months and any chemotherapy with 12 months of lapatinib; which is surprising considering the short duration of both trastuzumab and lapatinib in this arm. However, the magnitude of the benefit is smaller when compared to chemotherapy plus 12 months of trastuzumab and 12 months of lapatinib. The use of dose-dense chemotherapy plus 12 months of trastuzumab seems promising with favorable HRs compared to the other treatment options, but were not significant likely due to the lack of large trials including dd-ACT plus trastuzumab (dd-ACTH) in study.

Disease-free Survival Network

This network accounts for 14 trials and 30,219 patients. The design and the trials included in this network are summarized in table 7 and figure 3. This network differs from the overall survival network because the EXTENET(24) trial and the Shaughnessy(25) trial only reported disease-free survival results. Dual blockage of the HER2-pathway are the best ranked treatment options. Neratinib plus trastuzumab seems to be better than lapatinib with trastuzumab, but this difference is not yet significant (HR 0.81; 95%CI 0.57-1.14). These results must be confirmed with longer follow up and overall survival data. Trastuzumab plus dose-dense chemotherapy is a promising well-ranked option, but a careful examination of the hazard ratios shows that the results are quite unstable with important variation due to small number of patients studied (table 8 and table 9). As it was observed in the overall survival network, arms containing chemotherapy without any anti-HER2 targeted therapy or only lapatinib are probably the worst options and up to six months of trastuzumab is inferior to 12 months.

Another important finding is that taxane plus 12 months of trastuzumab revealed to be inferior to chemo plus lapatinib and trastuzumab (HR 0.74; 95% CI 0.57-0.97). In the overall survival network, this comparison yielded a very similar result, but it was not significant (HR 0.72; 0.48-1.06), probably due to smaller magnitude of effects in overall survival and higher number of patients included in the disease-free survival network.

Cardiotoxicity Network

This network consists of 21 trials accounting for 29,555 patients. Table 10 and figure 4 summarize this network. Ordered ranks for cardiotoxicity and all relative risks among treatment arms are presented in tables 11 and 12. The most cardiotoxic arms are those with dual blockage consisting of trastuzumab plus pertuzumab or neratinib. The combination of lapatinib and trastuzumab does not seem to increase cardiotoxicity. Subcutaneous trastuzumab given for 12 months concomitantly with anthracyclines is considered a cardiotoxic regimen ranking among the most toxic ones.

Twelve months of intravenous trastuzumab did not prove to be significantly more cardiotoxic than six months as well as its use concomitant with anthracyline. On the other hand, the use of pegylated doxorubicin with trastuzumab showed to be the safest regimen.

DISCUSSION

It is well established that chemotherapy plus trastuzumab is the backbone for the adjuvant and neoadjuvant treatment of the HER2-positive early and locally advanced breast cancer. This statement is based on a solid body of evidence that comes from several randomized clinical trials. A Cochrane review showed its benefits in terms of overall survival (HR 0.66; 95% confidence interval 0.57-0.77) and disease-free survival (HR 0.60; 95% confidence interval 0.50-0.70) (26). However, there

uncertainties remain, such as the optimal chemotherapy regimen that should be administered with trastuzumab and the length of trastuzumab therapy. Additionally, different strategies to inhibit the HER2-pathway, such as pertuzumab and lapatinib, have already been tested creating multiple possible comparisons, which cannot be assessed by classical meta-analysis methodology. The present review is the first one to model hazard ratios for time-to-event outcomes (overall survival and disease-free survival) and relative risks for dichotomous outcomes (cardiotoxicity) in a unique mathematical model (Mixed Comparison Treatment network meta-analysis – MTC).

The analysis of the network for overall survival showed that regimens containing chemotherapy plus trastuzumab and lapatinib are probably the best treatment options in this scenario. When compared to the gold standard treatment (chemotherapy plus trastuzumab for 12 months), the dual blockage with lapatinib was superior (HR 0.78; 95% CI 0.61-0.99). This finding is somehow unexpected after the negative overall survival results of the ALTTO trial. However, one should note that sample size for this trial was calculated for disease-free survival, which might have underpowered the study for overall survival. Beyond that, the threshold of significance was adjusted for the multiple comparisons in the trial which might have inserted a conservative bias in the analysis of these findings. In this scenario, the results of the trials evaluating the combination of trastuzumab plus pertuzumab are being expected.

Other important aspects that must be pointed out regarding overall survival are: (1) six months of trastuzumab is inferior to 12 months (HR 1.35; 95% CI 1.01-1.81) and (2) regimens including only taxanes and trastuzumab for 12 months (with no

anthracyclines) are superior to chemotherapy (HR 0.68; 95% credibility interval 0.50-0.93) and no significantly worse than the standard regimen (HR 1.09; 95% CI 0.80-1.47).

The disease-free survival network included two more trials that did not reported OS outcomes adding two more treatment arms in the model: (1) chemotherapy plus 12 months of trastuzumab followed by 12 months of neratinib and (2) chemotherapy with anthracycline, taxane and capecitabine plus 12 months of trastuzumab. This network shows that neratinib is a promising option, but we still have to wait until overall survival results are published.

The cardiotoxicity analysis showed that the most cardiotoxic arms are those containing trastuzumab plus pertuzumab, trastuzumab plus neratinib, or subcutaneous trastuzumab given concomitantly with anthracycline. No significant difference was observed between six or 12 months of trastuzumab, neither between its administration concomitant with anthracycline or sequential. The most striking result in this network is that the use of pegylated doxorubicin is the most safe regimen in terms of cardiotoxicity.

Putting this all together, it is clear that chemotherapy with anthracycline plus taxane associated with 12 months of trastuzumab is still the standard treatment for HER2-positive early and locally advanced breast cancer. Despite the lack of evidence of clear harm with the concomitant administration of trastuzumab and anthracycline, its use is not advisable, since there it is not expected to be of any benefit and has a

potential for toxicity. The combination of trastuzumab plus lapanib showed to be superior to other regiments (including the standard one) in terms of overall survival when all the evidence is analyzed together in a unique mathematical model. The ALTTO trial was considered negative, but the point estimate showed some benefit and, as discussed before, there might be some conservative bias in the analysis of the results. It is possible that a smaller benefit could be noticed only in the light of all evidence (direct and indirect). Considering the side effects expected with the addition of lapatinib (such as diarrhea), it is still premature to recommend dual blockage with trastuzumab plus lapatinib based on this analyses, but it seems that this sort of strategy is promising. The overall survival results of the trials studying trastuzumab plus pertuzumab and trastuzumab plus neratinib are expected in the near future and may help to support whether there is a clinical benefit long-term to dual HER2-blockage in women with curable HER2-positive breast cancer. In patients with a high risk for cardiotoxicity, chemotherapy regimens that omit an anthracycline or include pegylated doxorubicin is advisable. The efficacy of pegylated doxorubicin should be more investigated, since it proved to be a very safe drug in terms of cardiotoxicity.

TABLES AND FIGURES

Table 1: definition of disease-free events

	Local Recurrence	Regional Recurrence	Distant Metastases	Contralateral breast cancer	Other Second Primary Cancer	Death	No information
ALTTO							X
ExteNET							X
BCIRG006	X	X	X	X*	X	X	
FINHER	X	X	X	X*		X	
FINXX	X	X	X			X	
GEPARDQUATRO	X	X	X	X*	X	X	
GIM2	X	X	X	X*	X	X	
HANNAH	X	X	X	X	X	X	
HERA	X	X	X	X**	X***	X	
MAVROUDIS	X	X	X	X	X	X	
NEOALTTO	X	X	X	X	X	X	
NOAH	X	X	X	X		X	
NSABPB31_NCCTGN9831	X	X	X	X	X	X	

PACS	X	X	X	X		X	
PHARE	X	X	X	X	X	X	
PREFHER	X	X	X	X		X	
SHAUGHNESSY	X	X	X	X	X	X	
TEACH	X	X	X	X	X****	X	

* Invasive disease only
** Includes DCIS but not LCIS
*** Excludes basal-cell or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix
**** Excludes carcinoma of the skin, melanoma in situ or carcinoma in situ of the cervix

Figure 1: adapted PRISMA flow diagram

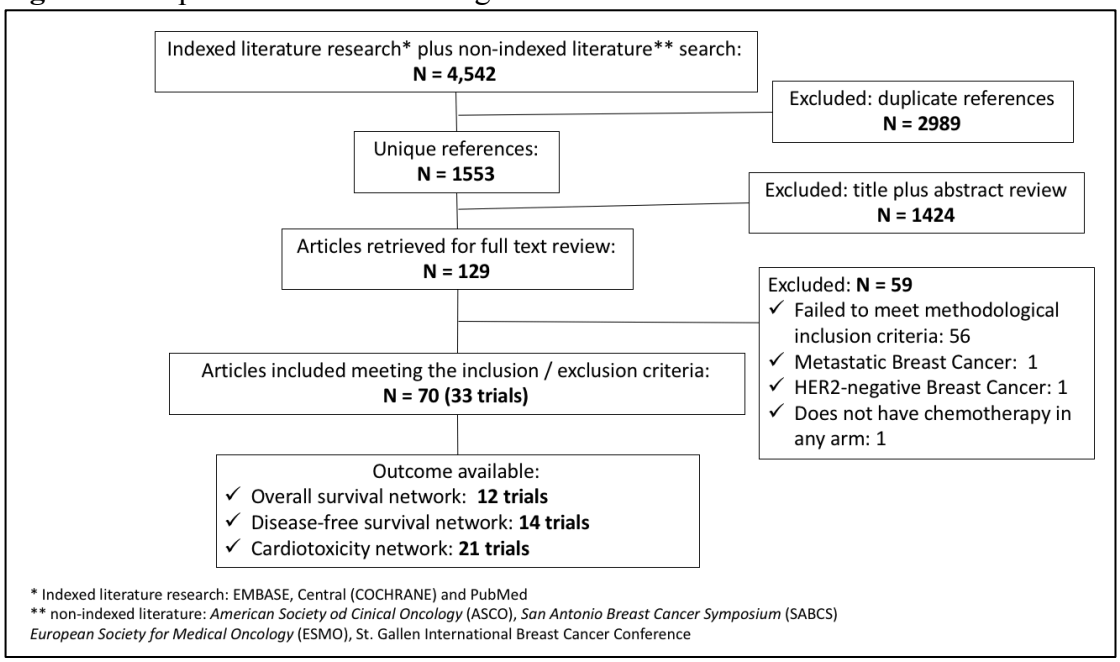


Table 2: description of the trials included in at least on network (overall survival, disease-free survival or cardiotoxicity) – part 1

STUDY	Chemo setting	Industry sponsored	Which industry	Phase	Number of patients	Multicentric	N Countries
ALTTO (27)(28)(29)	Adj*	Yes: fully	GSK	III	8381	Yes	44
BCIRG006 (30)(31)(32)	Adj*	Yes: fully	More than one industry	III	3222	Yes	41
CONSORT (33)	Adj*	Yes: fully	Schering-Plough	II	179	Yes	N/A
EXTENET (24)	Adj*	Yes: fully	Puma Biotech	III	2840	Yes	40
FINHER (34)(35)	Adj*	Yes: partially	More than one industry	III	232	Yes	N/A
GIM2 (36)	Adj*	Yes: partially	More than one industry	III	130	Yes	1
HERA/BIG01-01 (37)(10)(38)(39)(40)(41)(42)	Adj*	Yes: fully	Roche	III	3401	Yes	39
MAVROUDIS (43)(44)	Adj*	No	----	N/A	481	Yes	1
NCCTG N9831 (45)(46)(47)(48)(49)(50)(51)	Adj*	Yes: partially	Genentech	III	2184	N/A	N/A
NSABP B31 (46)(47)(50)(51)(52)(53)	Adj*	Yes: partially	Genentech	III	1736	N/A	N/A
PACS (54)	Adj*	Yes: partially	Roche	III	528	Yes	2

PHARE (55)(56)	Adj*	No	----	III	3380	Yes	1
SHAUGHNESSY (25)(57)	Adj*	Yes: fully	Roche	III	102	Yes	N/A
TEACH (58)(59)	Adj*	Yes: fully	GSK	III	3147	Yes	33
ABCSG-24 (60)(61)	Neo**	Yes: partially	More than one industry	III	93	Yes	1
ACOZOG-Z1041	Neo**	No	-----	III	280	yes	2
BUZDAR (62)(63)	Neo**	Yes: partially	Genentech	III	42	No	1
CHERLOB (64)	Neo**	Yes: fully	GSK	II	121	Yes	N/A
GEICAM2006-14 (65)(66)	Neo**	Yes: partially	GSK	II	102	Yes	1
GEPARQUINTO (67)(68)(69)	Neo**	Yes: partially	More than one industry	III	615	Yes	2
HANNAH (70)(71)	Neo**	Yes: partially	Roche	III	596	Yes	27
NEOALTO (72)(73)(74)(75)	Neo**	Yes: fully	GSK	III	455	1	23
NEOSPHERE (76)(77)	Neo**	Yes: fully	Roche	II	417	Yes	16
NOAH (78)(79)(80)	Neo**	Yes: fully	Roche	III	235	Yes	6
NSABPB41 (81)	Neo**	Yes: fully	GSK	III	523	Yes	3
TRYPHAENA (82)(83)	Neo**	Yes: fully	Roche	II	225	Yes	19

Table 2: description of the trials included in at least on network (overall survival, disease-free survival or cardiotoxicity) – part 2

STUDY	Year published	Median age (yr)	Node status	Minimum tumor size (mm)*	N (%) node negative	N (%) pre menopausal	N (%) hormone negative
ALTTO (27)(28)(29)	2015	51	Node + and -	10	3012 (40.0%)	3636 (43.0%)	3576 (42.7%)
BCIRG006 (30)(31)(32)	2011	N/A	Node + and -	N/A	922 (28.62%)	N/A	N/A
CONSORT (33)	2011	51.35	Node + and -	10	72 (40.0%)	N/A	77 (43.0%)
EXTENET (24)	2015	52	Node + and -	N/A	671 (23.0%)	1327 (47.0%)	1209 (42.0%)
FINHER (34)(35)	2011	50.65	Node + and -	20	37 (15.95%)	N/A	120 (51.72%)
GIM2 (36)	2015	N/A	Node +	------	0 (0.0%)	N/A	N/A
HERA/BIG01-01 (37)(10)(38)(39)(40)(41)(42)	2005	49	Node + and -	10	1099 (32.3%)	491 (14.4%)	1686 (49.6%)
MAVROUDIS (43)(44)	2015	55	Node + and -	N/A	101 (21.0%)	183 (38.0%)	159 (33.0%)
NCCTG N9831 (45)(46)(47)(48)(49)(50)(51)	2005	N/A	Node + and -	10	284 (13.0%)	N/A	1062 (48.63%)
NSABP B31 (46)(47)(50)(51)(52)(53)	2005	N/A	Node +	------	0 (0.0%)	N/A	987 (46.98%)
PACS (54)	2009	48	Node +	------	0 (0.0%)	226 (42.8%)	213 (40.34%)
PHARE (55) (56)	2013	54.5	Node + and -	N/A	1842 (54.5%)	N/A	1319 (39.02%)
SHAUGHNESSY (25)(57)	2015	N/A	Node + and -	10	N/A	N/A	N/A
TEACH (58)(59)	2013	51.5	Node + and -	N/A	1386 (44.04%)	1021 (32.44%)	1288 (40.93%)
ABCSG-24 (60)(61)	2013	49	Node + and -	N/A	44 (47.31%)	53 (56.98%)	36 (38.71%)
ACOZOG-Z1041	2013	N/A	Node + and -	20	101 (36.07%)	N/A	112 (40%)
BUZDAR (62)(63)	2005	50	Node + and -	20	17 (40.48%)	N/A	18 (42.86%)
CHERLOB (64)	2012	49.3	Node + and -	20	N/A	51 (42.15%)	48 (39.67%)
GEICAM2006-14 (65)(66)	2014	48	Node + and -	N/A	32 (31.0%)	57 (56.0%)	43 (42.0%)

GEPARQUINTO (67)(68)(69)	2011	50	Node + and -	10	186 (30.24%)	N/A	274 (44.55%)
HANNAH (70)(71)	2012	50	Node + and -	10	121 (23.0%)	N/A	257 (49.0%)
NEOALTO (72)(73)(74)(75)	2012	4966	Node + and -	20	N/A	N/A	223 (49.01%)
NEOSPHERE (76)(77)	2012	495	Node + and -	20	123 (29.5%)	N/A	219 (52.52%)
NOAH (78)(79)(80)	2010	N/A	Node + and -	50	35 (14.89%)	N/A	151 (64.25%)
NSABPB41 (81)	2013	N/A	Node + and -	20	261 (49.0%)	N/A	198 (37.0%)
TRYPHAENA	2013	49	Node + and -	20	68 (30.0%)	N/A	111 (49.0%)

Table 3: risk of bias evaluation of all trials that were included in at least on network (overall survival, disease-free survival or cardiotoxicity)

STUDY	RISK OF BIAS EVALUATION DOMINIUM (21)				
	Allocation sequence	Allocation conceal	Blinding	Incomplete outcome	Selective Reporting
ABCSG-24	Low risk	Unclear	High risk	Low risk	Low risk
ALTTO	Unclear	Unclear	High risk	Unclear	Unclear
BCIRG006	Unclear	Unclear	High risk	Low risk	Low risk
BUZDAR	Unclear	Unclear	High risk	Low risk	Low risk
CHERLOB	Low risk	Low risk	High risk	Low risk	Low risk
CONSORT	Low risk	Low risk	High risk	Low risk	High risk
EXTENET	Unclear	Unclear	Unclear	Unclear	Unclear
FINHER	Low risk	Low risk	High risk	Low risk	Low risk
GEICAM2006-14	Unclear	Low risk	High risk	Low risk	Low risk
GEPARQUINTO	Low risk	Low risk	High risk	Low risk	Low risk
GIM2	Low risk	Low risk	High risk	Low risk	Low risk
HANNAH	Unclear	Low risk	High risk	Low risk	Low risk
HERA/BIG01-01	Unclear	Unclear	High risk	Low risk	Low risk
MAVROUDIS	Low risk	Low risk	High risk	Low risk	Low risk
NCCTG N9831	Unclear	Unclear	High risk	Low risk	Low risk
NEOALTO	Low risk	Low risk	High risk	Low risk	Low risk
NEOSPHERE	Low risk	Low risk	High risk	Low risk	Low risk
NOAH	Low risk	Low risk	High risk	Low risk	Low risk
NSABP B31	Unclear	Unclear	High risk	Low risk	Low risk
NSABPB41	Low risk	Low risk	High risk	Low risk	Low risk
PACS	Unclear	Unclear	High risk	Low risk	Low risk
PHARE	Low risk	Low risk	High risk	Low risk	Low risk
SHAUGHNESSY	Unclear	Low risk	High risk	High risk	Low risk
TEACH	Low risk	Low risk	Low risk	Low risk	Low risk

TRYPHAENA	Unclear	Unclear	High risk	Low risk	Low risk

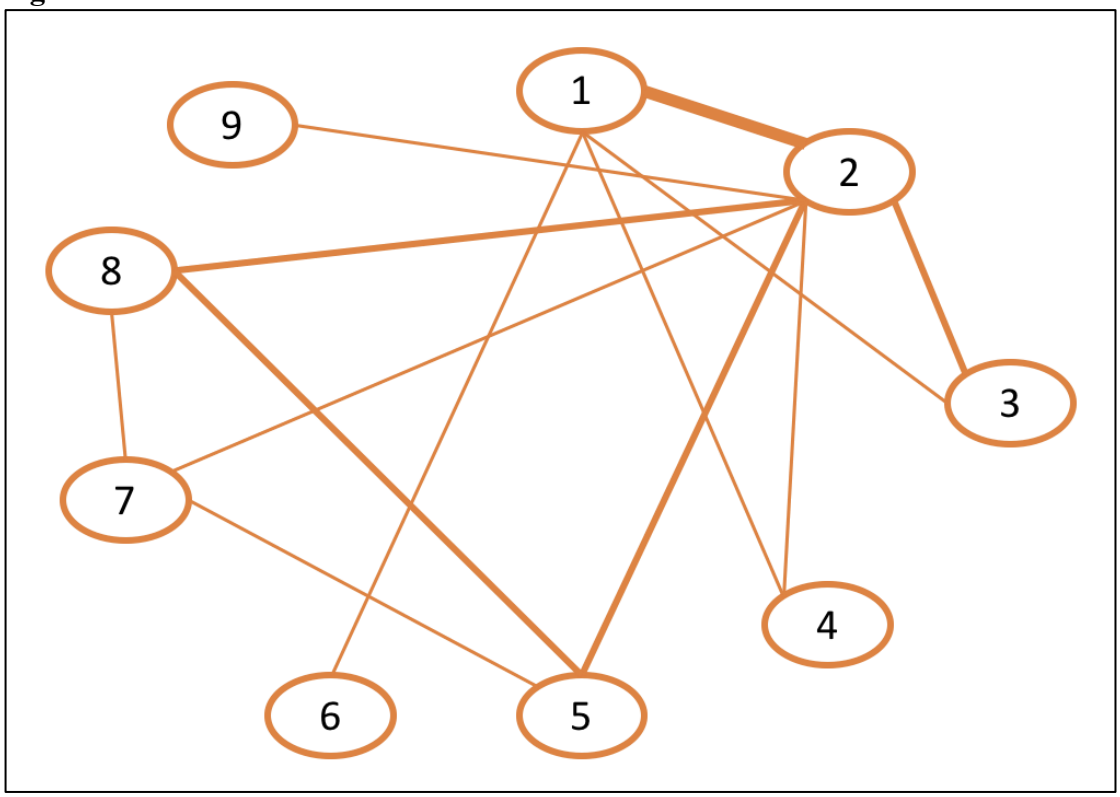
Table 4: network for overall survival

STUDY	COMPARISON	HR	COMPARISON	HR	COMPARISON	HR
BCIRG006	2 vs. 1	0.59 (0.42-0.85)	4 vs. 1	0.66 (0.47-0.93)	----------	--
HERA	2 vs. 1	0.66 (0.47-0.91)	----------	--	----------	--
NSABP_B31 AND NCCTGN9831	2 vs. 1	0.61 (0.50-0.75)	----------	--	----------	--
PACS	2 vs. 1	1.27 (0.68-2.38)	----------	--	----------	--
FINHER	3 vs. 1	0.41 (0.16-1.08)	----------	--	----------	--
TEACH	6 vs. 1	0.99 (0.74-1.31)	----------	--	----------	--
PHARE	3 vs. 2	1.46 (1.06-2.01)	----------	--	----------	--
MAVROUDIS	3 vs. 2	1.45 (0.57-3.67)	----------	--	----------	--
ALTTO	5 vs. 2	1.36 (1.09-1.72)	7 vs.2	0.91 (0.71-1.16)	8 vs. 2	0.80 (0.62-1.03)
NEOALTTO	5 vs. 2	0.86 (0.45-1.63)	8 vs. 2	0.62 (0.30-1.25)	----------	--
GIM2	9 vs 2	0.93 (0.35-2.54)	----------	--	----------	--

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo
05. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo

Figure 2: network for overall survival



Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo
05. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo

Table 5: ranking arms for overall survival

	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Arm 7	Arm 8	Arm 9
Rank 1	0.0%	0.44%	0.0%	2.27%	0.0%	0.0%	9.03%	52.35%	35.97%
Rank 2	0.0%	5.06%	0.37%	6.65%	0.0%	0.0%	40.7%	37.47%	9.8%
Rank 3	0.0%	32.80%	1.02%	13.63%	0.40%	0.0%	34.13%	8.62%	9.28%
Rank 4	0.0%	45.80%	4.23%	24.27%	4.74%	0.8%	11.23%	1.58%	7.41%
Rank 5	0.27%	15.33%	13.72%	32.31%	21.01%	3.84%	4.00%	0.48%	9.11%
Rank 6	2.76%	0.57%	27.51%	13.96%	38.36%	10.4%	0.41%	0.0%	5.8%
Rank 7	16.07%	0.0%	29.75%	5.52%	24.65%	18.00%	0.50%	0.0%	6.00%
Rank 8	45.21%	0.0%	13.40%	1.17%	8.12%	28.69%	0.0%	0.0%	3.41%
Rank 9	35.69%	0.0%	10.00%	0.41%	2.71%	38.25%	0.0%	0.0%	13.15%

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo
05. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo

Table 6: HRs for overall survival

1	**0.63** (0.54-0.73)	0.86 (0.62-1.17)	**0.68** (0.50-0.93)	0.81 (0.62-1.06)	0.99 (0.73-1.33)	**0.55** (0.41-0.74)	**0.49** (0.37-0.64)	0.58 (0.22-1.63)
0.63 (0.54-0.73)	**2**	**1.35** (1.01-1.81)	1.09 (0.80-1.47)	**1.29** (1.04-1.60)	**1.57** (1.14-2.17)	0.88 (0.69-1.12)	**0.78** (0.61-0.99)	0.92 (0.34-2.54)
0.86 (0.62-1.17)	**1.35** (1.01-1.81)	**3**	0.80 (0.52-1.21)	0.95 (0.66-1.37)	1.16 (0.76-1.78)	**0.65** (0.45-0.95)	**0.57** (0.40-0.84)	0.68 (0.24-1.94)
0.68 (0.50-0.93)	1.09 (0.80-1.47)	0.80 (0.52-1.21)	**4**	1.19 (0.82-1.73)	1.45 (0.96-2.20)	0.82 (0.55-1.20)	0.72 (0.48-1.06)	0.85 (0.30-2.46)
0.81 (0.62-1.06)	**1.29** (1.04-1.60)	0.95 (0.66-1.37)	1.19 (0.82-1.73)	**5**	1.21 (0.83-1.80)	**0.68** (0.54-0.86)	**0.60** (0.48-0.75)	0.71 (0.26-2.01)
0.99 (0.73-1.33)	**1.57** (1.14-2.17)	1.16 (0.76-1.78)	1.45 (0.96-2.20)	1.21 (0.83-1.80)	**6**	**0.56** (0.37-0.84)	**0.50** (0.32-0.74)	0.59 (0.21-1.71)
0.55 (0.41-0.74)	0.88 (0.69-1.12)	**0.65** (0.45-0.95)	0.82 (0.55-1.20)	**0.68** (0.54-0.86)	**0.56** (0.37-0.84)	**7**	0.88 (0.68-1.13)	1.04 (0.38-2.94)

0.49 (0.37-0.64)	**0.78** (0.61-0.99)	**0.57** (0.40-0.84)	0.72 (0.48-1.06)	**0.60** (0.48-0.75)	**0.50** (0.32-0.74)	0.88 (0.68-1.13)	**8**	1.19 (0.43-3.40)
0.58 (0.22-1.63)	0.92 (0.34-2.54)	0.68 (0.24-1.94)	0.85 (0.30-2.46)	0.71 (0.26-2.01)	0.59 (0.21-1.71)	1.04 (0.38-2.94)	1.19 (0.43-3.40)	**9**

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo
05. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo

Table 7: network for disease-free survival

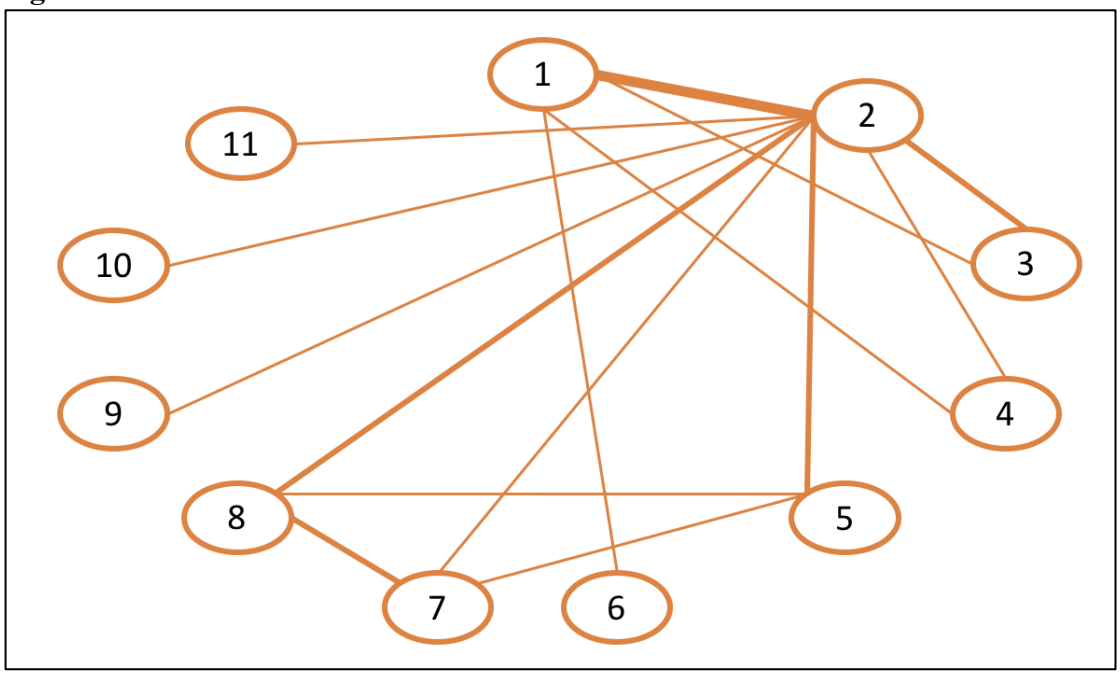
STUDY	COMPARISON	HR	COMPARISON	HR	COMPARISON	HR
BCIRG006	2 vs. 1	0.61 (0.48-0.76)	4 vs. 1	0.67 (0.54-0.83)	----------	--
HERA	2 vs. 1	0.64 (0.54-0.76)	----------	--	----------	--
NSABP_B31 AND NCCTGN9831	2 vs. 1	0.52 (0.45-0.60)	----------	--	----------	--
PACS	2 vs. 1	0.86 (0.61-1.22)	----------	--	----------	--
FINHER	3 vs. 1	0.42 (0.21-0.83)	----------	--	----------	--
TEACH	6 vs. 1	0.83 (0.70-1.00)	----------	--	----------	--
PHARE	3 vs. 2	1.28 (1.05-1.56)	----------	--	----------	--
MAVROUDIS	3 vs. 2	1.58 (0.86-2.10)	----------	--	----------	--
ALTTO	5 vs. 2	1.34 (1.13-1.60)	7 vs.2	0.96 (0.80-1.15)	8 vs. 2	0.84 (0.70-1.02)
NEOALTTO	5 vs. 2	1.06 (0.66-1.65)	8 vs. 2	0.78 (0.47-1.28)	----------	--
GIM2	9 vs 2	0.99 (0.49-1.99)	----------	--	----------	--
EXTENET	10 vs. 2	0.67 (0.50-0.91)	----------	--	----------	--
SHAUGHNESSY	11 vs. 2	1.07 (0.31-3.71)	----------	--	----------	--

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo

05. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANTHRA + TAXANE + CAP / TRASTUZUMAB 12 mo

Figure 3: network for disease-free survival



Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo
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06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANTHRA + TAXANE + CAP / TRASTUZUMAB 12 mo

Table 8: ranking for disease-free survival

	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Arm 7	Arm 8	Arm 9	Arm 10	Arm 11
Rank 1	0.0%	0.0%	0.0%	0.02%	0.0%	0.0%	0.33%	6.03%	12.95%	58.52%	22.16%
Rank 2	0.0%	0.3%	0.0%	0.37%	0.0%	0.0%	4.31%	39.67%	15.03%	30.60%	9.73%
Rank 3	0.0%	6.76%	0.00%	1.93%	0.0%	0.0%	25.47%	38.53%	12.39%	7.97%	6.89%
Rank 4	0.0%	29.15%	0.2%	5.49%	0.03%	0.0%	36.23%	13.28%	8.36%	2.28%	4.97%
Rank 5	0.0%	41.52%	2.55%	16.76%	1.33%	0.16%	21.79%	1.93%	8.56%	0.43%	4.97%
Rank 6	0.0%	20.03%	10.91%	33.71%	7.76%	2.36%	8.99%	0.49%	9.85%	0.17%	5.73%
Rank 7	0.0%	2.25%	25.13%	27.65%	21.33%	7.31%	2.53%	0.07%	7.84%	0.03%	5.85%
Rank 8	0.02%	0.0%	31.00%	9.75%	32.17%	16.73%	0.35%	0.0%	5.97%	0.0%	4.00%
Rank 9	2.11%	0.0%	21.75%	3.60%	26.60%	33.28%	0.0%	0.0%	6.99%	0.0%	5.67%
Rank 10	27.44%	0.0%	8.33%	0.72%	10.65%	38.75%	0.0%	0.0%	6.47%	0.0%	7.64%
Rank 11	70.43%	0.0%	0.13%	0.0%	0.13%	1.39%	0.0%	0.0%	5.60%	0.0%	22.37%

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo
05. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANTHRA + TAXANE + CAP / TRASTUZUMAB 12 mo

Table 9: HRs for disease-free survival

1	**0.53** (0.01-0.64)	**0.61** (0.01-0.75)	**0.54** (0.01-0.65)	**0.63** (0.01-0.76)	**0.69** (0.01-0.83)	**0.45** (0.01-0.55)	**0.39** (0.01-0.49)	**0.27** (0.01-0.58)	**0.28** (0.01-0.39)	**0.17** (0.01-0.62)
0.53 (0.01-0.64)	**2**	**1.27** (1.07-1.51)	1.12 (0.92-1.36)	**1.30** (1.11-1.53)	**1.41** (1.16-1.73)	0.95 (0.80-1.13)	**0.83** (0.70-0.99)	0.99 (0.48-2.01)	**0.67** (0.50-0.91)	1.07 (0.31-3.75)
0.61 (0.01-0.75)	**1.27** (1.07-1.51)	**3**	0.88 (0.68-1.14)	1.02 (0.81-1.29)	1.11 (0.86-1.45)	**0.74** (0.58-0.95)	**0.65** (0.51-0.84)	0.77 (0.37-1.61)	**0.53** (0.38-0.75)	0.84 (0.24-2.96)
0.54 (0.01-0.65)	1.12 (0.92-1.36)	0.88 (0.68-1.14)	**4**	1.16 (0.90-1.49)	1.26 (0.97-1.65)	0.84 (0.65-1.10)	**0.74** (0.57-0.97)	0.87 (0.42-1.84)	**0.60** (0.42-0.86)	0.96 (0.27-3.39)
0.63 (0.01-0.76)	**1.30** (1.11-1.53)	1.02 (0.81-1.29)	1.16 (0.90-1.49)	**5**	1.09 (0.84-1.42)	**0.72** (0.61-0.86)	**0.64** (0.54-0.76)	0.76 (0.37-1.57)	**0.51** (0.37-0.72)	0.83 (0.23-2.94)
0.69 (0.01-0.83)	**1.41** (1.16-1.73)	1.11 (0.86-1.45)	1.26 (0.97-1.65)	1.09 (0.84-1.42)	**6**	**0.67** (0.51-0.87)	**0.59** (0.45-0.77)	0.70 (0.33-1.44)	**0.47** (0.33-0.68)	0.76 (0.21-2.67)
0.45 (0.01-0.55)	0.95 (0.80-1.13)	**0.74** (0.58-0.95)	0.84 (0.65-1.10)	**0.72** (0.61-0.86)	**0.67** (0.51-0.87)	**7**	0.88 (0.73-1.06)	1.05 (0.50-2.17)	0.71 (0.50-1.06)	1.13 (0.32-4.03)

0.39 (0.01-0.49)	**0.83** (0.70-0.99)	**0.65** (0.51-0.84)	**0.74** (0.57-0.97)	**0.64** (0.54-0.76)	**0.59** (0.45-0.77)	0.88 (0.73-1.06)	**8**	1.19 (0.57-2.48)	0.81 (0.57-1.14)	1.28 (0.36-4.62)
0.27 (0.01-0.58)	0.99 (0.48-2.01)	0.77 (0.37-1.61)	0.87 (0.42-1.84)	0.76 (0.37-1.57)	0.70 (0.33-1.44)	1.05 (0.50-2.17)	1.19 (0.57-2.48)	**9**	0.68 (0.32-1.47)	1.09 (0.26-4.52)
0.28 (0.01-0.39)	**0.67** (0.50-0.91)	**0.53** (0.38-0.75)	**0.60** (0.42-0.86)	**0.51** (0.37-0.72)	**0.47** (0.33-0.68)	0.71 (0.50-1.06)	0.81 (0.57-1.14)	0.68 (0.32-1.47)	**10**	0.44 (0.02-1.58)
0.17 (0.01-0.62)	1.07 (0.31-3.75)	0.84 (0.24-2.96)	0.96 (0.27-3.39)	0.83 (0.23-2.94)	0.76 (0.21-2.67)	1.13 (0.32-4.03)	1.28 (0.36-4.62)	1.09 (0.26-4.52)	0.44 (0.02-1.58)	**11**

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo
05. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANTHRA + TAXANE + CAP / TRASTUZUMAB 12 mo

Table 10: network for cardiotoxicity

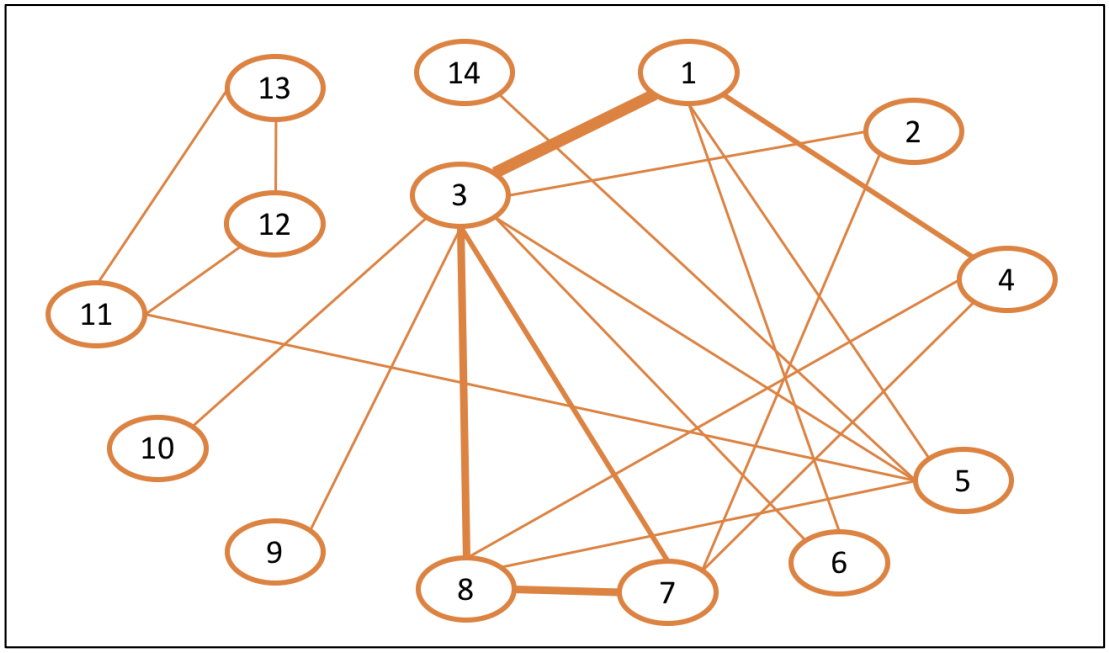
STUDY*	COMPARISON	RR	COMPARISON	RR
BCIRG006	3 vs. 1	1.70 (1.29-2.24)	6 vs. 1	1.18 (0.86-1.61)
HERA/BIG01-01	3 vs. 1	3.42 (2.50-4.67)	--------	--
NCCTG N9831	3 vs. 1	1.61 (1.03-2.51)	--------	--
NSABP B31	3 vs. 1	1.98 (1.65-2.37)	--------	--
PACS	3 vs. 1	2.50 (1.78-3.50)	--------	--
ABCSG-24	4 vs. 1	3.35 (0.36-31.00)	--------	--
BUZDAR	4 vs. 1	1.16 (0.44-3.06)	--------	--
NOAH	5 vs. 1	1.55 (0.93-2.59)	--------	--
PHARE	3 vs. 2	1.33 (1.01-1.79)	--------	--
GEICAM2006-14	7 vs. 2	0.48 (0.04-5.14)	--------	--

ACOSOG_Z1041	5 vs. 3	1.62 (0.99-2.64)	--------	--
ALTTO	7 vs. 3	0.77 (0.67-0.89)	8 vs. 3	1.00 (0.88-1.12)
NEOALTO	7 vs. 3	0.48 (0.03-7.58)	8 vs. 3	0.49 (0.03-7.68)
NSABPB41	8 vs. 3	0.76 (0.47-1.22)	--------	--
CONSORT	9 vs. 3	0.19 (0.07-0.51)	--------	--
EXTENET	10 vs. 3	1.20 (0.61-2.37)	--------	--
CHERLOB	7 vs. 4	0.31 (0.01-7.34)	8 vs. 4	0.26 (0.01-6.26)
GEPARQUINTO	8 vs. 5	0.25 (0.03-2.22)	--------	--
NEOSPHERE	11 vs. 5	1.73 (0.20-14.65)	--------	--
HANNAH	14 vs. 5	1.17 (0.40-3.44)	--------	--
TRYPHAENA	12 vs. 11	0.71 (0.31-1.60)	13 vs. 11	0.49 (0.20-1.19)

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB ≤6 mo (sequential, if anthracycline)
03. ANY CHEMO / TRASTUZUMAB 12 mo (sequential, if anthracycline)
04. ANY CHEMO / TRASTUZUMAB ≤6 mo (concomitant with, if anthracycline)
05. ANY CHEMO / TRASTUZUMAB 12 mo (concomitant with, if anthracycline)
06. TAXANE (no anthracycline)/ TRASTUZUMAB 12 mo
07. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB
08. ANY CHEMO / TRASTUZUMAB / LAPATINIB
09. PLD (peg_lipos_doxo) + TAXANE / TRASTUZUMAB 12 mo (concomitant with PLD)
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (sequential, if anthracycline)
12. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (concomitant, if anthracycline)
13. TAXANE (no athracycline) / TRASTUZUMAB 12 mo / PERTUZUMAB
14. ANTHRA + TAXANE / TRASTUZUMAB SC12 mo (concomitant with Anthracycline)

Figure 4: network for cardiotoxicity



Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB ≤6 mo (sequential, if anthracycline)
03. ANY CHEMO / TRASTUZUMAB 12 mo (sequential, if anthracycline)
04. ANY CHEMO / TRASTUZUMAB ≤6 mo (concomitant with, if anthracycline)
05. ANY CHEMO / TRASTUZUMAB 12 mo (concomitant with, if anthracycline)
06. TAXANE (no anthracycline)/ TRASTUZUMAB 12 mo
07. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB
08. ANY CHEMO / TRASTUZUMAB / LAPATINIB
09. PLD (peg_lipos_doxo) + TAXANE / TRASTUZUMAB 12 mo (concomitant with PLD)
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (sequential, if anthracycline)

12. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (concomitant, if anthracycline)
13. TAXANE (no athracycline) / TRASTUZUMAB 12 mo / PERTUZUMAB
14. ANTHRA + TAXANE / TRASTUZUMAB SC12 mo (concomitant with Anthracycline)

Table 11: ranking for cardiotoxicity

	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Arm 7	Arm 8	Arm 9	Arm 10	Arm 11	Arm 12	Arm 13	Arm 14
Rank 1	0.0%	0.40%	0.80%	4.17%	7.64%	0.0%	0.0%	0.40%	0.0%	14.98%	7.39%	40.48%	0.78%	22.95%
Rank 2	0.0%	1.48%	4.18%	4.56%	17.22%	0.0%	0.0%	2.23%	0.0%	12.59%	25.68%	15.15%	6.13%	10.79%
Rank 3	0.0%	2.91%	10.94%	4.47%	17.43%	0.0%	0.01%	6.33%	0.0%	11.14%	13.31%	6.68%	17.49%	9.01%
Rank 4	0.0%	5.07%	16.85%	5.27%	19.37%	0.0%	0.13%	12.24%	0.50%	12.93%	6.24%	3.83%	6.72%	11.37%
Rank 5	0.0%	9.63%	19.02%	5.32%	19.02%	0.0%	0.97%	17.36%	0.0%	11.13%	3.86%	2.59%	4.05%	7.06%
Rank 6	0.01%	15.17%	20.12%	6.25%	10.12%	0.0%	5.16%	19.66%	0.01%	8.92%	3.19%	2.94%	3.02%	5.46%
Rank 7	0.12%	16.80%	17.90%	6.85%	4.69%	0.11%	12.60%	19.16%	0.01%	6.40%	4.10%	3.87%	2.49%	4.92%
Rank 8	1.55%	18.28%	8.12%	9.68%	2.66%	1.03%	16.54%	15.42%	0.07%	6.95%	5.50%	4.94%	3.60%	5.66%
Rank 9	6.86%	18.36%	1.90%	9.79%	1.40%	4.22%	21.83%	6.25%	0.14%	6.06%	6.88%	5.74%	4.99%	5.58%
Rank 10	9.81%	9.66%	0.18%	12.91%	0.38%	8.86%	27.99%	0.96%	0.29%	4.94%	6.95%	3.24%	7.73%	6.12%
Rank 11	22.38%	2.26%	0.0%	16.35%	0.07%	14.90%	14.78%	0.0%	1.51%	3.12%	5.52%	5.05%	8.72%	5.35%
Rank 12	42.16%	0.01%	0.0%	5.50%	0.0%	30.85%	0.01%	0.0%	1.93%	0.49%	8.08%	3.96%	5.06%	1.94%
Rank 13	16.86%	0.0%	0.0%	8.30%	0.0%	39.04%	0.0%	0.0%	7.06%	0.34%	2.97%	1.13%	20.87%	3.43%
Rank 14	0.26%	0.0%	0.0%	0.58%	0.0%	0.98%	0.0%	0.0%	88.98%	0.02%	0.34%	0.12%	8.36%	0.37%

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB ≤6 mo (sequential, if anthracycline)
03. ANY CHEMO / TRASTUZUMAB 12 mo (sequential, if anthracycline)
04. ANY CHEMO / TRASTUZUMAB ≤6 mo (concomitant with, if anthracycline)
05. ANY CHEMO / TRASTUZUMAB 12 mo (concomitant with, if anthracycline)
06. TAXANE (no anthracycline)/ TRASTUZUMAB 12 mo
07. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB
08. ANY CHEMO / TRASTUZUMAB / LAPATINIB

09. PLD (peg_lipos_doxo) + TAXANE / TRASTUZUMAB 12 mo (concomitant with PLD)
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (sequential, if anthracycline)
12. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (concomitant, if anthracycline)
13. TAXANE (no athracycline) / TRASTUZUMAB 12 mo / PERTUZUMAB
14. ANTHRA + TAXANE / TRASTUZUMAB SC12 mo (concomitant with Anthracycline)

Table 12: RRs (relative risks) for cardiotoxicity

1	**1.80** (1.40-2.30)	**2.00** (1.80-2.30)	1.50 (0.68-2.30)	**2.40** (1.70-3.40)	0.95 (0.75-1.20)	**1.50** (1.30-1.80)	**2.00** (1.70-2.30)	**0.35** (0.11-0.89)	**2.30** (1.1-4.5)	2.30 (0.45-19.00)	3.00 (0.22-14.00)	1.50 (0.22-14.00)	2.40 (0.75-7.50)
1.80 (1.40-2.30)	**2**	1.10 (0.89-1.50)	0.85 (0.36-2.20)	1.30 (0.87-2.10)	**0.53** (0.38-0.74)	**0.86** (0.66-1.10)	1.10 (0.86-1.40)	**0.20** (0.06-0.51)	1.30 (0.62-2.70)	1.30 (0.25-11.00)	1.70 (0.28-16.00)	0.83 (0.12-7.80)	1.30 (0.41-4.30)
2.00 (1.80-2.30)	1.10 (0.89-1.50)	**3**	0.75 (0.33-1.80)	1.20 (0.82-1.70)	**0.47** (0.37-0.58)	**0.75** (0.67-0.85)	0.97 (0.89-1.10)	**0.17** (0.06-0.44)	1.10 (0.57-2.20)	1.10 (0.22-9.30)	1.50 (0.25-14.00)	0.73 (0.11-6.90)	1.20 (0.37-3.70)
1.50 (0.68-2.30)	0.85 (0.36-2.20)	0.75 (0.33-1.80)	**4**	1.60 (0.60-3.80)	0.63 (0.25-1.40)	1.00 (0.41-2.30)	1.30 (0.53-2.90)	**0.23** (0.05-0.79)	1.50 (0.50-4.40)	1.50 (0.24-14.00)	2.00 (0.28-21.00)	0.97 (0.12-11.00)	1.60 (0.37-6.30)
2.40 (1.70-3.40)	1.30 (0.87-2.10)	1.20 (0.82-1.70)	1.60 (0.60-3.80)	**5**	**0.40** (0.26-0.60)	**0.64** (0.44-0.93)	0.83 (0.57-1.20)	**0.15** (0.05-0.40)	0.96 (0.45-2.10)	0.97 (0.20-7.70)	1.30 (0.23-11.00)	0.62 (0.10-5.70)	1.00 (0.33-3.00)
0.95 (0.75-1.20)	**0.53** (0.38-0.74)	**0.47** (0.37-0.58)	0.63 (0.25-1.40)	**0.40** (0.26-0.60)	**6**	**1.60** (1.30-2.10)	**2.10** (1.60-2.60)	**0.37** (0.12-0.95)	**2.40** (1.20-4.90)	2.40 (0.47-20.00)	3.20 (0.54-30.00)	1.50 (0.23-15.00)	2.50 (0.78-7.90)
1.50 (1.30-1.80)	0.86 (0.66-1.10)	**0.75** (0.67-0.85)	1.00 (0.41-2.30)	**0.64** (0.44-0.93)	**1.60** (1.30-2.10)	**7**	0.61 (0.32-1.10)	0.55 (0.27-1.10)	**0.36** (0.22-0.57)	**0.52** (0.33-0.77)	0.61 (0.32-1.10)	0.90 (0.73-1.10)	1.20 (0.26-8.90)
2.00 (1.70-2.30)	1.10 (0.86-1.40)	0.97 (0.89-1.10)	1.30 (0.53-2.90)	0.83 (0.57-1.20)	**2.10** (1.60-2.60)	0.61 (0.32-1.10)	**8**	0.90 (0.60-1.40)	0.59 (0.29-1.20)	0.85 (0.43-1.70)	1.00 (0.78-1.30)	1.50 (0.77-2.90)	1.90 (0.48-14.00)
0.35 (0.11-0.89)	**0.20** (0.06-0.51)	**0.17** (0.06-0.44)	**0.23** (0.05-0.79)	**0.15** (0.05-0.40)	**0.37** (0.12-0.95)	0.55 (0.27-1.10)	0.90 (0.60-1.40)	**9**	0.66 (0.30-1.40)	0.94 (0.45-2.00)	1.10 (0.80-1.50)	1.60 (0.80-3.40)	2.10 (0.50-15.00)
2.30 (1.1-4.5)	1.30 (0.62-2.70)	1.10 (0.57-2.20)	1.50 (0.50-4.40)	0.96 (0.45-2.10)	**2.40** (1.20-4.90)	**0.36** (0.22-0.57)	0.59 (0.29-1.20)	0.66 (0.30-1.40)	**10**	1.40 (0.83-2.50)	1.70 (0.82-3.40)	**2.50** (1.50-4.20)	3.20 (0.69-25.00)
2.30 (0.45-19.00)	1.30 (0.25-11.00)	1.10 (0.22-9.30)	1.50 (0.24-14.00)	0.97 (0.20-7.70)	2.40 (0.47-20.00)	**0.52** (0.33-0.77)	0.85 (0.43-1.70)	0.94 (0.45-2.00)	1.40 (0.83-2.50)	**11**	1.20 (0.59-2.30)	**1.70** (1.10-2.80)	2.20 (0.49-18.00)

3.00 (0.22-14.00)	1.70 (0.28-16.00)	1.50 (0.25-14.00)	2.00 (0.28-21.00)	1.30 (0.23-11.00)	3.20 (0.54-30.00)	0.61 (0.32-1.10)	1.00 (0.78-1.30)	1.10 (0.80-1.50)	1.70 (0.82-3.40)	1.20 (0.59-2.30)	**12**	1.50 (0.79-2.80)	1.90 (0.48-14.00)
1.50 (0.22-14.00)	0.83 (0.12-7.80)	0.73 (0.11-6.90)	0.97 (0.12-11.00)	0.62 (0.10-5.70)	1.50 (0.23-15.00)	0.90 (0.73-1.10)	1.50 (0.77-2.90)	1.60 (0.80-3.40)	**2.50 (1.50-4.20)**	**1.70 (1.10-2.80)**	1.50 (0.79-2.80)	**13**	1.30 (0.28-10.00)
2.40 (0.75-7.50)	1.30 (0.41-4.30)	1.20 (0.37-3.70)	1.60 (0.37-6.30)	1.00 (0.33-3.00)	2.50 (0.78-7.90)	1.20 (0.26-8.90)	1.90 (0.48-14.00)	2.10 (0.50-15.00)	3.20 (0.69-25.00)	2.20 (0.49-18.00)	1.90 (0.48-14.00)	1.30 (0.28-10.00)	**14**

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB ≤6 mo (sequential, if anthracycline)
03. ANY CHEMO / TRASTUZUMAB 12 mo (sequential, if anthracycline)
04. ANY CHEMO / TRASTUZUMAB ≤6 mo (concomitant with, if anthracycline)
05. ANY CHEMO / TRASTUZUMAB 12 mo (concomitant with, if anthracycline)
06. TAXANE (no anthracycline)/ TRASTUZUMAB 12 mo
07. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB
08. ANY CHEMO / TRASTUZUMAB / LAPATINIB
09. PLD (peg_lipos_doxo) + TAXANE / TRASTUZUMAB 12 mo (concomitant with PLD)
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (sequential, if anthracycline)
12. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (concomitant, if anthracycline)
13. TAXANE (no athracycline) / TRASTUZUMAB 12 mo / PERTUZUMAB
14. ANTHRA + TAXANE / TRASTUZUMAB SC12 mo (concomitant with Anthracycline)

APPENDIX 1

Database: MEDLINE (through Pubmed)

Search date: 05/31/2015

PATIENTS (breast cancer**)**

1. Breast cancer **(300.158 papers)**
2. Breast neoplasms **(256.643 papers)**
3. Breast tumor **(274.421 papers)**
4. Breast tumour **(258.742 papers)**
5. (((Breast cancer) OR breast neoplasms) OR breast tumor) OR breast tumour **(303.383 papers)**

INTERVENTIONS/COMPARISONS (Isolated chemotherapy or chemotherapy associated with any anti-HER2 inhibitor in the adjuvant or neoadjuvant settings**)**

6. Adjuvant treatment **(181.541 papers)**
7. Adjuvant therapy **(164.203 papers)**
8. Adjuvant chemotherapy **(54.907 papers)**
9. Neoadjuvant treatment **(21.926 papers)**
10. Neoadjuvant therapy **(20.462 papers)**
11. Neoadjuvant chemotherapy **(18.368 papers)**
12. (((((Adjuvant treatment) OR Adjuvant therapy) OR Adjuvant chemotherapy) OR Neoadjuvant treatment) OR Neoadjuvant therapy) OR Neoadjuvant chemotherapy **(195.156 papers)**
13. HER2 pathway inhibitors **(450 papers)**
14. Trastuzumab **(7.002 papers)**
15. Herceptin **(7.370 papers)**
16. Lapatinib **(1.689 papers)**
17. Tykerb **(1.691 papers)**
18. Pertuzumab **(499 papers)**
19. Perjeta **(499 papers)**
20. T-DM1 **(146 papers)**
21. Trastuzumab emtansine **(209 papers)**
22. (((((((HER2 pathway inhibitors) OR trastuzumab) OR herceptin) OR lapatinib) OR tykerb) OR pertuzumab) OR perjeta) OR T-DM1) OR Trastuzumab emtansine **(8.616 papers)**
23. 12 AND 22 **(1.868 papers)**

PATIENTS (breast cancer**) PLUS INTERVENTIONS/COMPARISONS (**Isolated chemotherapy or chemotherapy associated with any anti-HER2 inhibitor in the adjuvant or neoadjuvant settings**)**

24. 5 AND 23 **(1.475 papers)**
25. FILTER: CLINICAL TRIALS **(245 papers)**
26. FILTER: HUMANS **(245 papers)**

Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Database: Cochrane Central Register of Controlled Trials

Search date: 06/01/2015.
http://crso.cochrane.org

PATIENTS (breast cancer**)**

1. Breast cancer **(14.905 papers)**
2. Breast neoplasms **(7.466 papers)**
3. Breast tumor **(256 papers)**

4. Breast tumour **(28 papers)**
5. (((Breast cancer) OR breast neoplasms) OR breast tumor) OR breast tumour **(16.143 papers)**

INTERVENTIONS/COMPARISONS (Isolated chemotherapy or chemotherapy associated with any anti-HER2 inhibitor in the adjuvant or neoadjuvant settings**)**

6. Adjuvant treatment **(1.756 papers)**
7. Adjuvant therapy **(3.432 papers)**
8. Adjuvant chemotherapy **(2.984 papers)**
9. Neoadjuvant treatment **(228 papers)**
10. Neoadjuvant therapy **(802 papers)**
11. Neoadjuvant chemotherapy **(925 papers)**
12. (((((Adjuvant treatment) OR Adjuvant therapy) OR Adjuvant chemotherapy) OR Neoadjuvant treatment) OR Neoadjuvant therapy) OR Neoadjuvant chemotherapy **(8.071 papers)**
13. HER2 pathway inhibitors **(0 papers)**
14. Trastuzumab **(614 papers)**
15. Herceptin **(99 papers)**
16. Lapatinib **(216 papers)**
17. Tykerb **(4 papers)**
18. Pertuzumab **(51 papers)**
19. Perjeta **(0 papers)**
20. T-DM1 **(17 papers)**
21. Trastuzumab emtansine **(21 papers)**
22. (((((((HER2 pathway inhibitors) OR trastuzumab) OR herceptin) OR lapatinib) OR tykerb) OR pertuzumab) OR perjeta) OR T-DM1) OR Trastuzumab emtansine **(756 papers)**
23. 12 AND 22 **(247 papers)**

PATIENTS (breast cancer**) PLUS INTERVENTIONS/COMPARISONS (**Isolated chemotherapy or chemotherapy associated with any anti-HER2 inhibitor in the adjuvant or neoadjuvant settings**)**

24. 5 AND 23 **(243 papers)**

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Database: EMBASE

Search date: 05/31/2015
http://www.embase.com/;jsessionid=522AD678F786F74155F1CCCF6AADA99C#quickSearch/default

PATIENTS (breast cancer**)**

1. Breast cancer **(453.995 papers)**
2. Breast neoplasms **(15.612 papers)**

3. Breast tumor **(227.449 papers)**
4. Breast tumour **(25.209 papers)**
5. (((Breast cancer) OR breast neoplasms) OR breast tumor) OR breast tumour **(456.382 papers)**

INTERVENTIONS/COMPARISONS (Isolated chemotherapy or chemotherapy associated with any anti-HER2 inhibitor in the adjuvant or neoadjuvant settings**)**

6. Adjuvant treatment **(115.282 papers)**
7. Adjuvant therapy **(153.136 papers)**
8. Adjuvant chemotherapy **(82.358 papers)**
9. Neoadjuvant treatment **(23.080 papers)**
10. Neoadjuvant therapy **(26.358 papers)**
11. Neoadjuvant chemotherapy **(22.455 papers)**
12. (((((Adjuvant treatment) OR Adjuvant therapy) OR Adjuvant chemotherapy) OR Neoadjuvant treatment) OR Neoadjuvant therapy) OR Neoadjuvant chemotherapy **(179.500 papers)**
13. HER2 pathway inhibitors **(651 papers)**
14. Trastuzumab **(25.856 papers)**
15. Herceptin **(7.739 papers)**
16. Lapatinib **(8.092 papers)**
17. Tykerb **(1.029 papers)**
18. Pertuzumab **(2.137 papers)**
19. Perjeta **(150 papers)**
20. T-DM1 **(346 papers)**
21. Trastuzumab emtansine **(854 papers)**
22. (((((((HER2 pathway inhibitors) OR trastuzumab) OR herceptin) OR lapatinib) OR tykerb) OR pertuzumab) OR perjeta) OR T-DM1) OR Trastuzumab emtansine **(29.993 papers)**
23. 12 AND 22 **(7.311 papers)**

PATIENTS (breast cancer**) E <u>PLUS</u> INTERVENTIONS/COMPARISONS (**Isolated chemotherapy or chemotherapy associated with any anti-HER2 inhibitor in the adjuvant or neoadjuvant settings**)**

24. 5 AND 23 **(6.488 papers)**
25. Excluding articles from that also appear at MEDLINE **(2.928 papers)**
26. FILTER: CLINICAL TRIALS **(1.229 papers)**
27. FILTER: HUMANS **(1.130 papers)**

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EMBASE + CENTRAL (COCHRANE) + PUBMED: 1614 trials, of which 61 were excluded due to duplicated references, resulting 1553 trials

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7. ARTIGO 2

Resposta Patológica Completa com Agentes anti-HER2 e Quimioterapia Neoadjuvante: uma metanálise em rede.

Complete Pathological Response with anti-HER2 Agents and Neoadjuvant Chemotherapy: a Network Meta-analysis.

Márcio Debiasi, Doutorando em Epidemiologia pela UFRGS;

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL (UFRGS)

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ABSTRACT

Background

The most common malignancy among females, breast cancer is a public health problem worldwide. Approximately 15 to 25% of all breast cancers are classified as HER2-positive, a subgroup of tumors with more aggressive phenotype and worse prognosis. Neoadjuvant treatment with chemotherapy associated with anti-HER2 therapy is a well established strategy for treating these tumors. However, due to the growing number of anti-HER2 agents, the best regimen is not known creating an opportunity to use network meta-analysis in order to derive more detailed inference regarding this issue.

Methods

This analysis included all phase II and III randomized clinical trials that evaluated the probability of achieving complete pathological response (CPR) with the different available neoadjuvant regimens of chemotherapy plus HER2-pathway inhibitors. Treatment effects within each trial were pooled as relative risks (RRs) for the dichotomous outcome CPR and modeled in a network meta-analysis based on the Bayesian framework that aimed to rank these schedules on their efficacy in achieving PCR.

Results

This network was included 17 trials accounting for 4,383 patients. Regimens composed of taxanes plus dual blockage with trastuzumab and lapatinib or pertuzumab proved to be superior to other treatment options. Taxane plus trastuzumab and pertuzumab was superior to the most studied and gold standard regimen of trastuzumab associated with chemotherapy (anthracycline plus taxane) (RR 1.80; 95% CI 1.00-3.30). On the other hand, schedules including only chemotherapy without any anti-HER2 targeted therapy and those including only dual

blockage with trastuzumab plus pertuzumab without chemotherapy are probably the worst options, followed by regimens that include chemo plus an anti-HER2 therapy other than trastuzumab (lapatinib or pertuzumab).

Conclusions

This analysis reiterates the concept of dual blockade of the HER2-pathway. Schedules containing chemotherapy plus trastuzumb and lapatinib or pertuzumab are probably the best options in this scenario.

INTRODUCTION

The most common malignancy among females, breast cancer is a public health problem worldwide, accounting for 1.68 million new cases and 522,000 deaths in 2012 according to the last report sponsored by the World Health Organization (WHO) (1). Approximately 15 to 25% of all breast cancers are classified as HER2-positive. It is a subgroup of tumors with a more aggressive clinical phenotype and worse prognosis due to the overexpression of HER2 receptor which mediates cell growth, proliferation, survival and distant dissemination (2)(3)(4)(5)(6)(7)(8).

The complex biology that drives the replication of HER2-positive breast cancer cells creates opportunities for the development of multiple therapies that target the HER2 pathway at different critical checkpoints. A diversity of regimens combining chemotherapy with different HER2-pathway inhibitors (such as trastuzumab, pertuzumab, lapatinib, etc) have already been tested in the neoadjuvant setting. In the current scenario, in which there are a large number of trials comparing a variety of

combinations of chemotherapy and anti-HER2 targeted therapies, it is impracticable to have adequate pairwise comparative data for all the existing treatment options. This situation occurs because the number of possible head-to-head comparisons gets strikingly high, once it expands in a quadratic proportion with the number of treatment options (9).

The classical method of pairwise meta-analysis is currently deemed to be the highest possible level of source evidence. However, due to its constraint of only incorporating information from direct randomized comparisons, it can not deal with the complexity of the network created by the available evidence on the neoadjuvant treatment of HER2-positive breast cancers. Mixed treatment comparison (MTC) is a generalization of classical meta-analysis. It includes in one mathematical model direct and indirect evidence from multiple treatment arms across studies provided that there is at least one linking-arm between them (9)(10)(11). MTC yields a clinically meaningful result ranking arms according to the probability of each one to be the best one for the considered outcome. The present review aims to rank the efficacy in terms of probability of achieving complete pathological response (CPR) of neoadjuvant regimens used to treat patients with early and locally advanced HER2-positive breast cancer.

METHODS

Search Strategy

MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials were searched without any restriction of language or year of publication. Different search algorithms were used for each database (see appendix 1). Because this report is part of a broader project that included also adjuvant trials, the term adjuvant is part of the search strategy presented in the appendix 1. The main international congress proceedings related to the subject of this review (American Society of Clinical Oncology (ASCO), San Antonio Breast Cancer Symposium (SABCS), European Society for Medical Oncology (ESMO), and St. Gallen International Breast Cancer Conference) were also searched with the view to avoid missing recently reported neoadjuvant trials.

Selection Criteria

For the purpose of this review, a set of prespecified eligibility criteria were defined as follows: phase II or III randomized controlled trials that compared chemotherapy plus any anti-HER2 therapy with chemotherapy alone or any different combination of chemotherapy plus any anti-HER2 therapy in the adjuvant or neoadjuvant settings. As stated before, the eligibility criteria include adjuvant trials because this report is part of a broader project that includes the adjuvant setting. Since this report focus on complete pathological response – an outcome that is only possible in the neoadjuvant trials – all the adjuvant trials retrieved were excluded.

Data Extraction

Two reviewers (PF and CA) independently extracted data regarding year of publication, industry sponsor, sample size, baseline patients` characteristics (median age, hormonal receptor status, node status, etc) and outcomes (number of patients included in each treatment arm and number of patients who achieved CPR). Studies` quality was assessed using The Cochrane Collaboration risk of bias tool (12). A third reviewer (MD) judged all discordances between the first two reviewers. All studies that had more than one report were gathered under a unique study identification. Data were retrieved from the most recent and complete publications.

Definition of Outcomes

The only outcome considered in this report is Complete Pathological Response (CPR). Other relevant outcomes evaluated in this review such as overall survival, disease-free survival and cardiotoxicity are published elsewhere. The definitions of CPR varied across the studies. According to the seventh edition of the American Joint Commettee on Cancer (AJCC), there are five definitions of CPR: (1) yT0 Nx: no invasive nor *in situ* tumor in the breast ignoring the ipsilateral axilla ; (2) yT0/is Nx: no invasive tumor in the breast (in situ tumor is accepted in the breast) ignoring the ipsilateral axilla; (3) yT0 yN0: no invasive nor *in situ* tumor in the breast neither in the ipsilateral axilla; (4) yT0/is yN0: no invasive tumor in the breast (in situ tumor is accepted in the breast) and no invasive nor in situ tumor in the ipsilateral axilla; (5) yT0/is yN0/is: no invasive tumor in the breast and in the axilla (in situ tumor is allowed in both). Table1 summarizes the definitions adopted in each included study.

Statistical Methods

Treatment effects size in terms of probability of achieving CPR were pooled using relative risks (RR). Direct and indirect evidence were modeled in a network meta-analysis using the Bayesian framework. Inconsistency, defined as disagreement between direct and indirect evidence within a closed loop, was assessed by the "split node method". Based on a null hypothesis that consistency is present, this method splits the evidence that compose each pairwise comparison and compares the fit of a model that assumes consistency throughout direct and indirect evidence in the network for that particular node with one that relaxes this assumption (13).

Point estimates and their credibility intervals (CI) were calculated for each comparison in the model. Based on these results, the area under the cumulative ranking curve (SUCRA) was used to rank treatments regimens, with higher ranks meaning higher probability of achieving CPR with a given regimen. Relative risks were modeled using the package GEMTC (version 0.7) of the software R (version 3.2.2).

RESULTS

Literature search

A total of 1553 unique references were retrieved applying the electronic search strategy described in the appendix 1. After reading title and abstract, 1424 references

were excluded. Among the 129 remaining references, 70 meet the inclusion and exclusion criteria for this review. This report is part of a broader review that included also adjuvant trials. For the purpose of evaluating CPR, 17 trials were included in the network. The CONSORT flowchart for study selection is summarized in the figure 1. All trials included in the CPR network are described in the table 2 and their risk of bias evaluation, in table 3.

Complete Pathological Response: network findings

This network is composed by 17 trials accounting for 4,383 patients. The studies included in this network and their respective relative risks are described in table 4. Figure 2 shows the design of the network. All the relative risks yielded by the multiple comparison Bayesian model are summarized in table 5. Based on these data, arms were ranked as shown in table 6. Regimens composed of taxanes plus dual blockage with trastuzumab and lapatinib or pertuzumab are probably the best options in terms of achieving CPR. These schedules compared favorably with most of the other schedules (table 5), but similarly between them (RR 1.10; 95% probability interval 0.70-1.60). Taxane plus trastuzumab and pertuzumab proved to be superior to the most studied and gold standard regimen of trastuzumab associated with chemotherapy (anthracycline plus taxane), increasing in 80% the probability of obtaining CPR (RR 1.80; 95% CI 1.00-3.30). Regimens containing carboplatin plus trastuzumab were well ranked, but one should be cautious when interpreting these findings due to the large variability in the credibility intervals of their point estimates.

On the other hand, schedules including only chemotherapy without any anti-HER2 targeted therapy and those including only dual blockage with trastuzumab plus pertuzumab without chemotherapy are probably the worst options, followed by regimens containing chemotherapy with one inhibitor of the HER2-pathway other than trastuzumab (lapatinib or pertuzumab). Compared to taxane plus trastuzumab and pertuzumab, which is probably the best choice, these treatment options performed poorly showing lower probabilities of achieving CPR: chemotherapy alone (RR 0.32; 95% CI 0.16-0.63); pertuzumab plus trastuzumab with no chemotherapy (RR 0.36; 95% CI 0.22-0.57); taxane plus lapatinib (RR 0.50; 95% CI 0.31-0.77); and taxane plus pertuzumab (RR 0.52; 95% CI 0.33-0.77). Inconsistency was not deemed to be an issue in this network because all closed loops were created within multi-arms trials.

DISCUSSION

Chemotherapy with anthracycline plus taxane associated with trastuzumab is currently deemed to be the gold standard option for the neoadjuvant treatment of HER2-positive early and locally advanced breast cancer (14)(15). In this setting, NCCN guidelines support the concomitant use of pertuzumab(16). In view of the significant increase in the number of trials investigating different anti-HER2 targeted therapies in the last 10 years, a network meta-analysis was carried out and published in 2014 by Nagayama and cols (17). This study included 10 trials accounting for

2,247 patients and identified that dual blocking of the HER2 pathway associated with chemotherapy increased the chance of achieving CPR (OR 2.29; 95% CI 1.02 – 5.02). The present report is also a Bayesian network meta-analysis, but it has some methodological advantages that offers the opportunity for a more detailed inference regarding neoadjuvant treatment of HER2-positive breast cancer: (1) it uses relative risks instead of odds ratios to pool treatments` effects, which is a more adequate outcome to be evaluated in prospective randomized clinical trials; (2) it includes more data (17 studies with 4,383 patients); and (3) it considers treatment arms into a more detailed way exploring the combinations of anti-HER2 targeted therapies with different chemotherapy backbones (anthracyclines, taxanes and carboplatin).

The present review reinforces the concept of dual blockage of the HER2 pathway. Regimens composed of taxanes plus trastuzumab and lapatinib or pertuzumab are probably those in which achieving CPR is more probable. The combination of trastuzumab with pertuzumab seems to be marginally superior to its counterpart with lapatinib, but this difference is not significant (RR 1.10; 95%CI 0.70-1.60). An important aspect of these findings is that adding pertuzumab to trastuzumab may allow clinicians to withhold the use of anthracyclines, because this schedule increased the probability of CPR in 80% when compared to the gold standard regimen of anthracycline plus taxane and trastuzumab (RR 1.80; 95% CI 1.00-3.30).

Despite being well ranked, with point estimates showing benefit for carboplatin-containing regimens plus trastuzumab, they did not prove to be superior to any of the other regimens due to the huge amplitude of their credibility intervals (table 5). For

instance, comparing carboplatin plus taxane and trastuzumab with chemotherapy alone (which is the worst treatment option included in the network) yields an impressive RR of 3.5, but the credibility interval varies from 0.93 to 25.00. Similarly, the comparison of this treatment arm with all other treatment arms in the network show favorable point estimates, but wide credibility intervals that cross the non-significance threshold. This situation emphasizes a caveat when interpreting results of Bayesian network meta-analysis: the rank table must not be taken as a definitive result. The so called rankogram is derived from the relative-risks table using the surface under the cumulative ranking curve (SUCRA). It is a useful tool that helps to guide the reader when looking at the relative-risks among the arms, but it can not be considered by itself.

It is well established that inhibiting the HER2 pathway is mandatory when treating HER2-positive breast cancer and, as expected, the worst strategy in the network was chemotherapy alone. However, the second worst schema was trastuzumab plus pertuzumab without chemotherapy showing that cytotoxic agents still have an important hole in this clinical scenario. Another remarkable insight brought by this analysis is that trastuzumab must be part of the regimen, since the third and forth worst strategies were those combining chemotherapy with pertuzumab or lapatinib without trastuzumab.

It is possible to infer from the judicious evaluation of the present network meta-anaysis that taxanes combined with dual blockage of the HER2-pathway is the best treatment option in terms of achieving PCR. Among the options for dual blockage,

trastuzumab plus pertuzumab seems to be marginally superior to trastuzumab plus lapatinib.

TABLES AND FIGURES

Table 1: definition of Complete Pathological Response

	yT0yNx	yT0/isNx	yT0yN0	yT0/isyN0	yT0/isyN0/is	NO INFORMATION
CALGB40601	X					
JBCRG-10						X
ABCSG-24		X				
ACOSOG_Z1041		X				
BUZDAR					X	
CHERLOB					X	
GEICAM		X				
GEPARDQUATRO		X	X			
GEPARQUINTO			X			
HANNAH		X				
LAPATAX		X				
NAKAMURA					X	
NEOALTTO		X				
NEOSPHERE		X				
NOAH	X		X			
NSABPB41		X				
REMAGUS					X	
TRYAPHAENA		X				
CHANG		x				

Figure 1: adapted PRISMA flow diagram

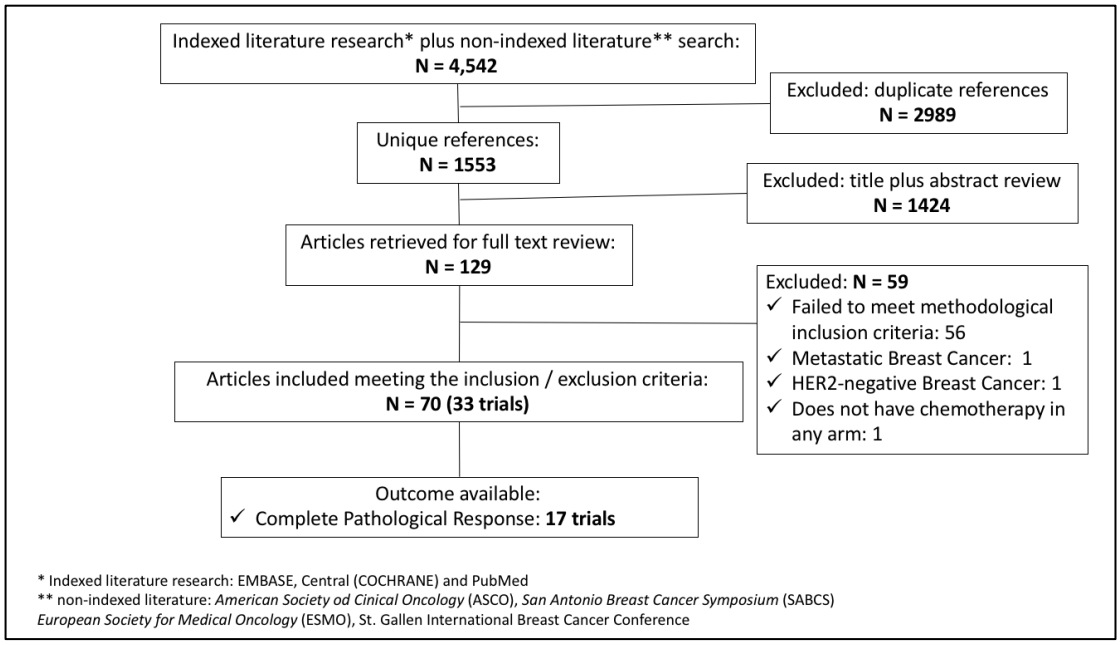


Table 2: description of the trials included in the CPR network – part 1

STUDY	Chemo setting	Industry sponsored	Which industry	Phase	Number of patients	Multicentric	N Countries
ABCSG-24 (18)(19)	Neo	Yes: partially	More than one industry	III	93	Yes	1
BUZDAR (20)(21)	Neo	Yes: partially	Genentech	III	42	No	1
CALGB40601 (22)	Neo	No	------	III	305	Yes	1
CHANG (23)	Neo	Yes: fully	More than one industry	II	30	No	1
CHERLOB (24)	Neo	Yes: fully	GSK	II	121	Yes	N/A
GEICAM2006-14 (25)(26)	Neo	Yes: partially	GSK	II	102	Yes	1
GEPARQUINTO (27)(28)(29)	Neo	Yes: partially	More than one industry	III	615	Yes	2
GEPARSIXTO (30)(31)	Neo	Yes: fully	More than one industry	II	273	Yes	1
HANNAH (32)(33)	Neo	Yes: partially	Roche	III	596	Yes	27
JBCRG-10 (34)(35)	Neo	No	-------	II	103	Yes	1
LAPATAX (36)(37)	Neo	Yes: partially	GSK	II	128	Yes	5
NEOALTO (38)(39)(40)(41)	Neo	Yes: fully	GSK	III	455	1	23
NEOSPHERE (42)(43)	Neo	Yes: fully	Roche	II	417	Yes	16
NOAH (44)(45)(46)	Neo	Yes: fully	Roche	III	235	Yes	6
NSABPB41 (47)	Neo	Yes: fully	GSK	III	523	Yes	3
REMAGUS02 (48)(49)	Neo	Yes: partially	More than one industry	II	120	Yes	1
TRYPHAENA (50)(51)	Neo	Yes: fully	Roche	II	225	Yes	19

Table 2: description of the trials included in the CPR network – part 2

STUDY	Year published	Median age (yr)	Node status	Minimum tumor size (mm)*	N (%) node negative	N (%) pre menopausal	N (%) hormone negative
ABCSG-24 (18)(19)	2013	49	Node + and -	N/A	44 (47.31%)	53 (56.98%)	36 (38.71%)
BUZDAR (20)(21)	2005	50	Node + and -	20	17 (40.48%)	N/A	18 (42.86%)
CALGB40601 (22)	2013	N/A	Node + and -	10	N/A	N/A	N/A
CHANG (23)	2010	N/A	Node + and -	20	N/A	N/A	N/A
CHERLOB (24)	2012	49.3	Node + and -	20	N/A	51 (42.15%)	48 (39.67%)
GEICAM2006-14 (25)(26)	2014	48	Node + and -	N/A	32 (31.0%)	57 (56.0%)	43 (42.0%)
GEPARQUINTO (27)(28)(29)	2011	50	Node + and -	10	186 (30.24%)	N/A	274 (44.55%)
GEPARSIXTO (30)(31)	2014	N/A	Node + and -	10	N/A	N/A	N/A
HANNAH (32)(33)	2012	50	Node + and -	10	121 (23.0%)	N/A	257 (49.0%)
JBCRG-10 (34)(35)	2012	54	Node + and -	N/A	N/A	N/A	N/A
LAPATAX (36)(37)	2014	48.7	Node + and -	20	43 (34.0%)	N/A	60 (47.0)
NEOALTO (38)(39)(40)(41)	2012	4966	Node + and -	20	N/A	N/A	223 (49.01%)
NEOSPHERE (42)(43)	2012	495	Node + and -	20	123 (29.5%)	N/A	219 (52.52%)
NOAH (44)(45)(46)	2010	N/A	Node + and -	50	35 (14.89%)	N/A	151 (64.25%)
NSABPB41 (47)	2013	N/A	Node + and -	20	261 (49.0%)	N/A	198 (37.0%)
REMAGUS02 (48)(49)	2010	47	Node + and -	30	43 (36.0)	N/A	49 (41.0%)
TRYPHAENA (50)(51)	2013	49	Node + and -	20	68 (30.0%)	N/A	111 (49.0%)

Table 3: risk of bias evaluation of all trials included in the CPR network

STUDY	RISK OF BIAS EVALUATION DOMINIUM (12)				
	Allocation sequence	Allocation conceal	Blinding	Incomplete outcome	Selective Reporting
ABCSG-24	Low risk	Unclear	High risk	Low risk	Low risk
BUZDAR	Unclear	Unclear	High risk	Low risk	Low risk
CALGB40601	Unclear	Unclear	Unclear	Unclear	Unclear
CHANG	Unclear	Unclear	Unclear	Low risk	High risk
CHERLOB	Low risk	Low risk	High risk	Low risk	Low risk
GEICAM2006-14	Unclear	Low risk	High risk	Low risk	Low risk
GEPARQUINTO	Low risk	Low risk	High risk	Low risk	Low risk
GEPARSIXTO	Low risk	Unclear	High risk	Low risk	Low risk
HANNAH	Unclear	Low risk	High risk	Low risk	Low risk
JBCRG-10	Unclear	Unclear	Unclear	Unclear	Unclear
LAPATAX	Unclear	Unclear	High risk	Low risk	Low risk
NEOALTO	Low risk	Low risk	High risk	Low risk	Low risk
NEOSPHERE	Low risk	Low risk	High risk	Low risk	Low risk

NOAH	Low risk	Low risk	High risk	Low risk	Low risk
NSABPB41	Low risk	Low risk	High risk	Low risk	Low risk
REMAGUS02	Unclear	Unclear	High risk	Low risk	High risk
TRYPHAENA	Unclear	Unclear	High risk	Low risk	Low risk

Table 4: network for CPR

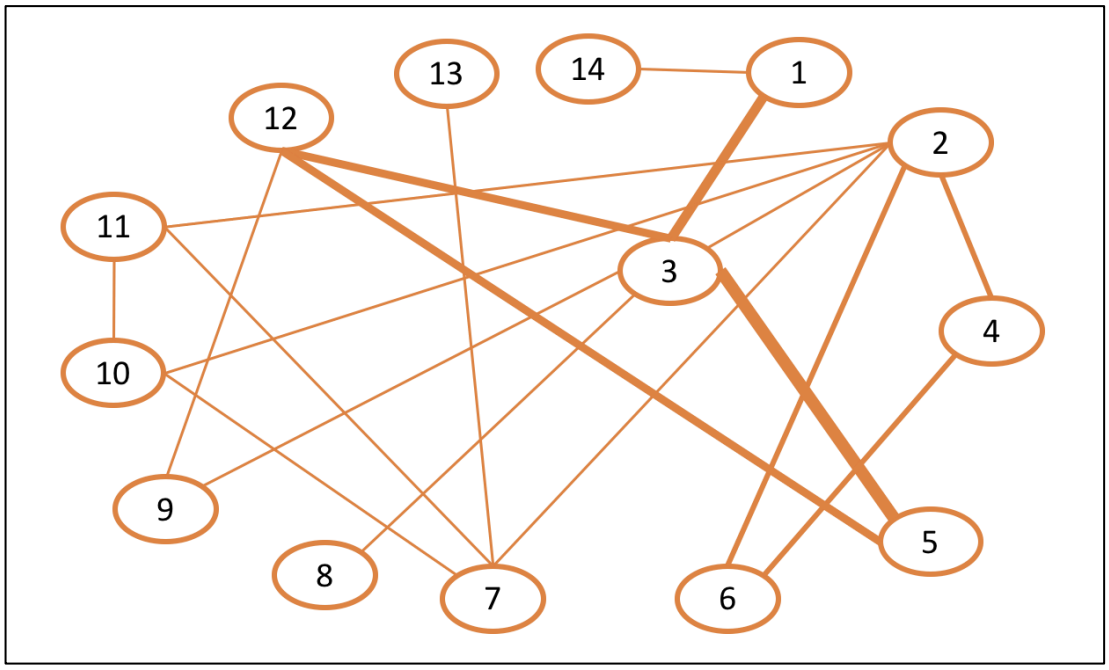
STUDY	COMPARISON	RR	COMPARISON	RR	COMPARISON	RR
ABCSG-24	3 vs. 1	1.46 (0.80-2.64)	----------	----------	----------	----------
BUZDAR	3 vs. 1	2.48 (1.10-5.57)	----------	----------	----------	----------
NOAH	3 vs. 1	1.97 (1.28-3.04)	----------	----------	----------	----------
REMAGUS02	3 vs. 1	1.36 (0.69-2.68)	----------	----------	----------	----------
CHANG	14 vs. 1	6.00 (0.82-44.00)	----------	----------	----------	----------
CALGB40601	4 vs. 2	0.78 (0.49-1.25)	6 vs. 2	1.27 (0.89-1.82)	----------	----------
NEOALTO	4 vs. 2	0.83 (0.53-1.30)	6 vs. 2	1.73 (1.18-2.53)	----------	----------
NEOSPHERE	7 vs. 2	1.65 (0.94-2.90)	10 vs. 2	0.61 (0.31-1.19)	11 vs. 2	0.86 (0.46-1.63)
JBCRG-10	2 vs. 3	1.14 (0.72-1.81)	----------	----------	----------	----------
CHERLOB	5 vs. 3	1.15 (0.42-3.19)	12 vs. 3	2.05 (0.82-5.15)	----------	----------
LAPATAX	5 vs. 3	0.70 (0.35-1.37)	12 vs. 3	1.00 (0.62-1.60)	----------	----------
NSABPB41	5 vs. 3	1.02 (0.80-1.30)	12 vs. 3	1.19 (0.94-1.49)	----------	----------
GEICAM2006-14	5 vs. 3	0.50 (0.28-0.90)	----------	----------	----------	----------
GEPARQUINTO	5 vs. 3	0.75 (0.57-0.98)	----------	----------	----------	----------
HANNAH	8 vs. 3	1.12 (0.92-1.36)	----------	----------	----------	----------
GEPARSIXTO	9 vs. 12	0.89 (0.65-1.24)	----------	----------	----------	----------
TRYPHAENA	7 vs. 13	1.11 (0.91-1.37)	----------	----------	----------	----------

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. CHEMO (taxane) plus TRASTUZUMAB
03. CHEMO (anthra + taxane) plus TRASTUZUMAB
04. CHEMO (taxane) plus LAPATINIB
05. CHEMO (anthra + taxane) plus LAPATINIB
06. CHEMO (taxane) plus TRASTUZUMAB plus LAPATINIB
07. CHEMO (taxane) plus TRASTUZUMAB plus PERTUZUMAB

08. CHEMO (anthra + taxane) plus TRASTUZUMABsc
09. CHEMO (anthra + taxane + CARBO) plus TRASTUZUMAB plus LAPATINIB
10. TRASTUZUMAB plus PERTUZUMAB (no chemo)
11. CHEMO (taxane) plus PERTUZUMAB
12. CHEMO (anthra + taxane) plus TRASTUZUMAB plus LAPATINIB
13. CHEMO (anthra + taxane) plus TRASTUZUMAB plus PERTUZUMAB
14. CHEMO (taxane + CARBO) plus TRASTUZUMAB

Figure 2: network for CPR



Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. CHEMO (taxane) plus TRASTUZUMAB
03. CHEMO (anthra + taxane) plus TRASTUZUMAB
04. CHEMO (taxane) plus LAPATINIB
05. CHEMO (anthra + taxane) plus LAPATINIB
06. CHEMO (taxane) plus TRASTUZUMAB plus LAPATINIB
07. CHEMO (taxane) plus TRASTUZUMAB plus PERTUZUMAB
08. CHEMO (anthra + taxane) plus TRASTUZUMABsc
09. CHEMO (anthra + taxane + CARBO) plus TRASTUZUMAB plus LAPATINIB
10. TRASTUZUMAB plus PERTUZUMAB (no chemo)
11. CHEMO (taxane) plus PERTUZUMAB
12. CHEMO (anthra + taxane) plus TRASTUZUMAB plus LAPATINIB
13. CHEMO (anthra + taxane) plus TRASTUZUMAB plus PERTUZUMAB
14. CHEMO (taxane + CARBO) plus TRASTUZUMAB

Table 5: RRs for CPR

1	**2.00** (1.20-3.50)	**1.70** (1.30-2.20)	1.50 (0.85-2.90)	**1.40** (1.00-2.00)	**2.90** (1.60-5.30)	**3.10** (1.60-6.00)	**1.90** (1.30-2.60)	**1.70** (1.10-2.70)	1.10 (0.53-2.30)	1.60 (0.78-3.30)	**1.90** (1.40-5.50)	**2.80** (1.40-5.50)	3.50 (0.93-25.00)
2.00 (1.20-3.50)	**2**	0.86 (0.52-1.30)	**0.78** (0.59-1.00)	0.72 (0.43-1.20)	**1.50** (1.20-1.80)	**1.50** (1.10-2.20)	0.95 (0.56-1.50)	0.86 (0.47-1.50)	**0.56** (0.59-0.93)	0.81 (0.50-1.30)	0.95 (0.57-1.50)	1.40 (0.92-2.10)	1.80 (0.42-13.00)
1.70 (1.30-2.20)	0.86 (0.52-1.30)	**3**	0.91 (0.54-1.60)	**0.85** (0.73-0.98)	**1.70** (1.10-2.90)	**1.80** (1.00-3.30)	1.10 (0.91-1.40)	1.00 (0.70-1.40)	0.66 (0.33-1.30)	0.94 (0.49-1.80)	1.10 (0.96-1.30)	1.60 (0.89-3.10)	2.10 (0.54-15.00)
1.50 (0.85-2.90)	**0.78** (0.59-1.00)	0.91 (0.54-1.60)	**4**	0.93 (0.51-1.60)	1.90 (1.50-2.40)	**2.00** (1.30-3.20)	1.20 (0.67-2.10)	1.10 (0.56-2.10)	0.72 (0.40-1.30)	1.00 (0.60-1.80)	1.20 (0.68-2.10)	**1.80** (1.10-3.00)	2.30 (0.53-18.00)
1.40 (1.00-2.00)	0.72 (0.43-1.20)	**0.85** (0.73-0.98)	0.93 (0.51-1.60)	**5**	**2.00** (1.20-3.50)	**2.10** (1.20-4.00)	**1.30** (1.00-1.70)	1.20 (0.82-1.70)	0.78 (0.38-1.60)	1.10 (0.57-2.20)	**1.30** (1.10-1.60)	**1.90** (1.00-3.70)	2.50 (0.63-18.00)
2.90 (1.60-5.30)	**1.50** (1.20-1.80)	**1.70** (1.10-2.90)	1.90 (1.50-2.40)	**2.00** (1.20-3.50)	**6**	1.10 (0.70-1.60)	0.65 (0.37-1.10)	0.58 (0.31-1.10)	**0.38** (0.22-0.66)	**0.55** (0.33-0.90)	0.65 (0.37-1.10)	0.95 (0.60-1.50)	1.20 (0.28-9.20)
3.10 (1.60-6.00)	**1.50** (1.10-2.20)	**1.80** (1.00-3.30)	**2.00** (1.30-3.20)	**2.10** (1.20-4.00)	1.10 (0.70-1.60)	**7**	0.61 (0.32-1.10)	0.55 (0.27-1.10)	**0.36** (0.22-0.57)	**0.52** (0.33-0.77)	0.61 (0.32-1.10)	0.90 (0.73-1.10)	1.20 (0.26-8.90)
1.90 (1.30-2.60)	0.95 (0.56-1.50)	1.10 (0.91-1.40)	1.20 (0.67-2.10)	**1.30** (1.00-1.70)	0.65 (0.37-1.10)	0.61 (0.32-1.10)	**8**	0.90 (0.60-1.40)	0.59 (0.29-1.20)	0.85 (0.43-1.70)	1.00 (0.78-1.30)	1.50 (0.77-2.90)	1.90 (0.48-14.00)
1.70 (1.10-2.70)	0.86 (0.47-1.50)	1.00 (0.70-1.40)	1.10 (0.56-2.10)	1.20 (0.82-1.70)	0.58 (0.31-1.10)	0.55 (0.27-1.10)	0.90 (0.60-1.40)	**9**	0.66 (0.30-1.40)	0.94 (0.45-2.00)	1.10 (0.80-1.50)	1.60 (0.80-3.40)	2.10 (0.50-15.00)
1.10 (0.53-2.30)	**0.56** (0.59-0.93)	0.66 (0.33-1.30)	0.72 (0.40-1.30)	0.78 (0.38-1.60)	**0.38** (0.22-0.66)	**0.36** (0.22-0.57)	0.59 (0.29-1.20)	0.66 (0.30-1.40)	**10**	1.40 (0.83-2.50)	1.70 (0.82-3.40)	**2.50** (1.50-4.20)	3.20 (0.69-25.00)
1.60 (0.78-3.30)	0.81 (0.50-1.30)	0.94 (0.49-1.80)	1.00 (0.60-1.80)	1.10 (0.57-2.20)	**0.55** (0.33-0.90)	**0.52** (0.33-0.77)	0.85 (0.43-1.70)	0.94 (0.45-2.00)	1.40 (0.83-2.50)	**11**	1.20 (0.59-2.30)	**1.70** (1.10-2.80)	2.20 (0.49-18.00)
1.90 (1.40-5.50)	0.95 (0.57-1.50)	1.10 (0.96-1.30)	1.20 (0.68-2.10)	**1.30** (1.10-1.60)	0.65 (0.37-1.10)	0.61 (0.32-1.10)	1.00 (0.78-1.30)	1.10 (0.80-1.50)	1.70 (0.82-3.40)	1.20 (0.59-2.30)	**12**	1.50 (0.79-2.80)	1.90 (0.48-14.00)
2.80 (1.40-5.50)	1.40 (0.92-2.10)	1.60 (0.89-3.10)	**1.80** (1.10-3.00)	**1.90** (1.00-3.70)	0.95 (0.60-1.50)	0.90 (0.73-1.10)	1.50 (0.77-2.90)	1.60 (0.80-3.40)	**2.50** (1.50-4.20)	**1.70** (1.10-2.80)	1.50 (0.79-2.80)	**13**	1.30 (0.28-10.00)
3.50 (0.93-25.00)	1.80 (0.42-13.00)	2.10 (0.54-15.00)	2.30 (0.53-18.00)	2.50 (0.63-18.00)	1.20 (0.28-9.20)	1.20 (0.26-8.90)	1.90 (0.48-14.00)	2.10 (0.50-15.00)	3.20 (0.69-25.00)	2.20 (0.49-18.00)	1.90 (0.48-14.00)	1.30 (0.28-10.00)	**1**

													4

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. CHEMO (taxane) plus TRASTUZUMAB
03. CHEMO (anthra + taxane) plus TRASTUZUMAB
04. CHEMO (taxane) plus LAPATINIB
05. CHEMO (anthra + taxane) plus LAPATINIB
06. CHEMO (taxane) plus TRASTUZUMAB plus LAPATINIB
07. CHEMO (taxane) plus TRASTUZUMAB plus PERTUZUMAB
08. CHEMO (anthra + taxane) plus TRASTUZUMABsc
09. CHEMO (anthra + taxane + CARBO) plus TRASTUZUMAB plus LAPATINIB
10. TRASTUZUMAB plus PERTUZUMAB (no chemo)
11. CHEMO (taxane) plus PERTUZUMAB
12. CHEMO (anthra + taxane) plus TRASTUZUMAB plus LAPATINIB
13. CHEMO (anthra + taxane) plus TRASTUZUMAB plus PERTUZUMAB
14. CHEMO (taxane + CARBO) plus TRASTUZUMAB

Table 6: ranking arms for CPR

	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Arm 7	Arm 8	Arm 9	Arm 10	Arm 11	Arm 12	Arm 13	Arm 14
Rank 1	0.0%	0.0%	0.01%	0.0%	0.0%	15.73%	24.01%	0.42%	0.42%	0.0%	0.01%	0.21%	5.34%	53.88%
Rank 2	0.0%	0.09%	0.02%	0.01%	0.0%	29.12%	40.40%	1.93%	1.52%	0.0%	0.05%	1.27%	20.41%	5.20%
Rank 3	0.0%	1.00%	0.12%	0.10%	0.0%	26.71%	25.22%	3.53%	2.22%	0.01%	0.46%	3.02%	32.05%	5.62%
Rank 4	0.0%	12.29%	0.62%	0.64%	0.02%	22.73%	6.03%	7.39%	4.47%	0.13%	4.16%	6.73%	25.83%	8.97%
Rank 5	0.0%	29.83%	2.14%	3.83%	0.04%	2.90%	1.71%	15.70%	8.26%	0.57%	10.21%	15.10%	5.95%	3.76%
Rank 6	0.0%	16.88%	5.84%	9.43%	0.34%	1.30%	1.18%	17.20%	9.15%	1.41%	10.60%	20.91%	3.31%	2.99%
Rank 7	0.01%	10.61%	14.01%	9.46%	0.97%	0.89%	0.81%	17.09%	10.72%	2.48%	8.20%	19.86%	2.54%	2.32%
Rank 8	0.05%	10.21%	21.49%	7.84%	3.29%	0.45%	0.45%	14.58%	12.04%	2.98%	6.76%	15.90%	1.98%	1.99%
Rank 9	0.16%	10.13%	22.67%	9.21%	9.42%	0.15%	0.14%	10.95%	12.71%	2.87%	7.68%	10.41%	1.50%	2.00%
Rank 10	0.78%	7.07%	18.88%	12.77%	18.80%	0.02%	0.04%	6.57%	12.61%	4.00%	10.64%	4.85%	0.71%	2.25%
Rank 11	3.42%	1.75%	10.95%	19.11%	24.23%	0.01%	0.01%	3.26%	11.72%	7.05%	14.39%	1.50%	0.31%	2.30%
Rank 12	9.64%	0.19%	3.22%	17.64%	26.95%	0.0%	0.0%	1.18%	9.12%	12.86%	15.90%	0.25%	0.04%	3.00%
Rank 13	29.45%	0.01%	0.06%	8.18%	15.61%	0.0%	0.0%	0.19%	4.56%	29.58%	9.09%	0.0%	0.01%	3.27%
Rank 14	56.49%	0.01%	0.0%	1.78%	0.33%	0.0%	0.0%	0.01%	0.47%	36.08%	2.40%	0.0%	0.0%	2.45%

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. CHEMO (taxane) plus TRASTUZUMAB

03. CHEMO (anthra + taxane) plus TRASTUZUMAB
04. CHEMO (taxane) plus LAPATINIB
05. CHEMO (anthra + taxane) plus LAPATINIB
06. CHEMO (taxane) plus TRASTUZUMAB plus LAPATINIB
07. CHEMO (taxane) plus TRASTUZUMAB plus PERTUZUMAB
08. CHEMO (anthra + taxane) plus TRASTUZUMABsc
09. CHEMO (anthra + taxane + CARBO) plus TRASTUZUMAB plus LAPATINIB
10. TRASTUZUMAB plus PERTUZUMAB (no chemo)
11. CHEMO (taxane) plus PERTUZUMAB
12. CHEMO (anthra + taxane) plus TRASTUZUMAB plus LAPATINIB
13. CHEMO (anthra + taxane) plus TRASTUZUMAB plus PERTUZUMAB
14. CHEMO (taxane + CARBO) plus TRASTUZUMAB

APPENDIX 1

Database: MEDLINE (through Pubmed)

Search date: 05/31/2015

PATIENTS (breast cancer**)**

1. Breast cancer **(300.158 papers)**
2. Breast neoplasms **(256.643 papers)**
3. Breast tumor **(274.421 papers)**
4. Breast tumour **(258.742 papers)**
5. (((Breast cancer) OR breast neoplasms) OR breast tumor) OR breast tumour **(303.383 papers)**

INTERVENTIONS/COMPARISONS (Isolated chemotherapy or chemotherapy associated with any anti-HER2 inhibitor in the adjuvant or neoadjuvant settings**)**

6. Adjuvant treatment **(181.541 papers)**
7. Adjuvant therapy **(164.203 papers)**
8. Adjuvant chemotherapy **(54.907 papers)**
9. Neoadjuvant treatment **(21.926 papers)**
10. Neoadjuvant therapy **(20.462 papers)**
11. Neoadjuvant chemotherapy **(18.368 papers)**
12. (((((Adjuvant treatment) OR Adjuvant therapy) OR Adjuvant chemotherapy) OR Neoadjuvant treatment) OR Neoadjuvant therapy) OR Neoadjuvant chemotherapy **(195.156 papers)**
13. HER2 pathway inhibitors **(450 papers)**
14. Trastuzumab **(7.002 papers)**
15. Herceptin **(7.370 papers)**
16. Lapatinib **(1.689 papers)**
17. Tykerb **(1.691 papers)**

18. Pertuzumab **(499 papers)**
19. Perjeta **(499 papers)**
20. T-DM1 **(146 papers)**
21. Trastuzumab emtansine **(209 papers)**
22. (((((((HER2 pathway inhibitors) OR trastuzumab) OR herceptin) OR lapatinib) OR tykerb) OR pertuzumab) OR perjeta) OR T-DM1) OR Trastuzumab emtansine **(8.616 papers)**
23. 12 AND 22 **(1.868 papers)**

PATIENTS (breast cancer**)** **PLUS** **INTERVENTIONS/COMPARISONS (**Isolated chemotherapy or chemotherapy associated with any anti-HER2 inhibitor in the adjuvant or neoadjuvant settings**)**

24. 5 AND 23 **(1.475 papers)**
25. FILTER: CLINICAL TRIALS **(245 papers)**
26. FILTER: HUMANS **(245 papers)**

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Database: Cochrane Central Register of Controlled Trials

Search date: 06/01/2015.
http://crso.cochrane.org

PATIENTS (breast cancer**)**

1. Breast cancer **(14.905 papers)**
2. Breast neoplasms **(7.466 papers)**
3. Breast tumor **(256 papers)**
4. Breast tumour **(28 papers)**
5. (((Breast cancer) OR breast neoplasms) OR breast tumor) OR breast tumour **(16.143 papers)**

INTERVENTIONS/COMPARISONS (Isolated chemotherapy or chemotherapy associated with any anti-HER2 inhibitor in the adjuvant or neoadjuvant settings**)**

6. Adjuvant treatment **(1.756 papers)**
7. Adjuvant therapy **(3.432 papers)**
8. Adjuvant chemotherapy **(2.984 papers)**
9. Neoadjuvant treatment **(228 papers)**
10. Neoadjuvant therapy **(802 papers)**
11. Neoadjuvant chemotherapy **(925 papers)**
12. (((((Adjuvant treatment) OR Adjuvant therapy) OR Adjuvant chemotherapy) OR Neoadjuvant treatment) OR Neoadjuvant therapy) OR Neoadjuvant chemotherapy **(8.071 papers)**
13. HER2 pathway inhibitors **(0 papers)**
14. Trastuzumab **(614 papers)**

15. Herceptin **(99 papers)**
16. Lapatinib **(216 papers)**
17. Tykerb **(4 papers)**
18. Pertuzumab **(51 papers)**
19. Perjeta **(0 papers)**
20. T-DM1 **(17 papers)**
21. Trastuzumab emtansine **(21 papers)**
22. (((((((HER2 pathway inhibitors) OR trastuzumab) OR herceptin) OR lapatinib) OR tykerb) OR pertuzumab) OR perjeta) OR T-DM1) OR Trastuzumab emtansine **(756 papers)**
23. 12 AND 22 **(247 papers)**

PATIENTS (breast cancer**)** **PLUS** **INTERVENTIONS/COMPARISONS (**Isolated chemotherapy or chemotherapy associated with any anti-HER2 inhibitor in the adjuvant or neoadjuvant settings**)**

24. 5 AND 23 **(243 papers)**

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Database: EMBASE

Search date: 05/31/2015
http://www.embase.com/;jsessionid=522AD678F786F74155F1CCCF6AADA99C#quickSearch/default

PATIENTS (breast cancer**)**

1. Breast cancer **(453.995 papers)**
2. Breast neoplasms **(15.612 papers)**
3. Breast tumor **(227.449 papers)**
4. Breast tumour **(25.209 papers)**
5. (((Breast cancer) OR breast neoplasms) OR breast tumor) OR breast tumour **(456.382 papers)**

INTERVENTIONS/COMPARISONS (Isolated chemotherapy or chemotherapy associated with any anti-HER2 inhibitor in the adjuvant or neoadjuvant settings**)**

6. Adjuvant treatment **(115.282 papers)**
7. Adjuvant therapy **(153.136 papers)**
8. Adjuvant chemotherapy **(82.358 papers)**
9. Neoadjuvant treatment **(23.080 papers)**
10. Neoadjuvant therapy **(26.358 papers)**
11. Neoadjuvant chemotherapy **(22.455 papers)**
12. (((((Adjuvant treatment) OR Adjuvant therapy) OR Adjuvant chemotherapy) OR Neoadjuvant treatment) OR Neoadjuvant therapy) OR Neoadjuvant chemotherapy **(179.500 papers)**
13. HER2 pathway inhibitors **(651 papers)**

14. Trastuzumab **(25.856 papers)**
15. Herceptin **(7.739 papers)**
16. Lapatinib **(8.092 papers)**
17. Tykerb **(1.029 papers)**
18. Pertuzumab **(2.137 papers)**
19. Perjeta **(150 papers)**
20. T-DM1 **(346 papers)**
21. Trastuzumab emtansine **(854 papers)**
22. (((((((HER2 pathway inhibitors) OR trastuzumab) OR herceptin) OR lapatinib) OR tykerb) OR pertuzumab) OR perjeta) OR T-DM1) OR Trastuzumab emtansine **(29.993 papers)**
23. 12 AND 22 **(7.311 papers)**

PATIENTS (breast cancer**) E PLUS INTERVENTIONS/COMPARISONS (**Isolated chemotherapy or chemotherapy associated with any anti-HER2 inhibitor in the adjuvant or neoadjuvant settings**)**

24. 5 AND 23 **(6.488 papers)**
25. Excluding articles from that also appear at MEDLINE **(2.928 papers)**
26. FILTER: CLINICAL TRIALS **(1.229 papers)**
27. FILTER: HUMANS **(1.130 papers)**

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EMBASE + CENTRAL (COCHRANE) + PUBMED: 1614 trials, of which 61 were excluded due to duplicated references, resulting 1553 trials

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8. CONCLUSÕES E CONSIDERAÇÕES FINAIS

A idéia primordial que representa a pedra angular da validação do constructo teórico a partir do qual foi concebida esta tese encontra-se publicada no livro *Epidemiology and People`s Health* da epidemiologista Nancy Krieger (Krieger, 2011). Tomo aqui a liberdade de traduzir uma passagem desta publicação: "O desenvolvimento científico advém da contestação do método corrente, identificando suas fragilidades e procurando por novas opções que possam melhor explicar a realidade". Minhas considerações finais e conclusões encontram neste trecho seu ponto de partirda e seu fim.

Comecemos, então, pela contextualização da realidade vigente nos dias atuais em relação ao tema aqui estudado. Esta tese tem por foco o tratamento adjuvante e neoadjuvante de pacientes com câncer de mama inicial e localmente avançado HER2-positivo. É senso comum que o câncer de mama constitui problema de saúde pública em todo o mundo, sendo a neoplasia maligna mais comum da mulher (excetuando-se tumores de pele) e que 15 a 25% destes tumores são classificados como HER2-positivos – um subgrupo cujo prognóstico é pior em virtude do comportamento biológico agressivo conferido pelas "vantagens" de crescimento celular conferidas pela superexpressão da proteína HER2 (Jemal, 2011; Siegel, 2012; Owens, 2004; Slamon, 1987; Slamon, 1989; Wolff, 2007; Yarden, 2001; Yaziji, 2004).

Entretanto, a história natural deste subtipo de câncer de mama foi drasticamente alterada em 2005 com a publicação de 3 ensaios clínicos randomizados que comprovaram a eficácia da combinação de quimioterapia com trastuzumabe em aumentar a probabilidade de cura destas mulheres (Piccart-Gebhart MJ 2005; Romond EH 2005). Estima-se redução relativa de 34% no risco de morte com a adição do trastuzumabe à quimioterapia neste cenário clínico (HR 0,66; IC95% 0,57-0,77) (Moja, 2012). Apesar da indubitável eficácia deste anticorpo monoclonal, a resistência por parte das células malignas ainda é uma realidade que se associa a uma taxa de recorrência da ordem de 10-15% em 5 anos (Gianni, 2011). Frente a esta situação, foram desenvolvidas medicações eficazes em inibir a via de crescimento mediada pelos receptors HER2 em diferentes pontos críticos da via de sinalização. Dentre estas medicações, destacam-se: lapatinibe, pertuzumabe, TDM-1 e neratinibe. Neste ponto, apresento um resumo da realidade vigente em relação ao câncer de mama HER2-poitivo: uma doença com alto potencial letal e que representa importante agravo à saúde da mulher em todo o mundo para a qual existem diversas opções terapêuticas eficazes testadas em uma infinidade de ensaios clínicos randomizados (33, contabilizados para esta revisão) cujo melhor tratamento ainda é desconhecido.

Remeto-me, então, mais uma vez, ao aforismo descrito no livro de Nancy Krieger e passo agora a descrever o método vigente utilizado para interpretar esse corpo de evidência e suas limitações. A revisão mais ampla até o momento publicada trata-se de uma metanálise clássica ("*pairwise*") publicada pela Cochrane que compara o impacto em termos de sobrevida global do trastuzumabe associado à quimioterapia

em relação à quimioterapia isolada, identificando o já referido benefício com a associação do anticorpo monoclonal (HR 0,66; IC95% 0,57-0,77) (Moja, 2012). Em virtude das restrições do método, ficam excluídos os estudos com mais de dois braços de tratamento, bem como todas as outras combinações de trastuzumabe com outros inibidores da via HER2. Dessa forma, apenas é sabido que adicionar trastuzumabe à quimioterapia aumenta a probabilidade de cura das pacientes, permanecendo ignoradas frente às limitações do método vigente perguntas de extrema relevância clínica, tais como: qual é a melhor combinação de quimioterapia? Qual deve ser a duração do tratamento com trastuzumabe? O duplo-bloqueio da via HER2 é mais eficaz em termos de redução de mortalidade?

Finalmente, descrita a realidade e criticado o método vigente, cabe a proposição da alternativa que melhor possa interpretar a complexidade do cenário atual. É sob esta perspectiva que se construiu esta tese. O MTC (*Mixed Treatment Comparison*) em sua abordagem Bayesiana constitui método consagrado na literatura para a comparação de múltiplos braços de tratamento organizados em complexas redes de evidência. Apesar da sua utilidade clínica e robustez matemática, este constitui método ainda pouco utilizado na literatura médica, provavelmente em virtude da complexidade da programação computacional necessária para a sua implementação e de algumas peculiaridades em relação à interpretação dos resultados, posto que se baseia em estatística Bayesiana (e não frequentista, como o fazem a maior parte dos métodos). Entretanto, este cenário está mudando e, segundo dados publicados pela *Agency of Health Care Research and Quality*, o número de metanálises baseadas em métodos Bayesianos de comparações múltiplas vêm se tornando cada vez mais maior

na literatura média na medida em que se tornam cada vez mais comuns as complexas redes de evidência (Coleman, 2012).

Para fins de realização desta tese, estipulou-se aferir o desempenho das diferentes opções terapêuticas no tratamento adjuvante e neoadjuvante do câncer de mama HER2 positivo inicial e localmente avançado em relação à sua eficácia e à sua segurança. A avaliação da eficácia foi dividida em um desfecho primordial (sobrevida global) e desfechos substitutos (sobrevida livre de doença e resposta patológica completa); já a segurança foi avaliada em relação à cardiotoxicidade e demais toxicidades graus 3 e 4. No total, foram incluídos mais de 30.000 pacientes arrolados em 33 ECRs, porém heterogeneidade no reporte e na disponibilidade dos desfechos fez com que fossem diferentes entre as redes os braços de tratamento e os estudos incluídos.

Em relação à sobrevida global, foram incluídos 12 ECRs com 27.227 pacientes, sendo utilizado *hazard ratio* como medida de efeito. Esta análise que avalia massiva quantidade de evidência em uma metodologia ainda inédita no câncer de mama, identificou o achado mais importante desta tese: a confirmação do conceito do duplo-bloqueio da via HER2 como alternativa superior às demais. Os esquemas com quimioterapia associada à trastuzumabe e lapatinibe se mostraram superiores ao demais, mas ainda são aguardados para 2017 os resultados dos estudos que avaliam o impacto em sobrevida global do duplo-bloqueio com pertuzumabe e trastuzumabe associados à quimioterapia. Outros achados importantes desta rede são: (1) quimioterapia isolada e bloqueio simples da via HER2 apenas com lapatinibe são as

piores opções; (2) tratuzumabe administrado por tempo não superior há 6 meses é pior do que 12 meses de trastuzumabe e (3) quimioterapia sem antraciclinas associada a 12 meses de trastuzumabe não é significativamente pior a esquemas que incluem antraciclinas e trastuzumabe.

Faz-se aqui necessário salientar importante aspecto alusivo à interpretação dos resultados do MTC, pois o regime de tratamento composto por quimioterapia em dose-densa (antraciclina + taxano) associado a 12 meses de trastuzumabe aparece bem colocado na lista de ranqueamento, com aproximadamente 36% de probabilidade de ser ele a melhor opção terapêutica. Todavia, o mesmo esquema apresenta 13% de probabilidade de ser o pior. Isso decorre da instabilidade dos números expressa em grandes intervalos de credibilidade em relação às estimativas pontuais referentes a este regime de tratamento quando comparado aos demais. À titulo de exemplificação, descreve-se aqui que todas as estimativas pontuais favoreceram este esquema, mas apresentaram amplos intervalos de credibilidade, todos cruzando o limiar de não-significância. Deste modo, os braços de tratamento cujos números apresentam menor variabilidade ocupam posições mais sólidas no ranqueamento enquanto aqueles com ampla variabilidade se encaixam nas posições restantes. Isso posto, fica evidente que a tabela de ranqueamento deve ser interpretada à luz dos achados descritos na tabela que resume as medidas de efeito correlacionando todas as opções de tratamento. O ranqueamento é útil como um guia que ajuda a identificar os braços de maior interesse na tabela principal (que pode se demonstrar difícil de interpretar em situações nas quais existem muitas opções terapêuticas em virtude da sobrecarga de informações).

Tendo-se em vista a maior disponibilidade de desfechos reportados, a rede que avaliou a sobrevida livre de progressão contou com dois estudos a mais (ExteNET e Shaughnessy), totalizando 14 ECRs e 30.219 pacientes. Como esperado, os achados referentes à esta análise reiteram as conclusões já identificadas na rede anterior, acrescentando o bloqueio sequencial com neratinibe após quimioterapia e 12 meses de trastuzumabe como uma opção promissora, para a qual se esperam os resultados de sobrevida global (estudo ExteNET).

A rede que concerne à resposta patológica completa foi composta por 17 ECRs com 4.383 pacientes. Percebe-se que, apesar de contar com um maior número de estudos, o número de sujeitos incluídos nesta análise é substancialmente menor. Isso se deve ao fato de que os estudos em neoadjuvância costumam arrolar menos pacientes do que as suas contrapartes no contexto adjuvante. Nesta avaliação, além da já referida combinação de lapatinibe com trastuzumabe, o duplo bloqueio também inclui trabalhos que avaliaram pertuzumabe associado ao trastuzumabe. Como esperado, a mais ampla inibição da via HER2 se mostrou superior às demais estratégias. Quando comparados entre si, os esquemas não apresentaram diferença significativa, mas parece haver uma vantagem marginal para aqueles que associavam o trastuzumabe ao pertuzumabe, e não ao lapatinibe.

Já em relação à cardiotoxicidade, foram incluídos 21 ECRs perfazendo 29.555 indivíduos. Nesta avaliação, os regimes mais cardiotóxicos foram os que utilizaram o trastuzumabe subcutâneo concomitante com antraciclina ou associaram trastuzumabe

ao pertuzumabe ou ao neratinibe. A associação do trastuzumabe com o lapatinibe é mais segura quando se considera a segurançaa cardíaca. O uso concomitante de trastuzumabe endovenoso com antraciclinas não foi significativamente mais tóxico, porém seu uso segue não sendo recomendado em virtude do dano potencial sem a perspectiva de incremento na eficácia. Em contrapartida, a utilização da doxorrubicina lipossomal demonstrou ser o esquema mais seguro. O planejamento inicial desta metanálise incluía avaliação de outras toxicidades graus 3 e 4. Infelizmente, esta apreciação não foi possível em virtude da inconstância em relação aos reportes dos efeitos adversos nos estudos.

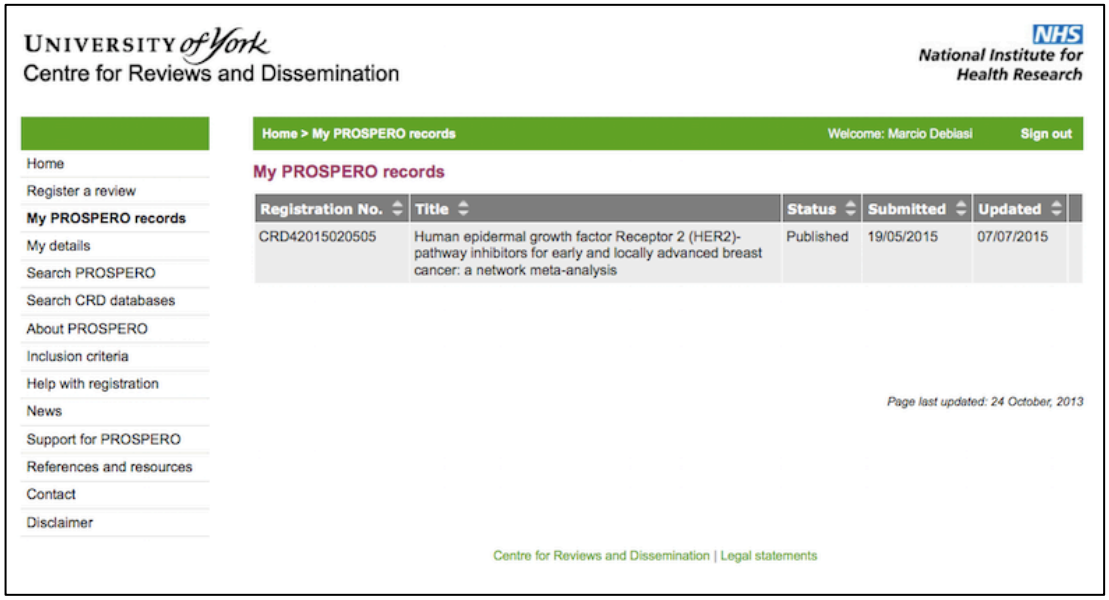
Finalmente, buscando-se valorizar os achados desta nova proposta de interpretação da rede de evidências acerca do tratamento adjuvante e neoadjuvante do câncer de mama HER2-positivo a partir de uma perspectiva clínica, conclui-se que o conceito do duplo bloqueio fica estabelecido como a melhor opção terapêutica em termos de eficácia e que a combinação de quimioterapia com trastuzumabe segue sendo a pedra angular deste tratamento. Nos cabe agora aguardar a publicação dos resultados de sobrevida global dos estudos que avaliam a associação de trastuzumabe com neratinibe ou pertuzumabe para definir a melhor estratégia dentro do conceito mais amplo do duplo bloqueio. É muito provável que os ganhos em termos de eficácia suplantem os incrementos em toxicidade associados com o uso concomitante do trastuzumabe com o pertuzumabe (toxicidade cardíaca) e com o lapatinibe (toxicidade gastrointestinal). Faz-se a ressalva de que a toxicidade gastrointestinal não foi modelada nesta análise em virtude da inconstância dos relatos entre os estudos. Assim, sugere-se que, da mesma forma como são rigorosamente

padronizados os reportes de eficácia, também o sejam os reportes de outras toxicidades além da cardiotoxicidade, de tal forma que estes importantes parâmetros dentro da tomada de decisão na oncologia possam ser avaliados de forma apropriada em modelos matemáticos. Revisões sistemáticas como essa, além de sugerirem mudanças de conduta, também são úteis em gerar hipóteses a serem testadas em experimentos subsequentes. Nesse sentido, destaca-se a promissora investigação da eficácia da doxorrubicina lipossomal, que demonstrou ser o regime mais seguro do ponto de vista cardiológico.

9. ANEXOS

9.1. REGISTRO NO *NATIONAL INSTITUTE FOR HEALTH AND RESEARCH*

www.crd.york.ac.uk/PROSPERO/



9.2. ESTRATÉGIA DE BUSCA DA LITERATURA

A fim de ampliar a sensibilidade da estratégia de busca no PubMed, os termos considerados como axiais dentro do processo de pesquisa na base de dados não foram designados como "Medical Subject Headings" (MeSH) em virtude de a ferramenta de busca do Pubmed contar atualmente com o sistema denominado "MeSH Translation Table", que automaticamente inclui o termo na estratégia de busca como "MeSH" e como "All Fields", caso seja identificada a correspondência. A tabela abaixo descreve todos os termos empregados na busca. Os termos axiais encontram-se descritos sem especificação, de modo que estes são automaticamente amplificados a partir da ferramenta "MeSH Translation Table". Para estes termos, são também expressos os termos MeSH a eles associados. Os demais termos relevantes à busca, porém não axias, foram restritos a "*Title and abstract*".

Os termos foram identificados a partir da pesquisa de "MeSH terms" no PUBMED e de "termos preferenciais" no EMTREE (EMBASE). Além disso, também foram pesquisadas revisões sistemáticas e matanálises já publicadas sobre o tema: (1) Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, GuarneriV,D'AmicoR. Trastuzumab containing regimens for early breast cancer. Cochrane. 2012; Petrelli F, Borgonovo K, Cabiddu M, Ghilardi M Barni S. Neoadjuvant chemotherapy and concomitant trastuzumab in breast cancer: a pooled analysis of two randomized trials.Anticancer drugs.2011;22(2):128; e (2) Nagayama A, Hayashida T, Jinno H, Takahashi M, Seki T, Matsumoto A, Murata T, Ashrafian H, Athanasiou T, Okabayashi K, Kitagawa Y. Comparative Effectiveness of Neoadjuvant Therapy for

HER2–Positive Breast Cancer: A Network Meta-Analysis. 2014;106(9).

Na base de dados da Cochrane, os termos "MeSH" também não foram utilizados porque pode levar até seis meses para uma revisão ser catalogada segundo os seus termos "MeSH". (pesquisado em 06/04/2015: http://onlinelibrary.wiley.com/cochranelibrary/search/mesh/quick#).

A tabela abaixo resume os termos associados aos diferentes itens da questão de pesquisa.

Questão de pesquisa	Grupos	Unitermos para busca
P – "*patient*" (paciente)	Pacientes com câncer de mama	TERMOS AXIAIS: Estes foram considerados como "all fields" e expandidos pela ferramenta "MeSH Translation Table" - Breast cancer - Breast neoplasms - Breast tumor - Breast tumour
I – "*intervention*" (intervenção)	Quimioterapia isolada ou associada a qualquer inibidor da via HER2 no contexto adjuvante ou neoadjuvante	TERMOS AXIAIS: Estes foram considerados como "all fields" e expandidos pela ferramenta "MeSH Translation Table" - Chemotherapy - Antineoplastic agents - HER2 pathway inhibitors - Trastuzumab - Herceptin - Lapatinib - Tykerb - Pertuzumab - Perjeta - TDM1

		- Trastuzumab emtansine - Adjuvant - Adjuvant treatment - Adjuvante therapy - Neoadjuvant - Neoadjuvant therapy - Neoadjuvant treatment
C – "*comparison*" (comparação)	Quimioterapia isolada ou associada a qualquer inibidor da via HER2 no contexto adjuvante ou neoadjuvante	TERMOS AXIAIS: Estes foram considerados como "all fields" e expandidos pela ferramenta "MeSH Translation Table" - Chemotherapy - Antineoplastic agente - HER2 pathway inhibitors - Trastuxumab - Herceptin - Lapatinib - Pertuzumab - TDM1 - Trastuzumab emtansine - Adjuvant - Adjuvant treatment - Adjuvante therapy - Adjuvant chemotherapy - Neoadjuvant - Neoadjuvant therapy - Neoadjuvant treatment - Neoadjuvant chemotherapy
O – "*outcome*" (desfecho)	Sobrevida global, sobrevida livre de doença e cardiotoxicidade	TERMOS AXIAIS: Estes foram considerados como "all fields" e expandidos pela ferramenta "MeSH Translation Table" - Adverse effects - Adverse event - Adverse drug reaction - Toxicity - Side effect - Toxic effect - Drug toxicity - Drug tolerance
		TERMOS SECUNDÁRIOS: - x

HISTÓRICO DE BUSCA

Banco de dados: MEDLINE (via Pubmed)

Esta base de dados foi pesquisada conforme orientado na publicação do *National Center for Biotechnology Information* "The NCBI Handbook [Internet]. 2nd edition, disponível em: http://www.ncbi.nlm.nih.gov/books/NBK153380/#NLMCatalog.Using_the_NLM_Catalog

A busca foi procedida em 31/05/2015 e encontra-se resumida abaixo:

PACIENTES (câncer de mama**)**

1. Breast cancer **(300.158)**
2. Breast neoplasms **(256.643)**
3. Breast tumor **(274.421)**
4. Breast tumour **(258.742)**
5. (((Breast cancer) OR breast neoplasms) OR breast tumor) OR breast tumour **(303.383)**

INTERVENÇÕES/COMPARAÇÕES (Quimioterapia isolada ou associada a qualquer inibidor da via HER2 no contexto adjuvante ou neoadjuvante**)**

6. Adjuvant treatment **(181.541)**
7. Adjuvant therapy **(164.203)**
8. Adjuvant chemotherapy **(54.907)**
9. Neoadjuvant treatment **(21.926)**
10. Neoadjuvant therapy **(20.462)**
11. Neoadjuvant chemotherapy **(18.368)**
12. (((((Adjuvant treatment) OR Adjuvant therapy) OR Adjuvant chemotherapy) OR Neoadjuvant treatment) OR Neoadjuvant therapy) OR Neoadjuvant chemotherapy **(195.156)**
13. HER2 pathway inhibitors **(450)**
14. Trastuzumab **(7.002)**
15. Herceptin **(7.370)**
16. Lapatinib **(1.689)**
17. Tykerb **(1.691)**
18. Pertuzumab **(499)**
19. Perjeta **(499)**
20. T-DM1 **(146)**
21. Trastuzumab emtansine **(209)**
22. (((((((HER2 pathway inhibitors) OR trastuzumab) OR herceptin) OR lapatinib) OR tykerb) OR pertuzumab) OR perjeta) OR T-DM1) OR Trastuzumab emtansine **(8.616)**
23. 12 AND 22 **(1.868)**

PACIENTES (cancer de mama**) E INTERVENÇÕES/COMPARAÇÕES (**Quimioterapia isolada ou associada a qualquer inibidor da via HER2 no contexto adjuvante ou neoadjuvante**)**

24. 5 AND 23 **(1.475)**
25. FILTER: CLINICAL TRIALS **(245)**
26. FILTER: HUMANS **(245)**

Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Cochrane Central Register of Controlled Trials

Pesquisado em 01/06/2015.
http://crso.cochrane.org

PACIENTES (câncer de mama**)**

1. Breast cancer **(14.905)**
2. Breast neoplasms **(7.466)**
3. Breast tumor **(256)**
4. Breast tumour **(28)**
5. (((Breast cancer) OR breast neoplasms) OR breast tumor) OR breast tumour **(16.143)**

INTERVENÇÕES/COMPARAÇÕES (Quimioterapia isolada ou associada a qualquer inibidor da via HER2 no contexto adjuvante ou neoadjuvante**)**

6. Adjuvant treatment **(1.756)**
7. Adjuvant therapy **(3.432)**
8. Adjuvant chemotherapy **(2.984)**
9. Neoadjuvant treatment **(228)**
10. Neoadjuvant therapy **(802)**
11. Neoadjuvant chemotherapy **(925)**
12. (((((Adjuvant treatment) OR Adjuvant therapy) OR Adjuvant chemotherapy) OR Neoadjuvant treatment) OR Neoadjuvant therapy) OR Neoadjuvant chemotherapy **(8.071)**
13. HER2 pathway inhibitors **(0)**
14. Trastuzumab **(614)**
15. Herceptin **(99)**
16. Lapatinib **(216)**
17. Tykerb **(4)**
18. Pertuzumab **(51)**
19. Perjeta **(0)**
20. T-DM1 **(17)**
21. Trastuzumab emtansine **(21)**

22. (((((((HER2 pathway inhibitors) OR trastuzumab) OR herceptin) OR lapatinib) OR tykerb) OR pertuzumab) OR perjeta) OR T-DM1) OR Trastuzumab emtansine **(756)**
23. 12 AND 22 **(247)**

PACIENTES (cancer de mama**) E INTERVENÇÕES/COMPARAÇÕES (**Quimioterapia isolada ou associada a qualquer inibidor da via HER2 no contexto adjuvante ou neoadjuvante**)**

24. 5 AND 23 **(243)**

Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Banco de dados: EMBASE

Pesquisado em 31/05/2015
http://www.embase.com/;jsessionid=522AD678F786F74155F1CCCF6AADA99C#quickSearch/default
Todos os termos sem restrição de data foram pesquisados apenas com restrição para estudos em humanos utilizando a ferramenta oferecida pelo site de busca que identifica a pesquisa mais ampla possível para os unitermos empregados ("*search as broad as possible*").

PACIENTES (câncer de mama**)**

1. Breast cancer **(453.995)**
2. Breast neoplasms **(15.612)**
3. Breast tumor **(227.449)**
4. Breast tumour **(25.209)**
5. (((Breast cancer) OR breast neoplasms) OR breast tumor) OR breast tumour **(456.382)**

INTERVENÇÕES/COMPARAÇÕES (Quimioterapia isolada ou associada a qualquer inibidor da via HER2 no contexto adjuvante ou neoadjuvante**)**

6. Adjuvant treatment **(115.282)**
7. Adjuvant therapy **(153.136)**
8. Adjuvant chemotherapy **(82.358)**
9. Neoadjuvant treatment **(23.080)**
10. Neoadjuvant therapy **(26.358)**
11. Neoadjuvant chemotherapy **(22.455)**
12. (((((Adjuvant treatment) OR Adjuvant therapy) OR Adjuvant chemotherapy) OR Neoadjuvant treatment) OR Neoadjuvant therapy) OR Neoadjuvant chemotherapy **(179.500)**
13. HER2 pathway inhibitors **(651)**
14. Trastuzumab **(25.856)**
15. Herceptin **(7.739)**
16. Lapatinib **(8.092)**

17. Tykerb **(1.029)**
18. Pertuzumab **(2.137)**
19. Perjeta **(150)**
20. T-DM1 **(346)**
21. Trastuzumab emtansine **(854)**
22. (((((((HER2 pathway inhibitors) OR trastuzumab) OR herceptin) OR lapatinib) OR tykerb) OR pertuzumab) OR perjeta) OR T-DM1) OR Trastuzumab emtansine **(29.993)**
23. 12 AND 22 **(7.311)**

PACIENTES (cancer de mama**) E INTERVENÇÕES/COMPARAÇÕES (**Quimioterapia isolada ou associada a qualquer inibidor da via HER2 no contexto adjuvante ou neoadjuvante**)**

24. 5 AND 23 **(6.488)**
25. Excluding articles from that also appear at MEDLINE **(2.928)**
26. FILTER: CLINICAL TRIALS **(1.229)**
27. FILTER: HUMANS **(1.130)**

Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

EMBASE + CENTRAL (COCHRANE) + PUBMED: 1614 trials, dos quais 61 foram excluídos por serem repetidos, sobrando 1553

Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Além das bases de dados indexadas já descritas, também foram pesquisadas publicações não indexadas ("literatura cinza" ou "*grey literature*") tais com anais de congressos na área de oncologia. As seguintes fontes foram pesquisadas:

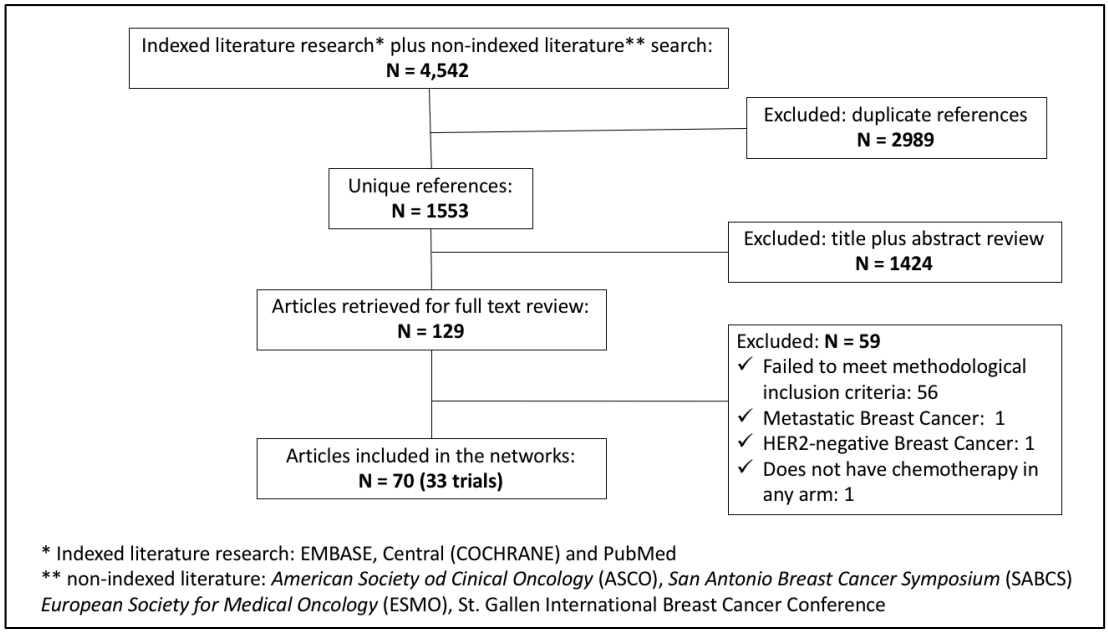
- *American Society of Cinical Oncology* (ASCO)
- *San Antonio Breast Cancer Symposium* (SABCS)
- *European Society for Medical Oncology* (ESMO)
- St. Gallen International Breast Cancer Conference

9.3. CRITÉRIOS DE INCLUSÃO DE ARTIGOS PARA A METANÁLISE

Para ser considerado elegível para esta metanálise, os trabalhos necessariamente precisavam apresentar TODOS os critérios de inclusão abaixo listados:

- Tipo de estudo: ensaios clínicos randomizado fase II ou III
- Participantes: pacientes com 18 ou mais anos de idade com câncer de mama inicial ou localmente avançado
- Intervenção/controle: por se tratar de uma metanálise em rede, que inclui múltiplos ensaios clínicos com diferentes braços de intervenção e controle, não é possível definir de forma única os grupos "intervenção" e "controle". Todavia, em linha gerais, o grupo "intervenção" abrange diferentes esquemas de quimioterapia associados a pelo menos um inibidor da via HER2; e o grupo "controle" pode incuir quimioterapia exclusiva ou quimioterapia associada a pelo menos um inibidor da via HER2

9.4. FLUXOGRAMA DA SELEÇÃO DOS ARTIGOS INCLUÍDOS NA METANÁLISE



9.5. ESTUDOS SELECIONADOS: REFERÊNCIAS

STUDY	CITATION IN THE THESIS	RREFERENCES
ABCSG-24	Steger, 2009	Steger G, Greil R, Jakesz R, Lang A, Mlineritsch B, Melbinzer-Zeinitzer E, et al. Final Results of ABCSG-24, a Randomized Phase III Study Comparing Epirubicin, Docetaxel, and Capecitabine (EDC) to Epirubicin and Docetaxel (ED) as Neoadjuvant Treatment for Early Breast Cancer and Comparing (ED/EDC) as Neoadjuvant Treatment for Early HER-2 Positive Breast Cancer. Cancer Res. 2009;69:1081.
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ACOSOG-Z1041	Buzdar, 2013a	Buzdar A, Suman VJ, Meric-Bernstam F, Leitch AM, Ellis MJ, Boughey JC, et al. ACOSOG Z1041 (Alliance): Definitive analysis of randomized neoadjuvant trial comparing FEC followed by paclitaxel plus trastuzumab (FEC → P+T) with paclitaxel plus trastuzumab followed by FEC plus trastuzumab (P+T → FEC+T) in HER2+ operable breast cancer. J Clin Oncol. 2013;31(suppl; abstr 502).
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BUZDAR	Buzdar, 2007	Buzdar AU, Valero V, Ibrahim NK, Francis D, Broglio KR, Theriault RL, et al. Neoadjuvant Therapy with Paclitaxel followed by 5-Fluorouracil, Epirubicin, and Cyclophosphamide Chemotherapy and Concurrent Trastuzumab in Human Epidermal Growth Factor Receptor2-Positive Operable Breast Cancer: An Update

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CALGB40601	Carey, 2013	Carey LA, Berry DA, Ollila D, Harris L, Krop IE, Weckstein D, et al. Clinical and translational results of CALGB 40601: A neoadjuvant phase III trial of weekly paclitaxel and trastuzumab with or without lapatinib for HER2-positive breast cancer. J Clin Oncol. 2013;31(suppl; abstr 500).
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CHERLOB	Guarneri, 2012	Guarneri V, Frassoldati A, Bottini A, Cagossi K, Bisagni G, Sarti S, et al. Preoperative Chemotherapy Plus Trastuzumab, Lapatinib, or Both in Human Epidermal Growth Factor Receptor 2–Positive Operable Breast Cancer: Results of the Randomized Phase II CHER-LOB Study. J Clin Oncol. 2012;30:1989-1995.
CONSORT	Rayson, 2012	Rayson D, Suter TM, Jackisch C, Vegt S, Bermejo B, Bosch J, et al. Cardiac safety of adjuvant pegylated liposomal doxorubicin with concurrent trastuzumab: a randomized phase II trial . Annals of Oncology. 2012;23:1780–88.
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HANNAH	Ismael, 2012	Ismael G, Hegg R, Muehlbauer S, Heinzmann D, Lum B, Kim SB, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I–III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol 2012; 13: 869–78.

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JBCRG-10	Masuda, 2010	Masuda N, Toi M, Ureno T, Aogi K, Iwata H, Ohno S, et al. A multicenter, randomized phase II study of neoadjuvant chemotherapy including trastuzumab with cyclophosphamide with docetaxel in patients with operable HER2-positive breast câncer (JBCRG-10 study). J Clin Oncol. 2010;28:15s(suppl;abstrTPS105).
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	Pierga, 2010	Pierga JY, Delaloge S, Espié M, Brain E, Sigal-Zafrani B, Mathieu MC. A multicenter randomized phase II study of sequential epirubicin/ cyclophosphamide followed by docetaxel with or without celecoxib or trastuzumab according to HER2 status, as primary chemotherapy for localized invasive breast cancer patients. Breast Cancer Res Treat. 2010;122:429–37.
SHAUGHNESSY	Pippen, 2011	Pippen JE, Paul D, Stokoe T, Blum JL, Krekow L, Holmes AL, et al. Randomized, phase III study of adjuvant doxorubicin plus cyclophosphamide (AC) followed by docetaxel (T) with or without capecitabine (X) in high-risk breast cancer: Exploratory ki67 analyses. J Clin Oncol. 2011;29:suppl;abstr 500.
	Shaughnessy, 2015	Shaughnessy J, Koeppen H, Xiao Y, Lackner MR, Paul D, Stokoe C, et al. Patients with Slowly Proliferative Early Breast Cancer Have Low Five-Year

		Recurrence Rates in a Phase III Adjuvant Trial of Capecitabine. Clin Cancer Res. 2015 (published online).
TEACH	Goss, 2013	Goss PE, Smith IE, Shaughnessy J, Ejlertsen B, Kaufmann M, Boyle F, et al. Adjuvant lapatinib for women with early-stage HER2-positive breast cancer: a randomised, controlled, phase 3 trial. Lancet Oncol. 2013;14: 88–96.
	Boyle, 2015	Boyle FM, Smith IE, Shaughnessy J, Ejlertsen B, Buzdar AU, Fumoleau P, et al. Health related quality of life of women in TEACH, a randomised placebo controlled adjuvant trial of lapatinib in early stage Human Epidermal Growth Factor Receptor (HER2) overexpressing breast cancer. European Journal of Cancer. 2015;51:685-96.
TRYPHAENA	Schneeweiss, 2011	Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, et al. S5-6: Neoadjuvant Pertuzumab and Trastuzumab Concurrent or Sequential with an Anthracycline-Containing or Concurrent with an Anthracycline-Free Standard Regimen: A Randomized Phase II Study (TRYPHAENA). Cancer Res. 2011;71:S5-6.
	Schneeweiss, 2012	Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Annals of Oncology. 2013;24: 2278–84.

9.6. ESTUDOS SELECIONADOS: CARACTERÍSTICAS GERAIS

Part 1:

STUDY	Chemo setting	Industry sponsored	Which industry	Phase	Number of patients	Multicentric	N Countries
ALTTO	Adj*	Yes: fully	GSK	III	8381	Yes	44
BCIRG006	Adj*	Yes: fully	More than one industry	III	3222	Yes	41
CONSORT	Adj*	Yes: fully	Schering-Plough	II	179	Yes	N/A
EXTENET	Adj*	Yes: fully	Puma Biotech	III	2840	Yes	40
FINHER	Adj*	Yes: partially	More than one industry	III	232	Yes	N/A
GIM2	Adj*	Yes: partially	More than one industry	III	130	Yes	1
HERA/BIG01-01	Adj*	Yes: fully	Roche	III	3401	Yes	39
MAVROUDIS	Adj*	No	----	N/A	481	Yes	1
NCCTG N9831	Adj*	Yes: partially	Genentech	III	2184	N/A	N/A
NSABP B31	Adj*	Yes: partially	Genentech	III	1736	N/A	N/A
PACS	Adj*	Yes: partially	Roche	III	528	Yes	2
PHARE	Adj*	No	----	III	3380	Yes	1
SHAUGHNESSY	Adj*	Yes: fully	Roche	III	102	Yes	N/A
TEACH	Adj*	Yes: fully	GSK	III	3147	Yes	33
ABCSG-24	Neo**	Yes: partially	More than one industry	III	93	Yes	1
ACOZOG-Z1041	Neo**	No	-----	III	280	yes	2
BUZDAR	Neo**	Yes: partially	Genentech	III	42	No	1
CALGB40601	Neo**	No	----	III	305	Yes	1
CHANG	Neo**	Yes: fully	More than one industry	II	30	No	1
CHERLOB	Neo**	Yes: fully	GSK	II	121	Yes	N/A
GEICAM2006-14	Neo**	Yes: partially	GSK	II	102	Yes	1
GEPARQUINTO	Neo**	Yes: partially	More than one industry	III	615	Yes	2
GEPARSIXTO	Neo**	Yes: fully	More than one industry	II	273	Yes	1
HANNAH	Neo**	Yes: partially	Roche	III	596	Yes	27
JBCRG-10	Neo**	No	----	II	103	Yes	1
LAPATAX	Neo**	Yes: partially	GSK	II	128	Yes	5
NCT00826267	Neo**	Yes: partially	Boehringer Ingelheim	II	29	Yes	4
NEOALTO	Neo**	Yes: fully	GSK	III	455	1	23
NEOSPHERE	Neo**	Yes: fully	Roche	II	417	Yes	16
NOAH	Neo**	Yes: fully	Roche	III	235	Yes	6
NSABPB41	Neo**	Yes: fully	GSK	III	523	Yes	3
REMAGUS02	Neo**	Yes: partially	More than one industry	II	120	Yes	1
TRYPHAENA	Neo**	Yes: fully	Roche	II	225	Yes	19

Adj*: adjuvante trastuzumab / Neo**: Neoajuvant tratuzumab / N/A: non-available / GSK: GlaxoSmithKline

Part 2

STUDY	Year published	Median age (yr)	Node status	Minimum tumor size (mm)*	N (%) node negative	N (%) pre menopausal	N (%) hormone negative
ALTTO	2015	51	Node + and -	10	3012 (40.0%)	3636 (43.0%)	3576 (42.7%)
BCIRG006	2011	N/A	Node + and -	N/A	922 (28.62%)	N/A	N/A
CONSORT	2011	51.35	Node + and -	10	72 (40.0%)	N/A	77 (43.0%)
EXTENET	2015	52	Node + and -	N/A	671 (23.0%)	1327 (47.0%)	1209 (42.0%)
FINHER	2011	50.65	Node + and -	20	37 (15.95%)	N/A	120 (51.72%)
GIM2	2015	N/A	Node +	------	0 (0.0%)	N/A	N/A
HERA/BIG01-01	2005	49	Node + and -	10	1099 (32.3%)	491 (14.4%)	1686 (49.6%)
MAVROUDIS	2015	55	Node + and -	N/A	101 (21.0%)	183 (38.0%)	159 (33.0%)
NCCTG N9831	2005	N/A	Node + and -	10	284 (13.0%)	N/A	1062 (48.63%)
NSABP B31	2005	N/A	Node +	------	0 (0.0%)	N/A	987 (46.98%)
PACS	2009	48	Node +	------	0 (0.0%)	226 (42.8%)	213 (40.34%)
PHARE	2013	54.5	Node + and -	N/A	1842 (54.5%)	N/A	1319 (39.02%)
SHAUGHNESSY	2015	N/A	Node + and -	10	N/A	N/A	N/A
TEACH	2013	51.5	Node + and -	N/A	1386 (44.04%)	1021 (32.44%)	1288 (40.93%)
ABCSG-24	2013	49	Node + and -	N/A	44 (47.31%)	53 (56.98%)	36 (38.71%)
ACOZOG-Z1041	2013	N/A	Node + and -	20	101 (36.07%)	N/A	112 (40%)
BUZDAR	2005	50	Node + and -	20	17 (40.48%)	N/A	18 (42.86%)
CALGB40601	2013	N/A	Node + and -	10	N/A	N/A	N/A
CHANG	2010	N/A	Node + and -	20	N/A	N/A	N/A
CHERLOB	2012	49.3	Node + and -	20	N/A	51 (42.15%)	48 (39.67%)
GEICAM2006-14	2014	48	Node + and -	N/A	32 (31.0%)	57 (56.0%)	43 (42.0%)
GEPARQUINTO	2011	50	Node + and -	10	186 (30.24%)	N/A	274 (44.55%)
GEPARSIXTO	2014	N/A	Node + and -	10	N/A	N/A	N/A
HANNAH	2012	50	Node + and -	10	121 (23.0%)	N/A	257 (49.0%)
JBCRG-10	2012	54	Node + and -	N/A	N/A	N/A	N/A
LAPATAX	2014	48.7	Node + and -	20	43 (34.0%)	N/A	60 (47.0%)
NCT00826267	2014	49	N/A	N/A	N/A	N/A	13 (44.8%)
NEOALTO	2012	4966	Node + and -	20	N/A	N/A	223 (49.01%)
NEOSPHERE	2012	495	Node + and -	20	123 (29.5%)	N/A	219 (52.52%)
NOAH	2010	N/A	Node + and -	50	35 (14.89%)	N/A	151 (64.25%)
NSABPB41	2013	N/A	Node + and -	20	261 (49.0%)	N/A	198 (37.0%)
REMAGUS02	2010	47	Node + and -	30	43 (36.0%)	N/A	49 (41.0%)
TRYPHAENA	2013	49	Node + and -	20	68 (30.0%)	N/A	111 (49.0%)

N/A: non-available
* applies for node-negative patients

9.7. ESTUDOS SELECIONADOS: RISCOS DE VIÉS

STUDY	RISK OF BIAS EVALUATION DOMINIUM (Higgins, 2011)				
	Allocation sequence	Allocation conceal	Blinding	Incomplete outcome	Selective Reporting
ABCSG-24	Low risk	Unclear	High risk	Low risk	Low risk
ACOZOG-Z1041	Low risk	Unclear	High risk	Low risk	Low risk
ALTTO	Unclear	Unclear	High risk	Unclear	Unclear
BCIRG006	Unclear	Unclear	High risk	Low risk	Low risk
BUZDAR	Unclear	Unclear	High risk	Low risk	Low risk
CALGB40601	Unclear	Unclear	Unclear	Unclear	Unclear
CHANG	Unclear	Unclear	Unclear	Low risk	High risk
CHERLOB	Low risk	Low risk	High risk	Low risk	Low risk
CONSORT	Low risk	Low risk	High risk	Low risk	High risk
EXTENET	Unclear	Unclear	Unclear	Unclear	Unclear
FINHER	Low risk	Low risk	High risk	Low risk	Low risk
GEICAM2006-14	Unclear	Low risk	High risk	Low risk	Low risk
GEPARQUINTO	Low risk	Low risk	High risk	Low risk	Low risk
GEPARSIXTO	Low risk	Unclear	High risk	Low risk	Low risk
GIM2	Low risk	Low risk	High risk	Low risk	Low risk
HANNAH	Unclear	Low risk	High risk	Low risk	Low risk
HERA/BIG01-01	Unclear	Unclear	High risk	Low risk	Low risk
JBCRG-10	Unclear	Unclear	Unclear	Unclear	Unclear
LAPATAX	Unclear	Unclear	High risk	Low risk	Low risk
MAVROUDIS	Low risk	Low risk	High risk	Low risk	Low risk
NCCTG N9831	Unclear	Unclear	High risk	Low risk	Low risk
NCT00826267	Low risk	Low risk	High risk	Low risk	Low risk
NEOALTO	Low risk	Low risk	High risk	Low risk	Low risk
NEOSPHERE	Low risk	Low risk	High risk	Low risk	Low risk
NOAH	Low risk	Low risk	High risk	Low risk	Low risk
NSABP B31	Unclear	Unclear	High risk	Low risk	Low risk
NSABPB41	Low risk	Low risk	High risk	Low risk	Low risk
PACS	Unclear	Unclear	High risk	Low risk	Low risk
PHARE	Low risk	Low risk	High risk	Low risk	Low risk
REMAGUS02	Unclear	Unclear	High risk	Low risk	High risk
SHAUGHNESSY	Unclear	Low risk	High risk	High risk	Low risk

TEACH	Low risk	Low risk	Low risk	Low risk	Low risk
TRYPHAENA	Unclear	Unclear	High risk	Low risk	Low risk

9.8. ESTUDOS SELECIONADOS: BRAÇOS DE TRATAMENTO

STUDY	Arms of treatment
ABCSG-24	**ARM 1** **ED – surgery OR EDC – surgery** →ED q 21 days / 6 cycles // EDC q 21 days / 6 cycles //**total chemo**: 18 weeks • epirubicin 75 mg/m² IV D1 • docetaxel 75 mg/m² IV D1 • capecitabine 1000 mg/m² PO D1-D14 **ARM 2** **EDH – surgery or EDCH – surgery** →ED q 21 days / 6 cycles // EDC q 21 days / 6 cycles // H q 21 days / 6 cycles // **total chemo**: 18 weeks / **total trastuzumab**: 18 weeks • epirubicin 75 mg/m² IV D1 • docetaxel 75 mg/m² IV D1 • capecitabine 1000 mg/m² PO D1-D14 • trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose
ACOZOG-Z1041	**ARM 1** **FEC$_{75}$ – TH (paclitaxel) – surgery – H** → T q 7 days / 12 cycles // FEC q 21 days / 4 cycles // H q 7 days / 26 cycles // **total chemo** 24 weeks / **total trastuzumab** 52 weeks • paclitaxel 80 mg/m² IV D1 • fluorouracil 600 mg/² IV D1 • epirubicin 75 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose until complete 52 weeks of treatment **ARM 2** **TH (paclitaxel) – FEC$_{75}$H – surgery – H** → T q 7 days / 12 cycles // FEC q 21 days / 4 cycles // H q 7 days / 26 cycles // **total chemo** 24 weeks / **total trastuzumab** 52 weeks • paclitaxel 80 mg/m² IV D1 • fluorouracil 600 mg/² IV D1 • epirubicin 75 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose until the for 52 week
ALTTO	**ARM 1** **Any chemotherapy - H** →q ?? 21 days / ?? cycles // H q 21 days / 17,5 cycles // **total chemo**: ?? // **total trastuzumab**: 52 weeks (1 year) • paclitaxel 80 mg/m² IV D1 • docetaxel 75 mg/m² IV D1 • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose until the end of chemotherapy and then 6mg/kg until the end of the planned period for treatment with trastuzumab **ARM 2** **Any chemotherapy - L** → q ?? 21 days / ?? cycles // L q 28 days / 13 cycles // H q 21 days / 18 cycles // **total chemo:** ?? weeks // **total lapatinib: 52 weeks**

	• Lapatinib 1000 mg PO D1-D28 **ARM 3** **Any chemotherapy - H - L** → q ?? days / ?? cycles // H q 7 days / 12 cycles // L q 28 days / 8,5 cycles // **total chemo:** ?? weeks // **total trastuzumab**: 12 weeks (1 year) // **total lapatinib**: 34 weeks • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg • lapatinib: 1500mg PO D1-D28 **ARM 4** **Any chemotherapy - LH** → q ?? 21 days / ?? cycles // L q 28 days / 13 cycles // H q 21 days / 18 cycles // **total chemo:** ?? weeks // **total lapatinib and trastuzumab**: 52 weeks (1 year) • Lapatinib 1000 mg PO D1-D28 • Trastuzumab 8mg/kg IV loading dose followed by 6mg/kg IV every 3 weeks for a total of 52 weeks
BCIRG006	**ARM 1** **AC-T (docetaxel 21/21 days)** → AC q 21 days / 4 cycles // T q 21 days / 4 cycles // **total** 24 weeks • doxorubicin 60 mg/m² IV D1 • cyclophospmide 600 mg/m² IV D1 • docetaxel 100 mg/m² IV D1 **ARM 2** **AC-TH (docetaxel 21/21 days)** → AC q 21 days / 4 cycles // T: q 21 days / 4 cycles // H q 7 days / 12 cycles followed by q 21 days / 13 cycles // **total chemo** 24 weeks / **total trastuzumab** 52 weeks (1 year) • doxorubicin 60 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 • docetaxel 100 mg/m² IV D1 • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose until the end of chemotherapy and then 6mg/kg until the end of the planned period for treatment with trastuzumab **ARM 3** **TCH** → TC q 21 days / 6 cycles // H q 7 days / 18 cycles followed by q 21 days / 12 cycles // **total chemo** 18 weeks / **total trastuzumab** 52 weeks (1 year) • carboplatin AUC6 IV D1 • docetaxel 75 mg/m² IV D1 • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose until the end of chemotherapy and then 6mg/kg until the end of the planned period for treatment with trastuzumab
BUZDAR	**ARM 1** **T (paclitaxel) – FEC_{75} – surgery** → T q 21 days / 4 cycles // FEC: q 21 days / 4 cycles // H: q 7 days / 24 cycles // **total chemo** 24 weeks • paclitaxel 225 mg/m² IV D1 (24-hours continue infusion) • fluorouracil 500 mg/m² IV D1 and D4 • epirubicin 75 mg/m² IV D1 • cyclophosphamide 500 mg/m² IV D1 **ARM 2** **TH (paclitaxel) – FEC_{75}H – surgery** → T q 21 days / 4 cycles // H: q 7 days / 24 cycles // FEC: q 21 days / 4 cycles // **total chemo** 24 weeks / **total trastuzumab** 24 weeks (6 months) • Trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose

	• paclitaxel 225 mg/m² IV D1 (24-hours continue infusion) • fluorouracil 500 mg/m² IV D1 and D4 • epirubicin 75 mg/m² IV D1 • cyclophosphamide 500 mg/m² IV D1
CALGB40601	**ARM 1** **TH (paclitaxel) - surgery** → T q 7 days / 16 cycles // H q 7 days / 16 cycles // **total chemo**: 16 weeks / **total trastuzumab**: 16 weeks • paclitaxel: 80 mg/m² IV D1 • trastuzumab: 2 mg/kg IV D1 **ARM 2** **THL (paclitaxel) – surgery** → T q 7 days / 16 cycles // H q 7 days / 16 cycles // L q 28 days / 4 cycles // **total chemo**: 16 weeks / **total trastuzumab**: 16 weeks / **total lapatinib**: 16 weeks • paclitaxel: 80 mg/m² IV D1 • trastuzumab: 2 mg/kg IV D1 • lapatinib: 750 mg PO D1-D28 **ARM 3** **TL (paclitaxel) – surgery** → T q 7 days / 16 cycles // H q 7 days / 16 cycles // L q 28 days / 4 cycles // **total chemo**: 16 weeks / **total trastuzumab**: 16 weeks / **total lapatinib**: 16 weeks • paclitaxel: 80 mg/m² IV D1 • lapatinib: 750 mg PO D1-D28
CHANG	**ARM 1** **TC (docetaxel) – surgery – TC – H** → T q 21 days / 8 cycles // C q 21 days / 8 cycles // H q 21 days / 17 cycles // **total chemo**: 24 weeks / **total trastuzumab**: 52 weeks (1 year) • docetaxel 75 mg/m² IV D1 • carboplatin AUC 6 D1 • trastuzumab: 6 mg/kg IV D1 **ARM 2** **TCH (docetaxel) – surgery – TC – H** → T q 21 days / 8 cycles // C q 21 days / 8 cycles // H q 7 days / 12 cycles followed by q 21 days / 13 cycles // **total chemo**: 24 weeks / **total trastuzumab**: 52 weeks (1 year) • docetaxel 75 mg/m² IV D1 • carboplatin AUC 6 D1 • trastuzumab: 4mg/kg IV in the first dose followed by 2 mg/kg in each subsequent dose; afther chemo, 6 mg/kg IV D1
CHERLOB	**ARM 1** **TH (paclitaxel) – FEC_{75}H – surgery** → T q 7 days / 12 cycles // FEC q 21 days / 4 cycles // H q 7 days / 26 cycles // **total chemo** 24 weeks / **total trastuzumab** 26 weeks • paclitaxel 80 mg/m² IV D1 • fluorouracil 600 mg/² IV D1 • epirubicin 75 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose until the for 26 week **ARM 2** **TL (paclitaxel) – FEC_{75}L – surgery** → T q 7 days / 12 cycles // FEC q 21 days / 4 cycles // L q 28 days / 6.5 cycles // **total chemo** 24 weeks / **total lapatinib** 26 weeks • paclitaxel 80 mg/m² IV D1

	• fluorouracil 600 mg/^{2} IV D1 • epirubicin 75 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1 • lapatinib: 1500 mg VO D1-D28 **ARM 3** **THL –FEC$_{75}$HL – surgery** → T q 7 days / 12 cycles // FEC q 21 days / 4 cycles // H q 7 days / 26 cycles // L q 28 days / 6.5 cycles // **total chemo** 24 weeks / **total trastuzumab** 26 weeks / **total lapatinib** 26 weeks • paclitaxel 80 mg/m^2 IV D1 • fluorouracil 600 mg/^{2} IV D1 • epirubicin 75 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1 • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose until the for 52 weeks • lapatinib: 1000 mg VO D1-D28
CONSORT	**ARM 1** **AC-TH (paclitaxel 21/21 days or weekly)*** → AC q 21 days / 4 cycles // T: q 21 days / 4 cycles or q 7 days / 12 cycles // H q 7 days / 52 cycles // **total chemo** 24 weeks / **total trastuzumab** 52 weeks (1 year) • doxorubicin 60 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1 • paclitaxel 175 mg/m^2 IV D1 OR paclitaxel 80mg/m^2 IV D1 • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose **ARM 2** **PLDCH - TH** → PLDC q 21 days / 4 courses // T q 7 days / 12 cycles // **total chemo**: 24 weeks // **total trastuzumab**: 52 weeks • pegylated liposomal doxorubicin: 35 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1 • paclitaxel 80 mg/m^2 IV D1 • trastuzumab 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose
EXTENET	**ARM 1** **Any chemotherapy (adjuvant or neoadjuvant) – Any adjuvant trastuzumab** → at least 4 cycles // H q ?? days / ?? cycles // **total chemo** ?? / **total trastuzumab ??** **ARM 2** **Any chemotherapy (adjuvant or neoadjuvant) – Any adjuvant trastuzumab – N** → q ?? days / at least 4 cycles // H q ?? days / ?? cycles // N q 28 days / 12 cycles // **total chemo** ?? / **total trastuzumab** ?? // **total neratinib**: 52 weeks • Neratinib: 240 mg PO D1-D28
FINHER	**ARM 1** **V or T (docetaxel) - FEC$_{60}$** → V q 21 days / 3 cycles // FEC q 21 days / 3 cycles // **total chemo** 18 weeks • docetaxel 100 mg/m^2 IV D1 • Vinorelbine 25 mg/m^2 IV D1/D8/D15 (D15 of the third cycle was not administered in order not to delay the first dose of FEC) • fluorouracil 600 mg/m^2 IV D1 • epirubicin 60 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1 **ARM 2** **VH or TH (docetaxel) - FEC$_{60}$** → V q 21 days / 3 cycles// H q 7 days / 9 cycles //

	FEC q 21 days / 3 cycles // **total chemo** 18 weeks / **total trastuzumab** 9 weeks • docetaxel 100 mg/m² IV D1 • vinorelbine 25 mg/m² IV D1/D8/D15 (D15 of the third cycle was not administered in order not to delay the first dose of FEC • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose • fluorouracil 600 mg/m² IV D1 • epirubicin 60 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1
GEICAM2006-14	**ARM 1** **EC – TH (docetaxel) – surgery** → EC q 21 days / 4 cycles // T q 21 days / 4 cycles // H q 21 days / 4 cycles // **total chemo:** 24 weeks / **total trastuzumab:** 12 weeks (patients might have received more trastuzumab after surgery, but there is no outcome reported after the surgery) • epirubicin 90 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 • docetaxel 100 mg/m² IV D1 • trastuzumab 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose **ARM 2** **EC – TL (docetaxel) – surgery** → EC q 21 days / 4 cycles // T q 21 days / 4 cycles // L q 21 days / 4 cycles // **total chemo:** 24 weeks / **total lapatinib:** 12 weeks (patients might have received more trastuzumab after surgery, but there is no outcome reported after the surgery) • epirubicin 90 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 • docetaxel 100 mg/m² IV D1 • lapatinib 1250 mg PO D1-D21
GEPARQUINTO	**ARM 1** **ECH – TH (docetaxel) – surgery – H**→ EC q 21 days / 4 cycles // T q 21 days / 4 cycles // **total chemo** 24 weeks / **total trastuzumab** 52 weeks (1 year) • epirubicin 90 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 • docetaxel 100 mg/m² IV D1 • trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose until the for 52 weeks **ARM 2** **ECL – TL – surgery – H**→ EC q 21 days / 4 cycles // T q 21 days / 4 cycles // L q 28 days / 6 cycles // H q 21 days / 18 cycles // **total chemo** 24 weeks / **total lapatinib** 24 weeks / **total trastuzumab** 54 weeks (1 year) • epirubicin 90 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 • docetaxel 100 mg/m² IV D1 • lapatinib: 1000-1250 mg VO D1-D28 • trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose until the for 52 weeks
GEPARSIXTO	**ARM 1** **PLDTHL (paclitaxel) – surgery** → PLDT q 7 days / 18 cycles // H q 21 days / 6 cycles // L q 21 days / 6 cycles // **total chemo**: 18 weeks / **total trastuzumab**: 18 weeks / **total lapatinib**: 18 weeks • pegylated liposomal doxorubicin 20 mg/m² IV D1 • paclitaxel 80 mg/m² IV D1 • trastuzumab 8 mg/kg IV in the first dose followed by 6 mg/kg IV in each subsequent dose • lapatinib 750 mg PO D1-D21 **ARM 2**

	PLDCTHL (paclitaxel) – surgery → PLDCT q 7 days / 18 cycles // H q 21 days / 6 cycles // L q 21 days / 6 cycles // **total chemo**: 18 weeks / **total trastuzumab**: 18 weeks / **total lapatinib**: 18 weeks • carboplatin AUC 1,5 – 2,0 IV D1 • pegylated liposomal doxorubicin 20 mg/m² IV D1 • paclitaxel 80 mg/m² IV D1 • trastuzumab 8 mg/kg IV in the first dose followed by 6 mg/kg IV in each subsequent dose • lapatinib 750 mg PO D1-D21
GIM2	**ARM 1** **FEC_{90} or EC – T (paclitaxel) – H** → FEC q 21 days / 4 cycles // EC q 21 days / 4 cycles // T q 21 days / 4 cycles // H q 21 days / 17 cycles // **total chemo**: 24 weeks / **total trastuzumab**: 52 weeks • fluorouracil 600 mg/m² IV D1 • epirubicin 90 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 • paclitaxel 175 mg/m² IV D1 • trastuzumab 8 mg/kg IV in the first dose, followed by 6 mg/ kg IV in each subsequent dose **ARM 2** **ddFEC_{90} or ddEC – ddT (paclitaxel) – H** → FEC q 14 days / 4 cycles // EC q 14 days / 4 cycles // T q 14 days / 4 cycles // H q 21 days / 17 cycles // **total chemo**: 16 weeks (dose-dense) / **total trastuzumab**: 52 weeks • fluorouracil 600 mg/m² IV D1 • epirubicin 90 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 • paclitaxel 175 mg/m² IV D1 • trastuzumab 8 mg/kg IV in the first dose, followed by 6 mg/ kg IV in each subsequent dose
HANNAH	**ARM 1** **TH – FEC_{75}H – surgery – H** →T q 21 days / 4 cycles // FEC q 21 days / 4 cycles // H q 21 days / 18 cycles // **total chemo**: 24 weeks / **total trastuzumab**: 52 weeks (1 year) • docetaxel 75 mg/m² IV D1 • fluorouracil 500 mg/m² IV D1 • epirubicin 75 mg/m² IV D1 • cyclophosphamide 500 mg/m² IV D1 • trastuzumab 8 mg/kg IV in the first dose, followed by 6 mg/kg IV in each subsequent dose **ARM 2** **TsH – FEC_{75}sH – surgery – sH** →T q 21 days / 4 cycles // FEC q 21 days / 4 cycles // sH q 21 days / 18 cycles // **total chemo**: 24 weeks / **total subcutaneous trastuzumab**: 52 weeks (1 year) • docetaxel 75 mg/m² IV D1 • fluorouracil 500 mg/m² IV D1 • epirubicin 75 mg/m² IV D1 • cyclophosphamide 500 mg/m² IV D1 • subcutaneous trastuzumab 600 mg SC D1
HERA/BIG01-01	**ARM 1** **Any chemotherapy (adjuvant or neoadjuvant)** → at least 4 cycles // **total chemo** ?? **ARM 2** **Any chemotherapy (adjuvant or neoadjuvant) - H** → q ?? days / at least 4 cycles

	// H q 21 days / 17 cycles // **<u>total chemo</u>** ?? / **<u>total trastuzumab</u>** 52 weeks (1 year) • Trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose
JBCRG-10	**<u>ARM 1</u>** **FEC$_{100}$ – TCH OR TCH – FEC$_{100}$ – surgery** → FEC q 21 days / 4 cycles // TC q 21 days / 4 cycles // H q 21 days / 4 cycles // **total chemo:** 24 weeks / **total trastuzumab:** 12 weeks • fluorouracil 500 mg/m^2 D1 • epirubicin 100 mg/m^2 D1 • cyclophosphamide 500 mg/m^2 D1 • docetaxel 75 mg/m^2 D1 • cyclophosphamide 600 mg/m^2 D1 • trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose **<u>ARM 2</u>** **TCH – surgery** → TC q 21 days / 6 cycles // H q 21 days / 6 cycles // **<u>total chemo</u>**: 18 weeks / **<u>total trastuzumab</u>**: 18 weeks • docetaxel 75 mg/m^2 D1 • cyclophosphamide 600 mg/m^2 D1 • trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose
LAPATAX	**<u>ARM 1</u>** **TH – FEC$_{100}$ – surgery** → T q 21 days / 3 cycles // FEC q 21 days / 3 cycles // H q 21 days / 3 cycles // **<u>total chemo</u>**: 18 weeks / **<u>total trastuzumab</u>**: 9 weeks • docetaxel 100 mg/m^2 IV D1 • fluorouracil 500 mg/m^2 IV D1 • epirubicin 100 mg/m^2 IV D1 • cyclophosphamide 500 mg/m^2 IV D1 • trastuzumab 4 mg/kg IV in the first dose, followed by 2 mg/kg IV in each subsequent dose **<u>ARM 2</u>** **TL – FEC$_{100}$ – surgery** → T q 21 days / 3 cycles // FEC q 21 days / 3 cycles // L q 21 days / 3 cycles // **<u>total chemo</u>**: 18 weeks / **<u>total lapatinib</u>**: 9 weeks • docetaxel 100 mg/m^2 IV D1 • fluorouracil 500 mg/m^2 IV D1 • epirubicin 100 mg/m^2 IV D1 • cyclophosphamide 500 mg/m^2 IV D1 • lapatinib 1000 mg PO D1-D21 **<u>ARM 3</u>** **THL – FEC$_{100}$ – surgery** → T q 21 days / 3 cycles // FEC q 21 days / 3 cycles // H q 21 days / 3 cycles // L q 21 days / 3 cycles // **<u>total chemo</u>**: 18 weeks / **<u>total trastuzumab</u>**: 9 weeks / **<u>total lapatinib</u>**: 9 weeks • docetaxel 100 mg/m^2 IV D1 • fluorouracil 500 mg/m^2 IV D1 • epirubicin 100 mg/m^2 IV D1 • cyclophosphamide 500 mg/m^2 IV D1 • lapatinib 1000 mg PO D1-D21 • trastuzumab 4 mg/kg IV in the first dose, followed by 2 mg/kg IV in each subsequent dose
MAVROUDIS	**<u>ARM 1</u>** **FEC$_{75}$ – TH** → FEC$_{75}$ q 14 days / 4 cycles // T q 14 days / 4 cycles // H q 14 days / 4

	cycles followed by q 21 days / 15 cycles // **total chemo**: 16 weeks // **total trastuzumab**: 52 weeks (1 year) • fluorouracil 700 mg/m² IV D1 • epirubicin 75 mg/m² IV D1 • cyclophosphamide 700 mg/m² IV D1 • docetaxel 75 mg/m² IV D1 • trastuzumab 4mg/kg in combination with chemotherapy, followed by 6mg/kg in each subsequent dose for a total of 12 months **ARM 2** **FEC_{75} – TH** → FEC_{75} q 14 days / 4 cycles // T q 14 days / 4 cycles // H q 14 days / 4 cycles followed by q 21 days / 6 cycles // **total chemo**: 16 weeks // **total trastuzumab**: 24 weeks (6 months) • fluorouracil 700 mg/m² IV D1 • epirubicin: 75 mg/m² IV D1 • cyclophosphamide 700 mg/m² IV D1 • docetaxel 75 mg/m² IV D1 • trastuzumab 4mg/kg in combination with chemotherapy, followed by 6mg/kg in each subsequent dose for a total of 6 months
NCCTG N9831	**ARM 1** **AC-T (paclitaxel 21/21 days or weekly)** → AC q 21 days / 4 cycles // T: q 21 days / 4 cycles or q 7 days / 12 cycles // **total** 24 weeks • doxorubicin 60 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 • paclitaxel 175 mg/m² IV D1 OR paclitaxel 80mg/m² IV D1 **ARM 2** **AC-TH (paclitaxel 21/21 days or weekly)** → AC q 21 days / 4 cycles // T: q 21 days / 4 cycles or q 7 days / 12 cycles // H q 7 days / 52 cycles // **total chemo** 24 weeks / **total trastuzumab** 52 weeks (1 year) • doxorubicin 60 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 • paclitaxel 175 mg/m² IV D1 OR paclitaxel 80mg/m² IV D1 • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose
NCT00826267	**ARM 1** **A – any chemo – surgery** →A q 21 days / 2 cycles // chemo ?? days / ?? cycles // **total afatinib**: 6 weeks / **total chemo**: ?? • afatinib 50 mg PO D1-D21 **ARM 2** **L – any chemo – surgery** →L q 21 days / 2 cycles // chemo ?? days / ?? cycles // **total lapatinib**: 6 weeks / **total chemo**: ?? • lapatinib 1500 mg PO D1-D21 **ARM 3** **H – any chemo – surgery** →H q 21 days / 2 cycles // chemo ?? days / ?? cycles // **total trastuzumab**: 6 weeks / **total chemo**: ?? • trastuzumab 4 mg/kg IV in the first dose, followed by 2 mg/kg IV in each subsequent dose
NEOALTO	**ARM 1** **H – TH (paclitaxel) – surgery – FEC_{100} – H** → H q 7 days / 52 cycles // T q 7 days / 12 cycles // **total chemo**: 19 weeks / **total trastuzumab** 52 weeks (1 year) • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose until the for 52 weeks

	• paclitaxel 80 mg/m² IV D1/D8/D15 • Fluorouracil 500 mg/m² IV D1 • Epirubicin 100 mg/m² IV D1 • Cyclophosphamide 500 mg/m² IV D1 **ARM 2** **L – TL (paclitaxel) – surgery – FEC$_{100}$ – L** → L q 28 days / 12 cycles // T q 7 days / 12 cycles // **total chemo**: 19 weeks / **total lapatinib** 52 weeks (1 year) • lapatinib: 1500mg PO D1-D28 • paclitaxel 80 mg/m² IV D1/D8/D15 • Fluorouracil 500 mg/m² IV D1 • Epirubicin 100 mg/m² IV D1 • Cyclophosphamide 500 mg/m² IV D1 **ARM 3** **HL – THL (paclitaxel) – surgery – FEC$_{100}$ – HL** → H q 7 days / 52 cycles // L q 28 days / 12 cycles // T q 7 days / 12 cycles // **total chemo**: 19 weeks / **total lapatinib** 52 weeks (1 year) / **total trastuzumab** 52 weeks (1 year) • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose until the for 52 weeks • lapatinib: 1000mg PO D1-D28 • paclitaxel 80 mg/m² IV D1/D8/D15 • Fluorouracil 500 mg/m² IV D1 • Epirubicin 100 mg/m² IV D1 • Cyclophosphamide 500 mg/m² IV D1
NEOSPHERE	**ARM 1** **HT (docetaxel) – surgery – FEC$_{90}$H** → H q 21 days / 18 cycles // T q 21 days / 4 cycles // FECH q 21 days / 3 cycles // **total chemo**: 21 weeks / **total trastuzumab** 52 weeks (1 year) • trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose until the for 52 weeks • docetaxel 75-100 mg/m² IV D1 • fluorouracil 600 mg/² IV D1 • epirubicin 90 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 **ARM 2** **PertHT (docetaxel) – surgery – FEC$_{90}$H** → Pert q 21 days / 4 cycles // T q 21 days / 4 cycles // FECH q 21 days / 3 cycles // H q 21 / 52 cycles // **total chemo**: 21 weeks / **total pertuzumab** 12 weeks / **total trastuzumab** 52 weeks (1 year) • pertuzumab: 840mg in the first dose, followed by 420mg in each subsequent cycle • docetaxel 75-100 mg/m² IV D1 • trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose until the for 52 weeks • fluorouracil 600 mg/² IV D1 • epirubicin 90 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1 **ARM 3** **PertH – surgery – TH (docetaxel) – FEC$_{90}$H** → Pert q 21 days / 4 cycles // H q 21 / 52 cycles //T q 21 days / 4 cycles // FEC q 21 days / 3 cycles // **total chemo**: 21 weeks / **total pertuzumab** 12 weeks / **total trastuzumab** 52 weeks (1 year) • pertuzumab: 840mg in the first dose, followed by 420mgg in each subsequent cycle • trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose until the for 52 weeks • docetaxel 75-100 mg/m² IV D1 • fluorouracil 600 mg/² IV D1 • epirubicin 90 mg/m² IV D1 • cyclophosphamide 600 mg/m² IV D1

	ARM 4 **PertT (docetaxel) – surgery – $FEC_{90}H$** → Pert q 21 days / 4 cycles // T q 21 days / 4 cycles //H q 21 / 52 cycles // FEC q 21 days / 3 cycles // **total chemo**: 21 weeks / **total pertuzumab** 12 weeks / **total trastuzumab** 52 weeks (1 year) • pertuzumab: 840mg in the first dose, followed by 420mgg in each subsequent cycle • docetaxel 75-100 mg/m^2 IV D1 • trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose until the for 52 weeks • fluorouracil 600 mg/^{2} IV D1 • epirubicin 90 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1
NOAH	**ARM 1** **AT (paclitaxel) – T (paclitaxel) – CMF – surgery**→ AT q 21 days / 3 cycles // T q 21 days / 4 cycles // CMF q 28 days / 3 cycles // **total chemo** 33 weeks • doxorubicin 60 mg/m^2 IV D1 • paclitaxel 150 mg/m^2 IV D1 • paclitaxel 175 mg/m^2 IV D1 • fluorouracil 600 mg/m^2 IV D1 and D8 • cyclophosphamide 600 mg/m^2 IV D1 and D8 • methotrexate 40mg/m2 IV D1 and D8 **ARM 2** **ATH (paclitaxel) – TH (paclitaxel) – CMFH – surgery – H**→ AT q 21 days / 3 cycles // T q 21 days / 4 cycles // CMF q 28 days / 3 cycles // **total chemo** 33 weeks / **total trastuzumab** 52 weeks (1 year) • doxorubicin 60 mg/m^2 IV D1 • paclitaxel 150 mg/m^2 IV D1 • paclitaxel 175 mg/m^2 IV D1 • fluorouracil 600 mg/m^2 IV D1 and D8 • cyclophosphamide 600 mg/m^2 IV D1 and D8 • methotrexate 40mg/m2 IV D1 and D8 • trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose until the for 52 weeks
NSABP B31	**ARM 1** **AC-T (paclitaxel 21/21 days or weekly)** → AC q 21 days / 4 cycles // T: q 21 days / 4 cycles or q 7 days / 12 cycles // **total** 24 weeks • doxorubicin 60 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1 • paclitaxel 175 mg/m^2 IV D1 OR paclitaxel 80mg/m^2 IV D1 **ARM 2** **AC-TH (paclitaxel 21/21 days or weekly)** → AC q 21 days / 4 cycles // T: q 21 days / 4 cycles or q 7 days / 12 cycles // H q 7 days / 52 cycles // **total chemo** 24 weeks / **total trastuzumab** 52 weeks (1 year) • doxorubicin 60 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1 • paclitaxel 175 mg/m^2 IV D1 OR paclitaxel 80mg/m^2 IV D1 • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose
NSABPB41	**ARM 1** **AC – TH (paclitaxel) – surgery – H** →AC q 21 days / 4 cycles // T q 7 days / 12 cycles // H q 7 days / 12 cycles followed by q 21 days / 14 cycles // **total chemo**: 24 weeks // **total trastuzumab**: 52 weeks (1 year) • doxorubicin 60 mg/m^2 IV D1

	• cyclophosphamide 600 mg/m^2 IV D1 • paclitaxel 80 mg/m^2 IV D1 • trastuzumab 4 mg/kg IV in the first dose followed by 2 mg/kg IV weekly until the end of chemotherapy; after surgery, 6 mg/kg IV D1 **ARM 2** **AC – TL (paclitaxel) – surgery – H** →AC q 21 days / 4 cycles // T q 7 days / 12 cycles // L q 21 days / 4 cycles // H q 21 days / 14 cycles // **total chemo**: 24 weeks / **total lapatinib**: 12 weeks / **total trastuzumab**: 52 weeks (1 year) • doxorubicin 60 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1 • paclitaxel 80 mg/m^2 IV D1 • lapatinib 1500 mg PO D1-D21 • trastuzumab 6 mg/kg IV D1 **ARM 3** **AC – THL (paclitaxel) – surgery – H** →AC q 21 days / 4 cycles // T q 7 days / 12 cycles // L q 21 days / 4 cycles // H q 7 days / 12 cycles followed by q 21 days / 14 cycles // **total chemo**: 24 weeks / **total lapatinib**: 12 weeks / **total trastuzumab**: 52 weeks (1 year) • doxorubicin 60 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1 • paclitaxel 80 mg/m^2 IV D1 • lapatinib 1500 mg PO D1-D21 • trastuzumab 4 mg/kg IV in the first dose followed by 2 mg/kg IV weekly until the end of chemotherapy; after surgery, 6 mg/kg IV D1
PACS	**ARM 1** **ET (docetaxel) – H* or FEC$_{100}$ – H** → ET q 21 days / 6 cycles // H q 21 days / 17 cycles // **total chemo**: 18 weeks / **total trastuzumab** 52 weeks (1 year) • epirubicin 75 mg/m^2 IV D1 • docetaxel 75 mg/m^2 IV D1 • Trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose OR • fluorouracil 500 mg/m^2 IV D1 • epirubicin 100 mg/m^2 IV D1 • cyclophosphamide 500 mg/m^2 IV D1 • Trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose **ARM 2** **ET (docetaxel) or FEC$_{100}$** → ET q 21 days / 6 cycles // **total chemo** 18 weeks • epirubicin 75 mg/m^2 IV D1 • docetaxel 75 mg/m^2 IV D1 OR • fluorouracil 500 mg/m^2 IV D1 • epirubicin 100 mg/m^2 IV D1 • cyclophosphamide 500 mg/m^2 IV D1
PHARE	**ARM 1** **Any chemotherapy (adjuvant or neoadjuvant) - H** → q ?? days / at least 4 cycles // H q 21 days / 17 cycles // **total chemo** ?? / **total trastuzumab** 52 weeks (1 year) • Trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose **ARM 2** **Any chemotherapy (adjuvant or neoadjuvant) - H** → q ?? days / at least 4 cycles

	// H q 21 days / 8 cycles // **total chemo** ?? / **total trastuzumab** 24 weeks (6 months) • Trastuzumab: 8mg/kg in the first dose, followed by 6mg/kg in each subsequent dose
REMAGUS02	**ARM 1** **EC – T (docetaxel) – surgery – H** →EC q 21 days / 4 cycles // T q 21 days / 4 cycles // H q 21 days / 18 cycles // **total chemo**: 24 weeks / **total trastuzumab**: 54 weeks (1 year) • epirubicin 75 mg/m^2 IV D1 • cyclophosphamide 750 mg/m^2 IV D1 • docetaxel 100 mg/m^2 IV D1 • trastuzumab 8 mg/kg IV in the first dose, followed by 6 mg/kg IV in each subsequent dose **ARM 2** **EC – TH (docetaxel) – surgery – H** → EC q 21 days / 4 cycles // T q 21 days / 4 cycles // H q 21 days / 22 cycles // **total chemo**: 24 weeks / **total trastuzumab**: 66 weeks • epirubicin 75 mg/m^2 IV D1 • cyclophosphamide 750 mg/m^2 IV D1 • docetaxel 100 mg/m^2 IV D1 • trastuzumab 8 mg/kg IV in the first dose, followed by 6 mg/kg IV in each subsequent dose
SHAUGHNESSY	**ARM 1** **AC-TH (docetaxel 21/21 days)*** → AC q 21 days / 4 cycles // T: q 21 days / 4 cycles // H q 7 days / 12 cycles followed by q 21 days / 13 cycles // **total chemo** 24 weeks / **total trastuzumab** 52 weeks (1 year) • doxorubicin 60 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1 • docetaxel 100 mg/m^2 IV D1 • trastuzumab: 4mg/kg in the first dose, followed by 2mg/kg in each subsequent dose until the end of chemotherapy and then 6mg/kg until the end of the planned period for treatment with trastuzumab **ARM 2** **AC – XT – H** →AC q 21 days / 4 cycles / XT q 21 days / 4 cycles // H q 21 days / 18 cycles // **total chemo**: 24 weeks / **total trastuzumab**: 52 weeks • doxorubicin 60 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1 • docetaxel 100 mg/m^2 IV D1 • capecitabine 825 mg/m^2 PO D1-D21
TEACH	**ARM 1** **Any chemotherapy (adjuvant or neoadjuvant) - L** → at least 4 cycles // L q 28 days / 12 cycles // **total chemo** ?? / **total lapatinib** 52 weeks (1 year) • lapatinib: 1500 mg VO D1-D28 **ARM 2** **Any chemotherapy (adjuvant or neoadjuvant)** → at least 4 cycles // **total chemo** ??
TRYPHAENA	**ARM 1** **FEC$_{100}$PertH – TPertH (docetaxel) – surgery – H** →FEC q 21 days / 3 cycles // T q 21 days / 3 cycles // Pert q 21 days / 6 cycles // H q 21 days / 18 cycles // **total chemo**: 18 weeks / **total pertuzumab**: 18 weeks / **total trastuzumab**: 52 weeks (1 year)

	• fluorouracil 500 mg/m^2 IV D1 • epirubicin 100 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1 • docetaxel 75 mg/m^2 IV D1 • pertuzumab 840 mg IV in the first dose, followed by 420 mg IV in each subsequent dose • trastuzumab 8 mg/kg IV in the first dose, followed by 6 mg/kg IV in each subsequent dose **ARM 2** **FEC$_{100}$ – TPertH (docetaxel) – surgery – H** →FEC q 21 days / 3 cycles // T q 21 days / 3 cycles // Pert q 21 days / 3 cycles // H q 21 days / 18 cycles // **total chemo**: 18 weeks / **total pertuzumab**: 9 weeks / **total trastuzumab**: 52 weeks (1 year) • fluorouracil 500 mg/m^2 IV D1 • epirubicin 100 mg/m^2 IV D1 • cyclophosphamide 600 mg/m^2 IV D1 • docetaxel 75 mg/m^2 IV D1 • pertuzumab 840 mg IV in the first dose, followed by 420 mg IV in each subsequent dose • trastuzumab 8 mg/kg IV in the first dose, followed by 6 mg/kg IV in each subsequent dose **ARM 3** **TCPertH (docetaxel) – surgery – H** →TC q 21 days / 6 cycles // Pert q 21 days / 6 cycles // H q 21 days / 18 cycles // **total chemo**: 18 weeks / **total pertuzumab**: 18 weeks / **total trastuzumab**: 52 weeks (1 year) • docetaxel 75 mg/m^2 IV D1 • carboplatin AUC 6 IV D1 • pertuzumab 840 mg IV in the first dose, followed by 420 mg IV in each subsequent dose • trastuzumab 8 mg/kg IV in the first dose, followed by 6 mg/kg IV in each subsequent dose

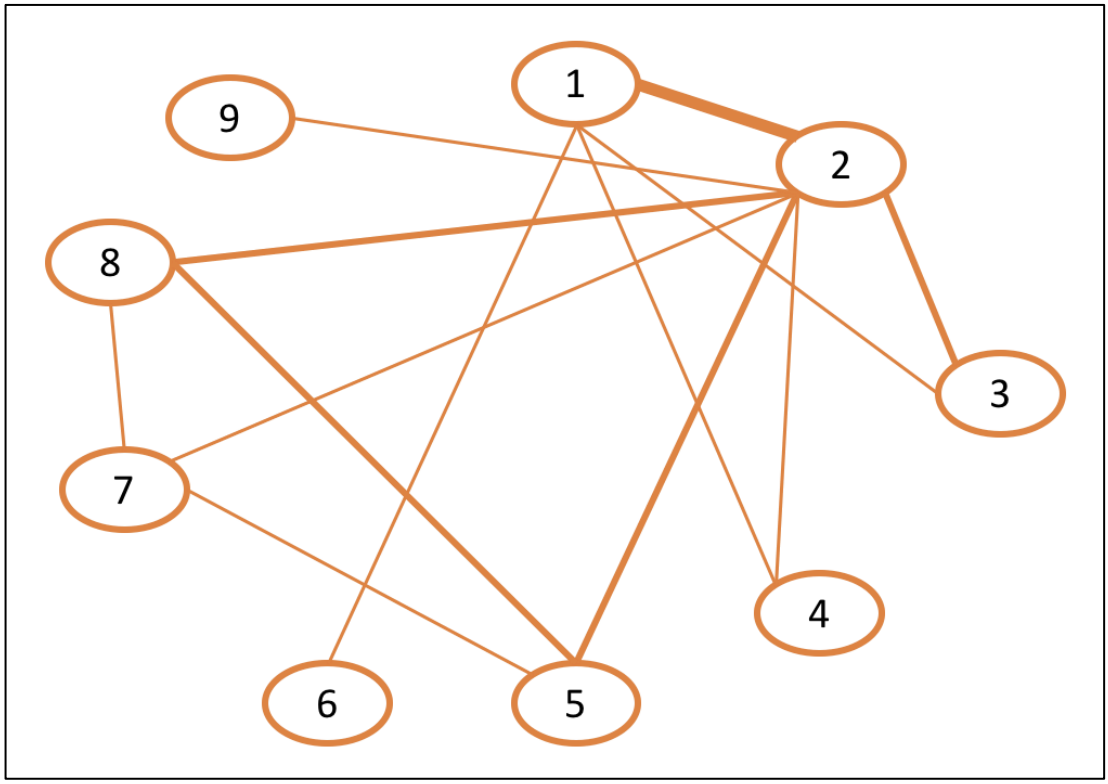
9.9. REDE 1: SOBREVIDA GLOBAL

Legend for treatment arms

10. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
11. ANY CHEMO / TRASTUZUMAB 12 mo
12. ANY CHEMO / TRASTUZUMAB ≤6 mo
13. TAXANE / TRASTUZUMAB 12 mo
14. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
15. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
16. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
17. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
18. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo

STUDY	COMPARISON	HR	COMPARISON	HR	COMPARISON	HR
BCIRG006	2 vs. 1	0.59 (0.42-0.85)	4 vs. 1	0.66 (0.47-0.93)	----------	--
HERA	2 vs. 1	0.66 (0.47-0.91)	----------	--	----------	--
NSABP_B31 AND NCCTGN9831	2 vs. 1	0.61 (0.50-0.75)	----------	--	----------	--
PACS	2 vs. 1	1.27 (0.68-2.38)	----------	--	----------	--
FINHER	3 vs. 1	0.41 (0.16-1.08)	----------	--	----------	--
TEACH	6 vs. 1	0.99 (0.74-1.31)	----------	--	----------	--
PHARE	3 vs. 2	1.46 (1.06-2.01)	----------	--	----------	--
MAVROUDIS	3 vs. 2	1.45 (0.57-3.67)	----------	--	----------	--
ALTTO	5 vs. 2	1.36 (1.09-1.72)	7 vs.2	0.91 (0.71-1.16)	8 vs. 2	0.80 (0.62-1.03)
NEOALTTO	5 vs. 2	0.86 (0.45-1.63)	8 vs. 2	0.62 (0.30-1.25)	----------	--
GIM2	9 vs 2	0.93 (0.35-2.54)	----------	--	----------	--

Network design for Overall Survival (OS)



Legend for treatment arms

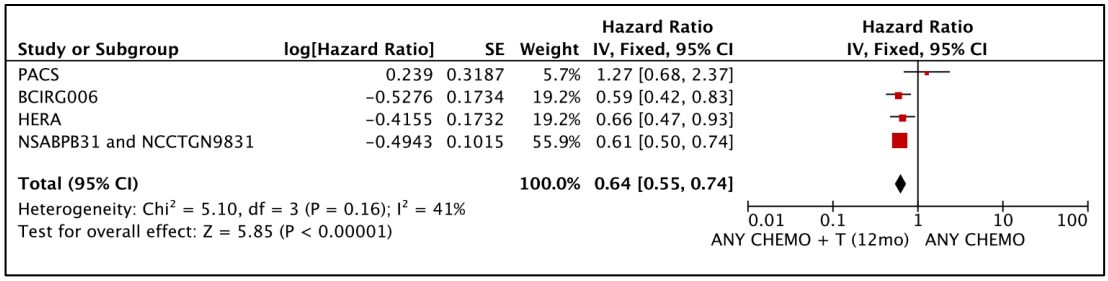
01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo
05. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo

9.10. REDE 1: SOBREVIDA GLOBAL – DEFINIÇÃO

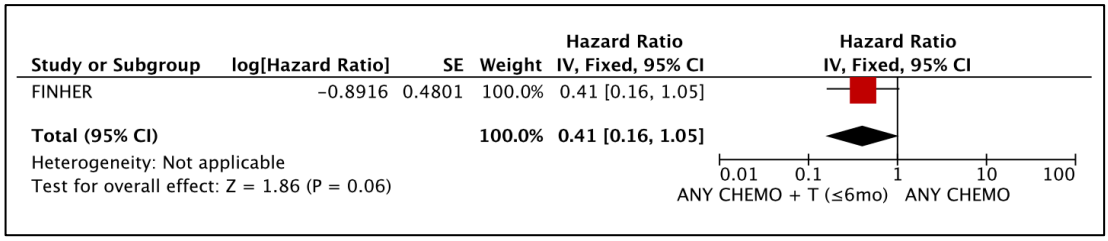
Todos os estudos incuídos nessa rede utilizaram análise por intenção de tratamento e definiram sobrevida global da mesma forma: tempo medido da randomização até a censura do dado ou ocorrência de evento (morte)

9.11. REDE 1: SOBREVIDA GLOBAL – COMPARAÇÕES "*PAIRWISE*"

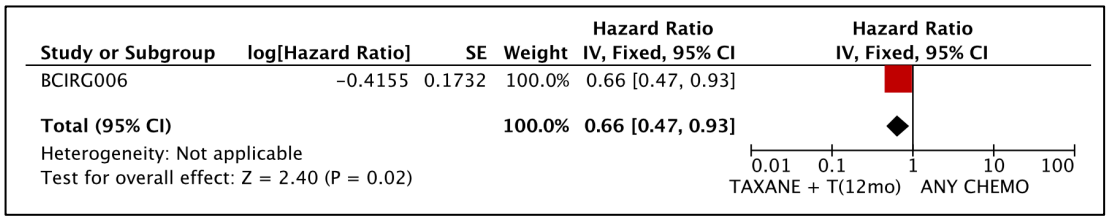
9.11.1. Comparison 1: ANY CHEMO ALONE (NO ANTI-HER2 THERAPY) (arm 1) vs ANY CHEMO / TRASTUZUMAB 12 months (arm 2)



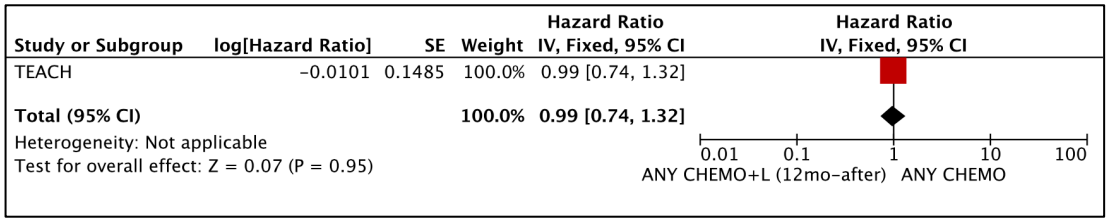
9.11.2. Comparison 2: ANY CHEMO ALONE (NO ANTI-HER2 THERAPY) (arm 1) vs ANY CHEMO / TRASTUZUMAB ≤6 months (arm 3)



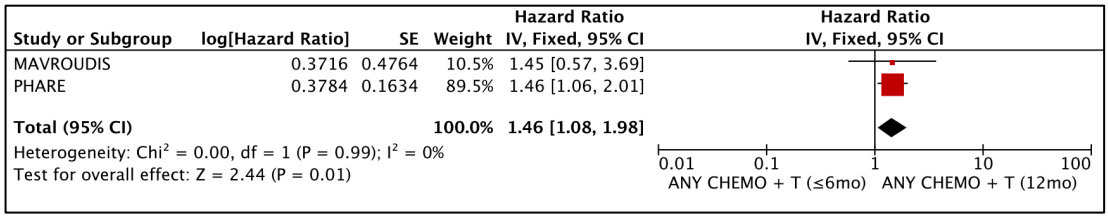
9.11.3. Comparison 3: ANY CHEMO ALONE (NO ANTI-HER2 THERAPY) (arm 1) vs TAXANE / TRASTUZUMAB 12 months (arm 4)



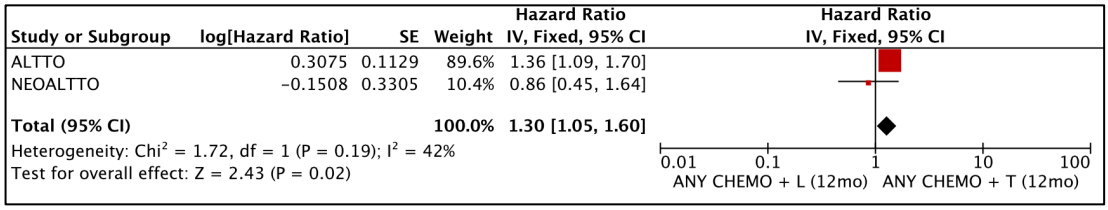
9.11.4. Comparison 4: ANY CHEMO ALONE (NO ANTI-HER2 THERAPY) (arm 1) vs ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12 months (initiated at any time after adjuvant therapy) (arm 6)



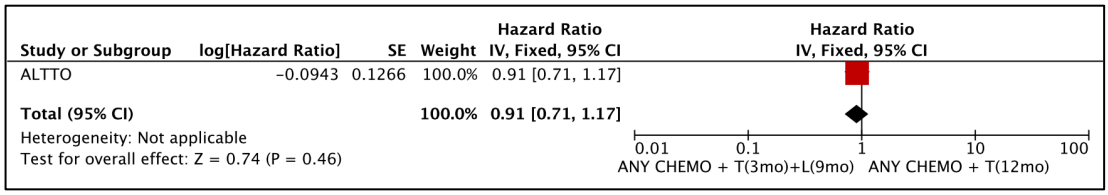
9.11.5. Comparison 5: ANY CHEMO / TRASTUZUMAB 12 months (arm 2) vs ANY CHEMO / TRASTUZUMAB ≤6 months (arm 3)



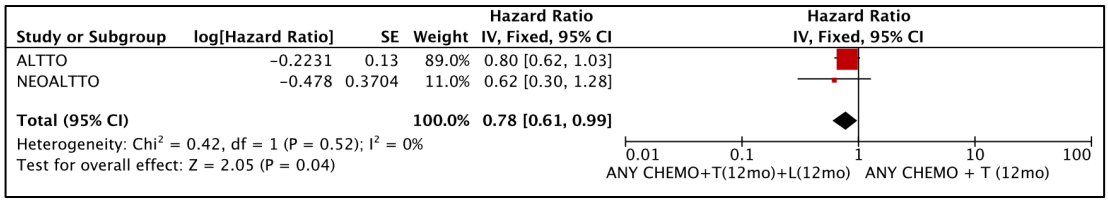
9.11.6. Comparison 6: ANY CHEMO / TRASTUZUMAB 12 months (arm 2) vs ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12 months (arm 5)



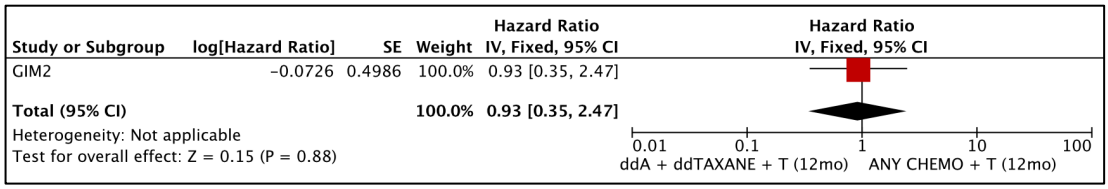
9.11.7. Comparison 7: ANY CHEMO / TRASTUZUMAB 12 months (arm 2) vs ANY CHEMO / TRASTUZUMAB 3 months / LAPATINIB 9 months (arm 7)



9.11.8. Comparison 8: ANY CHEMO / TRASTUZUMAB 12 months (arm 2) vs ANY CHEMO / TRASTUZUMAB 12 months / LAPATINIB 12 months (arm 8)



9.11.9. Comparison 9: ANY CHEMO / TRASTUZUMAB 12 months (arm 2) vs ddANTHRA + ddTAXANE / TRASTUZUMAB 12 months (arm 9)



9.12. REDE 1: SOBREVIDA GLOBAL – RANQUEAMENTO

	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Arm 7	Arm 8	Arm 9
Rank 1	0.0%	0.44%	0.0%	2.27%	0.0%	0.0%	9.03%	52.35%	35.97%
Rank 2	0.0%	5.06%	0.37%	6.65%	0.0%	0.0%	40.7%	37.47%	9.8%
Rank 3	0.0%	32.80%	1.02%	13.63%	0.40%	0.0%	34.13%	8.62%	9.28%
Rank 4	0.0%	45.80%	4.23%	24.27%	4.74%	0.8%	11.23%	1.58%	7.41%
Rank 5	0.27%	15.33%	13.72%	32.31%	21.01%	3.84%	4.00%	0.48%	9.11%
Rank 6	2.76%	0.57%	27.51%	13.96%	38.36%	10.4%	0.41%	0.0%	5.8%
Rank 7	16.07%	0.0%	29.75%	5.52%	24.65%	18.00%	0.50%	0.0%	6.00%
Rank 8	45.21%	0.0%	13.40%	1.17%	8.12%	28.69%	0.0%	0.0%	3.41%
Rank 9	35.69%	0.0%	10.00%	0.41%	2.71%	38.25%	0.0%	0.0%	13.15%

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo
05. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo

9.13. REDE 1: SOBREVIDA GLOBAL – *HAZARD RATIOS* GERAIS

1	**0.63** (0.54-0.73)	0.86 (0.62-1.17)	**0,68** (0.50-0.93)	0.81 (0.62-1.06)	0.99 (0.73-1.33)	**0,55** (0.41-0.74)	**0,49** (0.37-0.64)	0.58 (0.22-1.63)
0.63 (0.54-0.73)	**2**	**1.35** (1.01-1.81)	1.09 (0.80-1.47)	**1.29** (1.04-1.60)	**1.57** (1.14-2.17)	0.88 (0.69-1.12)	**0,78** (0.61-0.99)	0.92 (0.34-2.54)
0.86 (0.62-1.17)	**1.35** (1.01-1.81)	**3**	0.80 (0.52-1.21)	0.95 (0.66-1.37)	1.16 (0.76-1.78)	**0,65** (0.45-0.95)	**0,57** (0.40-0.84)	0.68 (0.24-1.94)
0,68 (0.50-0.93)	1.09 (0.80-1.47)	0.80 (0.52-1.21)	**4**	1.19 (0.82-1.73)	1.45 (0.96-2.20)	0.82 (0.55-1.20)	0.72 (0.48-1.06)	0.85 (0.30-2.46)
0.81 (0.62-1.06)	**1.29** (1.04-1.60)	0.95 (0.66-1.37)	1.19 (0.82-1.73)	**5**	1.21 (0.83-1.80)	**0,68** (0.54-0.86)	**0,60** (0.48-0.75)	0.71 (0.26-2.01)
0.99 (0.73-1.33)	**1.57** (1.14-2.17)	1.16 (0.76-1.78)	1.45 (0.96-2.20)	1.21 (0.83-1.80)	**6**	**0,56** (0.37-0.84)	**0,50** (0.32-0.74)	0.59 (0.21-1.71)
0,55 (0.41-0.74)	0.88 (0.69-1.12)	**0,65** (0.45-0.95)	0.82 (0.55-1.20)	**0,68** (0.54-0.86)	**0,56** (0.37-0.84)	**7**	0.88 (0.68-1.13)	1.04 (0.38-2.94)
0,49 (0.37-0.64)	**0,78** (0.61-0.99)	**0,57** (0.40-0.84)	0.72 (0.48-1.06)	**0,60** (0.48-0.75)	**0,50** (0.32-0.74)	0.88 (0.68-1.13)	**8**	1.19 (0.43-3.40)
0.58 (0.22-1.63)	0.92 (0.34-2.54)	0.68 (0.24-1.94)	0.85 (0.30-2.46)	0.71 (0.26-2.01)	0.59 (0.21-1.71)	1.04 (0.38-2.94)	1.19 (0.43-3.40)	**9**

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo
05. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo

9.14. REDE 1: SOBREVIDA GLOBAL – *HAZARD RATIOS* CONTRA QUIMIOTERAPIA ISOLADA

	ANY CHEMOTHERAPY ALONE
ANY CHEMO / TRASTUZUMAB 12 mo	**0.63 (0.54-0.73)**
ANY CHEMO / TRASTUZUMAB ≤6 mo	0.86 (0.62-1.17)
TAXANE / TRASTUZUMAB 12 mo	**0,68 (0.50-0.93)**
ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo	0.81 (0.62-1.06)
ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)	0.99 (0.73-1.33)
ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo	**0,55 (0.41-0.74)**
ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo	**0,49 (0.37-0.64)**
ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo	0.58 (0.22-1.63)

9.15. REDE 1: SOBREVIDA GLOBAL – AVALIAÇÃO DA INCONSISTÊNCIA

A única alça fechada não formada exclusivamente por estudos de múltiplos braços nesta rede é composta pelos regimes de tratamento 1, 2 e 3. Não foi identificada inconsistência utilizando-se o método de Bucher ($p = 0.22$).

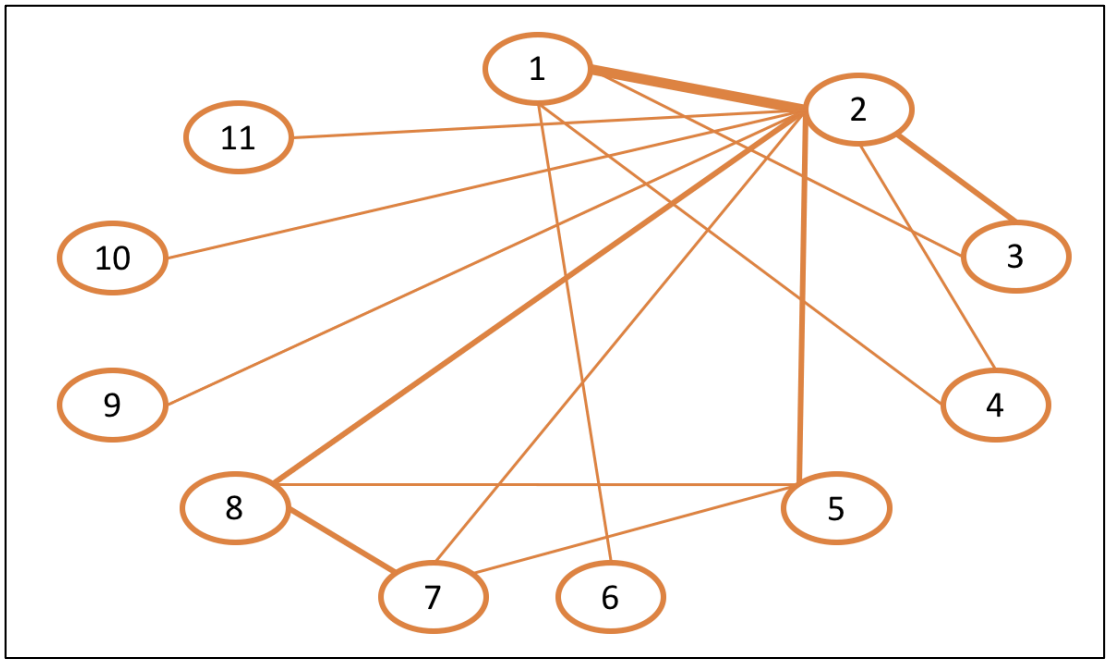
9.16. REDE 2: SOBREVIDA LIVRE DE DOENÇA

Legend for treatment arms

12. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
13. ANY CHEMO / TRASTUZUMAB 12 mo
14. ANY CHEMO / TRASTUZUMAB ≤6 mo
15. TAXANE / TRASTUZUMAB 12 mo
16. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
17. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
18. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
19. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
20. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo
21. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
22. ANTHRA + TAXANE + CAP / TRASTUZUMAB 12 mo

STUDY	COMPARISON	HR	COMPARISON	HR	COMPARISON	HR
BCIRG006	2 vs. 1	0.61 (0.48-0.76)	4 vs. 1	0.67 (0.54-0.83)	----------	--
HERA	2 vs. 1	0.64 (0.54-0.76)	----------	--	----------	--
NSABP_B31 AND NCCTGN9831	2 vs. 1	0.52 (0.45-0.60)	----------	--	----------	--
PACS	2 vs. 1	0.86 (0.61-1.22)	----------	--	----------	--
FINHER	3 vs. 1	0.42 (0.21-0.83)	----------	--	----------	--
TEACH	6 vs. 1	0.83 (0.70-1.00)	----------	--	----------	--
PHARE	3 vs. 2	1.28 (1.05-1.56)	----------	--	----------	--
MAVROUDIS	3 vs. 2	1.58 (0.86-2.10)	----------	--	----------	--
ALTTO	5 vs. 2	1.34 (1.13-1.60)	7 vs.2	0.96 (0.80-1.15)	8 vs. 2	0.84 (0.70-1.02)
NEOALTTO	5 vs. 2	1.06 (0.66-1.65)	8 vs. 2	0.78 (0.47-1.28)	----------	--
GIM2	9 vs 2	0.99 (0.49-1.99)	----------	--	----------	--
EXTENET	10 vs. 2	0.67 (0.50-0.91)	----------	--	----------	--
SHAUGHNESSY	11 vs. 2	1.07 (0.31-3.71)	----------	--	----------	--

Network design for Disease-Free Survival (DFS)



Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo
05. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANTHRA + TAXANE + CAP / TRASTUZUMAB 12 mo

9.17. REDE 2: SOBREVIDA LIVRE DE DOENÇA – DEFINIÇÕES

Em virtude da grande heterogeneidade encontrada nas definições de sobrevida livre de doença utilizadas nos estudos, foi optado por compilar em uma tabela única a definição de cada estudo.

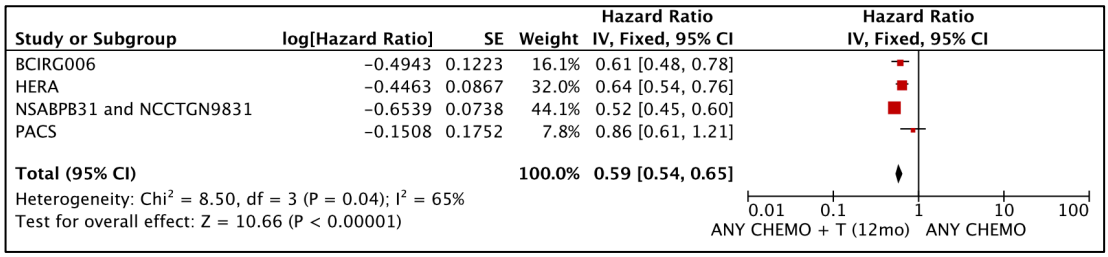
	Local Recurrence	Regional Recurrence	Distant Metastases	Contralateral breast cancer	Other Second Primary Cancer	Death	No information
ALTTO							X
ExteNET							X
BCIRG006	X	X	X	X*	X	X	
FINHER	X	X	X	X*		X	
FINXX	X	X	X			X	
GEPARDQUATRO	X	X	X	X*	X	X	
GIM2	X	X	X	X*	X	X	
HANNAH	X	X	X	X	X	X	
HERA	X	X	X	X**	X***	X	
MAVROUDIS	X	X	X	X	X	X	
NEOALTTO	X	X	X	X	X	X	
NOAH	X	X	X	X		X	
NSABPB31_NCCTGN9831	X	X	X	X	X	X	
PACS	X	X	X	X		X	
PHARE	X	X	X	X	X	X	
PREFHER	X	X	X	X		X	
SHAUGHNESSY	X	X	X	X	X	X	
TEACH	X	X	X	X	X****	X	

* Invasive disease only
** Includes DCIS but not LCIS
*** Excludes basal-cell or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix
**** Excludes carcinoma of the skin, melanoma in situ or carcinoma in situ of the cervix

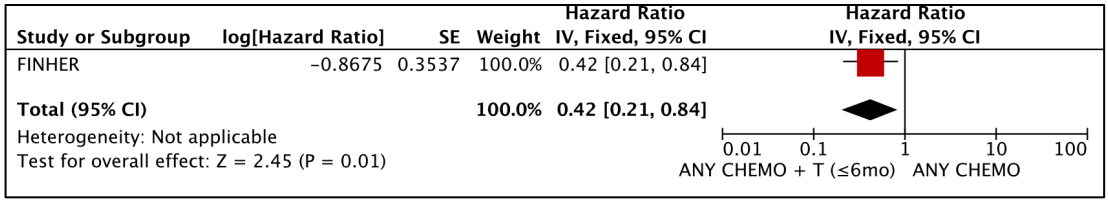
9.18. REDE 2: SOBREVIDA LIVRE DE DOENÇA – COMPARAÇÕES

"PAIRWISE"

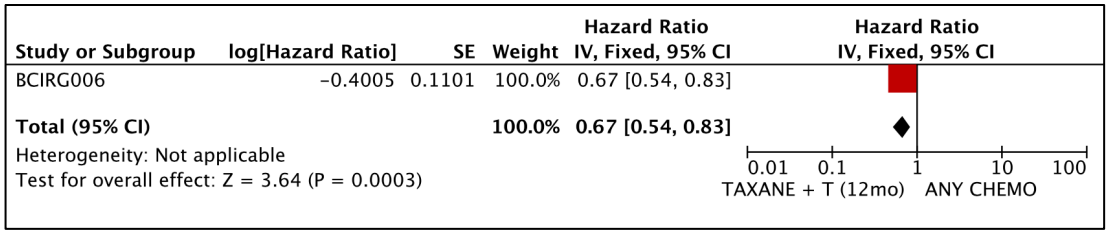
9.17.1. Comparison 1: ANY CHEMO ALONE (NO ANTI-HER2 THERAPY) (arm 1) vs ANY CHEMO / TRASTUZUMAB 12 months (arm 2)



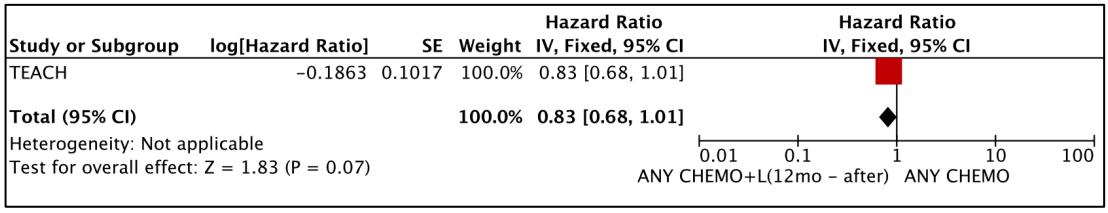
9.17.2. Comparison 2: ANY CHEMO ALONE (NO ANTI-HER2 THERAPY) (arm 1) vs ANY CHEMO / TRASTUZUMAB ≤ 6 months (arm 3)



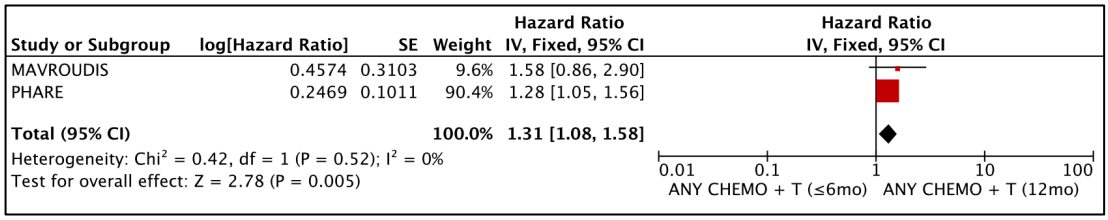
9.17.3. Comparison 3: ANY CHEMO ALONE (NO ANTI-HER2 THERAPY) (arm 1) vs TAXANE / TRASTUZUMAB 12 months (arm 4)



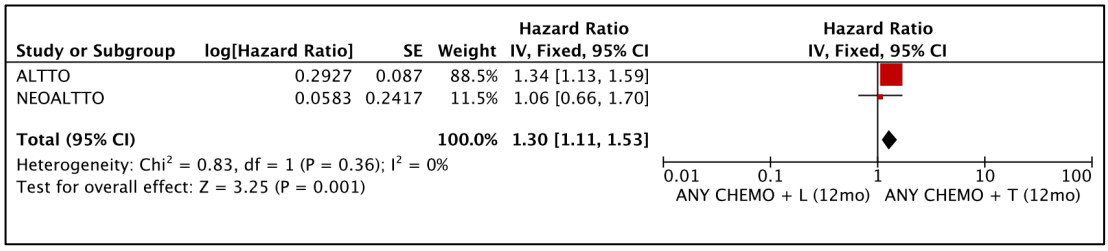
9.17.4. Comparison 4: ANY CHEMO ALONE (NO ANTI-HER2 THERAPY) (arm 1) vs ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12 months (initiated at any time after adjuvant therapy) (arm 6)



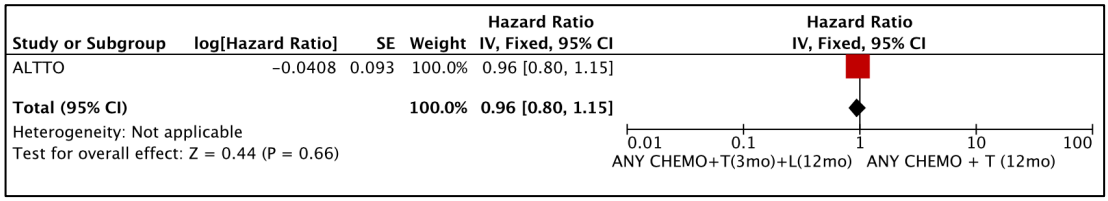
9.17.5. Comparison 5: ANY CHEMO / TRASTUZUMAB 12 months (arm 2) vs ANY CHEMO / TRASTUZUMAB ≤ 6 months (arm 3)



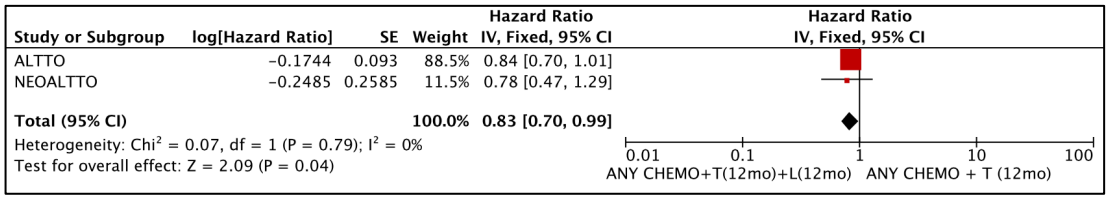
9.17.6. Comparison 6: ANY CHEMO / TRASTUZUMAB 12 months (arm 2) vs ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12 months (arm 5)



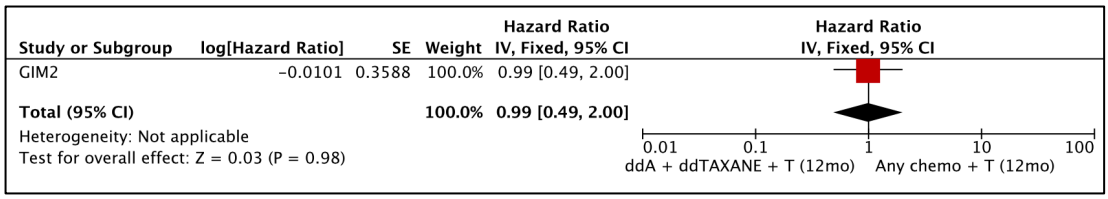
9.17.7. Comparison 7: ANY CHEMO / TRASTUZUMAB 12 months (arm 2) vs ANY CHEMO / TRASTUZUMAB 3 months / LAPATINIB 9 months (arm 7)



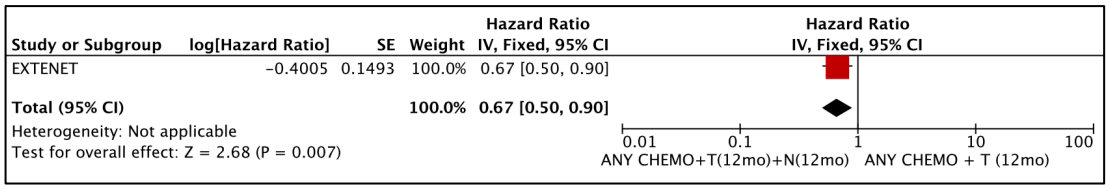
9.17.8. Comparison 8: ANY CHEMO / TRASTUZUMAB 12 months (arm 2) vs ANY CHEMO / TRASTUZUMAB 12 months / LAPATINIB 12 months (arm 8)



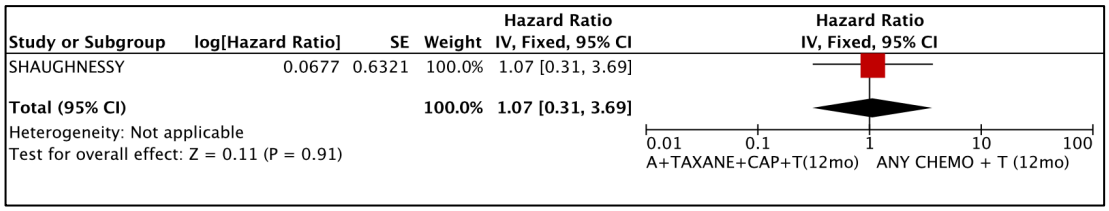
9.17.9. Comparison 9: ANY CHEMO / TRASTUZUMAB 12 months (arm 2) vs ddANTHRA + ddTAXANE / TRASTUZUMAB 12 months (arm 9)



9.17.10. Comparison 10: ANY CHEMO / TRASTUZUMAB 12 months (arm 2) vs ANY CHEMO / TRASTUZUMAB 12 months / NERATINIB 12 months (arm 10)



9.17.11. Comparison 11: ANY CHEMO / TRASTUZUMAB 12 months (arm 2) vs ANTHRA + TAXANE + CAP / TRASTUZUMAB 12 months (arm 11)



9.19. REDE 2: SOBREVIDA LIVRE DE DOENÇA – RANQUEAMENTO

	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Arm 7	Arm 8	Arm 9	Arm 10	Arm 11
Rank 1	0.0%	0.0%	0.0%	0.02%	0.0%	0.0%	0.33%	6.03%	12.95%	58.52%	22.16%
Rank 2	0.0%	0.3%	0.0%	0.37%	0.0%	0.0%	4.31%	39.67%	15.03%	30.60%	9.73%
Rank 3	0.0%	6.76%	0.00%	1.93%	0.0%	0.0%	25.47%	38.53%	12.39%	7.97%	6.89%
Rank 4	0.0%	29.15%	0.2%	5.49%	0.03%	0.0%	36.23%	13.28%	8.36%	2.28%	4.97%
Rank 5	0.0%	41.52%	2.55%	16.76%	1.33%	0.16%	21.79%	1.93%	8.56%	0.43%	4.97%
Rank 6	0.0%	20.03%	10.91%	33.71%	7.76%	2.36%	8.99%	0.49%	9.85%	0.17%	5.73%
Rank 7	0.0%	2.25%	25.13%	27.65%	21.33%	7.31%	2.53%	0.07%	7.84%	0.03%	5.85%
Rank 8	0.02%	0.0%	31.00%	9.75%	32.17%	16.73%	0.35%	0.0%	5.97%	0.0%	4.00%
Rank 9	2.11%	0.0%	21.75%	3.60%	26.60%	33.28%	0.0%	0.0%	6.99%	0.0%	5.67%
Rank 10	27.44%	0.0%	8.33%	0.72%	10.65%	38.75%	0.0%	0.0%	6.47%	0.0%	7.64%
Rank 11	70.43%	0.0%	0.13%	0.0%	0.13%	1.39%	0.0%	0.0%	5.60%	0.0%	22.37%

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo
05. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANTHRA + TAXANE + CAP / TRASTUZUMAB 12 mo

9.20. REDE 2: SOBREVIDA LIVRE DE DOENÇA – *HAZARD RATIOS* GERAIS

1	**0.53** (0.01-0.64)	**0.61** (0.01-0.75)	**0.54** (0.01-0.65)	**0.63** (0.01-0.76)	**0.69** (0.01-0.83)	**0.45** (0.01-0.55)	**0.39** (0.01-0.49)	**0.27** (0.01-0.58)	**0.28** (0.01-0.39)	**0.17** (0.01-0.62)
0.53 (0.01-0.64)	**2**	**1.27** (1.07-1.51)	1.12 (0.92-1.36)	**1.30** (1.11-1.53)	**1.41** (1.16-1.73)	0.95 (0.80-1.13)	**0.83** (0.70-0.99)	0.99 (0.48-2.01)	**0.67** (0.50-0.91)	1.07 (0.31-3.75)
0.61 (0.01-0.75)	**1.27** (1.07-1.51)	**3**	0.88 (0.68-1.14)	1.02 (0.81-1.29)	1.11 (0.86-1.45)	**0.74** (0.58-0.95)	**0.65** (0.51-0.84)	0.77 (0.37-1.61)	**0.53** (0.38-0.75)	0.84 (0.24-2.96)
0.54 (0.01-0.65)	1.12 (0.92-1.36)	0.88 (0.68-1.14)	**4**	1.16 (0.90-1.49)	1.26 (0.97-1.65)	0.84 (0.65-1.10)	**0.74** (0.57-0.97)	0.87 (0.42-1.84)	**0.60** (0.42-0.86)	0.96 (0.27-3.39)
0.63 (0.01-0.76)	**1.30** (1.11-1.53)	1.02 (0.81-1.29)	1.16 (0.90-1.49)	**5**	1.09 (0.84-1.42)	**0.72** (0.61-0.86)	**0.64** (0.54-0.76)	0.76 (0.37-1.57)	**0.51** (0.37-0.72)	0.83 (0.23-2.94)
0.69 (0.01-0.83)	**1.41** (1.16-1.73)	1.11 (0.86-1.45)	1.26 (0.97-1.65)	1.09 (0.84-1.42)	**6**	**0.67** (0.51-0.87)	**0.59** (0.45-0.77)	0.70 (0.33-1.44)	**0.47** (0.33-0.68)	0.76 (0.21-2.67)
0.45 (0.01-0.55)	0.95 (0.80-1.13)	**0.74** (0.58-0.95)	0.84 (0.65-1.10)	**0.72** (0.61-0.86)	**0.67** (0.51-0.87)	**7**	0.88 (0.73-1.06)	1.05 (0.50-2.17)	0.71 (0.50-1.06)	1.13 (0.32-4.03)
0.39 (0.01-0.49)	**0.83** (0.70-0.99)	**0.65** (0.51-0.84)	**0.74** (0.57-0.97)	**0.64** (0.54-0.76)	**0.59** (0.45-0.77)	0.88 (0.73-1.06)	**8**	1.19 (0.57-2.48)	0.81 (0.57-1.14)	1.28 (0.36-4.62)
0.27 (0.01-0.58)	0.99 (0.48-2.01)	0.77 (0.37-1.61)	0.87 (0.42-1.84)	0.76 (0.37-1.57)	0.70 (0.33-1.44)	1.05 (0.50-2.17)	1.19 (0.57-2.48)	**9**	0.68 (0.32-1.47)	1.09 (0.26-4.52)
0.28 (0.01-0.39)	**0.67** (0.50-0.91)	**0.53** (0.38-0.75)	**0.60** (0.42-0.86)	**0.51** (0.37-0.72)	**0.47** (0.33-0.68)	0.71 (0.50-1.06)	0.81 (0.57-1.14)	0.68 (0.32-1.47)	**10**	0.44 (0.02-1.58)
0.17 (0.01-0.62)	1.07 (0.31-3.75)	0.84 (0.24-2.96)	0.96 (0.27-3.39)	0.83 (0.23-2.94)	0.76 (0.21-2.67)	1.13 (0.32-4.03)	1.28 (0.36-4.62)	1.09 (0.26-4.52)	0.44 (0.02-1.58)	**11**

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB 12 mo
03. ANY CHEMO / TRASTUZUMAB ≤6 mo
04. TAXANE / TRASTUZUMAB 12 mo
05. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo
06. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)
07. ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo
08. ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo
09. ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANTHRA + TAXANE + CAP / TRASTUZUMAB 12 mo

9.21. REDE 2: SOBREVIDA LIVRE DE DOENÇA – *HAZARD RATIOS* CONTRA QUIMIOTERAPIA ISOLADA

	ANY CHEMOTHERAPY ALONE
ANY CHEMO / TRASTUZUMAB 12 mo	**0.53 (0.01-0.64)**
ANY CHEMO / TRASTUZUMAB ≤6 mo	**0.61 (0.01-0.75)**
TAXANE / TRASTUZUMAB 12 mo	**0.54 (0.01-0.65)**
ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo	**0.63 (0.01-0.76)**
ANY CHEMO / NO TRASTUZUMAB / LAPATINIB 12mo (initiated at any time after adjuvant therapy)	**0.69 (0.01-0.83)**
ANY CHEMO / TRASTUZUMAB 3mo / LAPATINIB 9mo	**0.45 (0.01-0.55)**
ANY CHEMO / TRASTUZUMAB 12mo / LAPATINIB 12mo	**0.39 (0.01-0.49)**
ddANTHRA + ddTAXANE / TRASTUZUMAB 12 mo	**0.27 (0.01-0.58)**
ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo	**0.28 (0.01-0.39)**
ANTHRA + TAXANE + CAP / TRASTUZUMAB 12 mo	**0.17 (0.01-0.62)**

9.22. REDE 2: SOBREVIDA LIVRE DE DOENÇA – AVALIAÇÃO DA INCONSISTÊNCIA

A única alça fechada não formada exclusivamente por estudos de múltiplos braços nesta rede é composta pelos regimes de tratamento 1, 2 e 3. Não foi identificada inconsistência utilizando-se o método de Bucher ($p = 0.40$).

9.23. REDE 3: RESPOSTA PATOLÓGICA COMPLETA

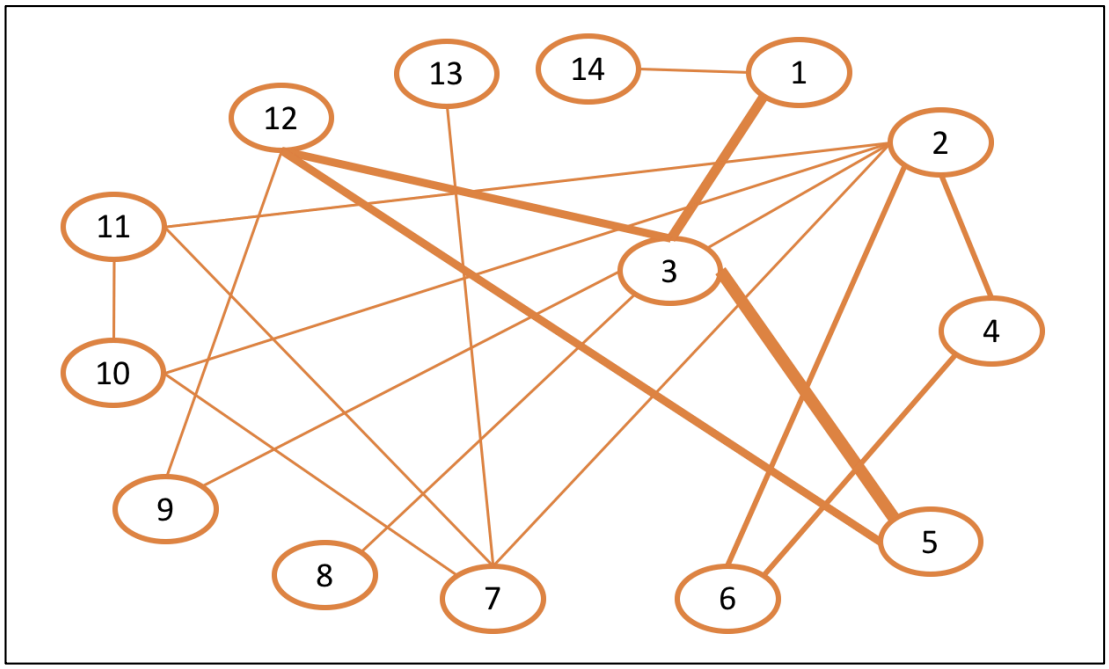
Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. CHEMO (taxane) plus TRASTUZUMAB
03. CHEMO (anthra + taxane) plus TRASTUZUMAB
04. CHEMO (taxane) plus LAPATINIB
05. CHEMO (anthra + taxane) plus LAPATINIB
06. CHEMO (taxane) plus TRASTUZUMAB plus LAPATINIB
07. CHEMO (taxane) plus TRASTUZUMAB plus PERTUZUMAB
08. CHEMO (anthra + taxane) plus TRASTUZUMABsc
09. CHEMO (anthra + taxane + CARBO) plus TRASTUZUMAB plus LAPATINIB
10. TRASTUZUMAB plus PERTUZUMAB (no chemo)
11. CHEMO (taxane) plus PERTUZUMAB
12. CHEMO (anthra + taxane) plus TRASTUZUMAB plus LAPATINIB
13. CHEMO (anthra + taxane) plus TRASTUZUMAB plus PERTUZUMAB
14. CHEMO (taxane + CARBO) plus TRASTUZUMAB

STUDY	COMPARISON	RR	COMPARISON	RR	COMPARISON	RR
ABCSG-24	3 vs. 1	1.46 (0.80-2.64)	----------	----------	----------	----------
BUZDAR	3 vs. 1	2.48 (1.10-5.57)	----------	----------	----------	----------
NOAH	3 vs. 1	1.97 (1.28-3.04)	----------	----------	----------	----------
REMAGUS02	3 vs. 1	1.36 (0.69-2.68)	----------	----------	----------	----------
CHANG	14 vs. 1	6.00 (0.82-44.00)	----------	----------	----------	----------
CALGB40601	4 vs. 2	0.78 (0.49-1.25)	6 vs. 2	1.27 (0.89-1.82)	----------	----------
NEOALTO	4 vs. 2	0.83 (0.53-1.30)	6 vs. 2	1.73 (1.18-2.53)	----------	----------
NEOSPHERE	7 vs. 2	1.65 (0.94-2.90)	10 vs. 2	0.61 (0.31-1.19)	11 vs. 2	0.86 (0.46-1.63)
JBCRG-10	2 vs. 3	1.14 (0.72-1.81)	----------	----------	----------	----------
CHERLOB	5 vs. 3	1.15 (0.42-3.19)	12 vs. 3	2.05 (0.82-5.15)	----------	----------
LAPATAX	5 vs. 3	0.70 (0.35-1.37)	12 vs. 3	1.00 (0.62-1.60)	----------	----------
NSABPB41	5 vs. 3	1.02 (0.80-1.30)	12 vs. 3	1.19 (0.94-1.49)	----------	----------
GEICAM2006-14	5 vs. 3	0.50 (0.28-0.90)	----------	----------	----------	----------
GEPARQUINTO	5 vs. 3	0.75 (0.57-0.98)	----------	----------	----------	----------
HANNAH	8 vs. 3	1.12 (0.92-1.36)	----------	----------	----------	----------

GEPARSIXTO	9 vs. 12	0.89 (0.65-1.24)	----------	----------	----------	----------
TRYPHAENA	7 vs. 13	1.11 (0.91-1.37)	----------	----------	----------	----------

Network design for Complete Pathological Response (CPR)



Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. CHEMO (taxane) plus TRASTUZUMAB
03. CHEMO (anthra + taxane) plus TRASTUZUMAB
04. CHEMO (taxane) plus LAPATINIB
05. CHEMO (anthra + taxane) plus LAPATINIB
06. CHEMO (taxane) plus TRASTUZUMAB plus LAPATINIB
07. CHEMO (taxane) plus TRASTUZUMAB plus PERTUZUMAB
08. CHEMO (anthra + taxane) plus TRASTUZUMABsc
09. CHEMO (anthra + taxane + CARBO) plus TRASTUZUMAB
10. TRASTUZUMAB plus PERTUZUMAB (no chemo)
11. CHEMO (taxane) plus PERTUZUMAB
12. CHEMO (anthra + taxane) plus TRASTUZUMAB plus LAPATINIB
13. CHEMO (anthra + taxane) plus TRASTUZUMAB plus PERTUZUMAB
14. CHEMO (taxane + CARBO) plus TRASTUZUMAB

9.24. REDE 3: RESPOSTA PATOLÓGICA COMPLETA – DEFINIÇÕES

Em virtude da grande heterogeneidade encontrada nas definições de resposta patológica completa utilizadas nos estudos, foi optado por compilar em uma tabela única a definição de cada estudo. A classificação a seguir é baseada na sétima edição do manual para estadiamento do cancer de mama publicado pela AJCC ("*American Joint Commettee on Cancer*"):

- yT0 Nx: ausência de lesão invasora e de lesão *in situ* na mama; ignorando axila ipsilateral
- yT0/is Nx: ausência de lesão invasora na mama (aceita lesão *in situ* na mama); ignorando axila ipsilateral
- yT0 yN0: ausência de lesão invasora e de lesão *in situ* tanto na mama quanto na axila ipsilateral
- yT0/is yN0): ausência de lesão invasora na mama (aceita lesão *in situ* na mama); ausência de lesão invasora e de lesão *in situ* axila ipsilateral
- yT0/is yN0/is: ausência de lesão invasora na mama (aceita lesão *in situ* na mama); ausência de lesão invasora na axila ipsilateral (aceita lesão *in situ* na axila ipsilateral)

	yT0yNx	yT0/isNx	yT0yN0	yT0/isyN0	yT0/isyN0/is	NO INFORMATION
CALGB40601	X					
JBCRG-10						X
ABCSG-24		X				
ACOSOG_Z1041		X				
BUZDAR					X	
CHERLOB					X	
GEICAM		X				
GEPARDQUATRO		X	X			
GEPARQUINTO			X			
HANNAH		X				
LAPATAX		X				

NAKAMURA					X	
NEOALTTO		X				
NEOSPHERE		X				
NOAH	X		X			
NSABPB41		X				
REMAGUS					X	
TRYAPHAENA		X				
CHANG		x				

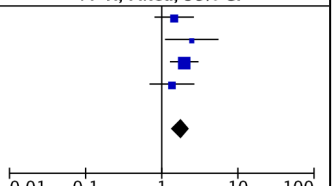
9.25. REDE 3: RESPOSTA PATOLÓGICA COMPLETA – COMPARAÇÕES

"*PAIRWISE*"

9.23.1. Comparison 1: ANY CHEMO ALONE (arm 1) vs CHEMO (anthra + taxane) plus TRASTUZUMAB (arm 3)

Study or Subgroup	Anthra + taxane + T Events	Total	Any chemo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ABCSG-24	17	44	13	49	23.6%	1.46 [0.80, 2.64]
BUZDAR	15	23	5	19	10.5%	2.48 [1.10, 5.57]
NOAH	45	117	23	118	44.0%	1.97 [1.28, 3.04]
REMAGUS02	16	62	11	58	21.8%	1.36 [0.69, 2.68]
Total (95% CI)		**246**		**244**	**100.0%**	**1.77 [1.33, 2.36]**
Total events	93		52			

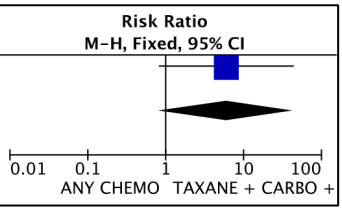
Heterogeneity: $Chi^2 = 1.89$, df = 3 (P = 0.59); $I^2 = 0\%$
Test for overall effect: Z = 3.87 (P = 0.0001)



9.23.2. Comparison 2: ANY CHEMO ALONE (arm 1) vs CHEMO (taxane + CARBO) plus TRASTUZUMAB (arm 14)

Study or Subgroup	Taxane + Carbo + T Events	Total	Any chemo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHANG	6	15	1	15	100.0%	6.00 [0.82, 44.00]
Total (95% CI)		**15**		**15**	**100.0%**	**6.00 [0.82, 44.00]**
Total events	6		1			

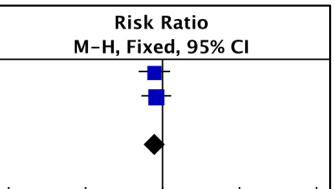
Heterogeneity: Not applicable
Test for overall effect: Z = 1.76 (P = 0.08)



9.23.3. Comparison 3: CHEMO (taxane) plus TRASTUZUMAB (arm 2) vs CHEMO (taxane) plus LAPATINIB (arm 4)

Study or Subgroup	Taxane + L Events	Total	Taxane + T Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CALGB40601	21	67	24	60	46.0%	0.78 [0.49, 1.25]
NEOALTTO	38	154	22	74	54.0%	0.83 [0.53, 1.30]
Total (95% CI)		**221**		**134**	**100.0%**	**0.81 [0.58, 1.12]**
Total events	59		46			

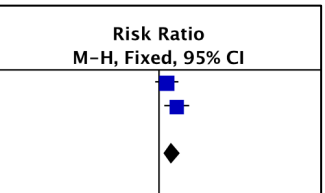
Heterogeneity: $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0\%$
Test for overall effect: Z = 1.29 (P = 0.20)



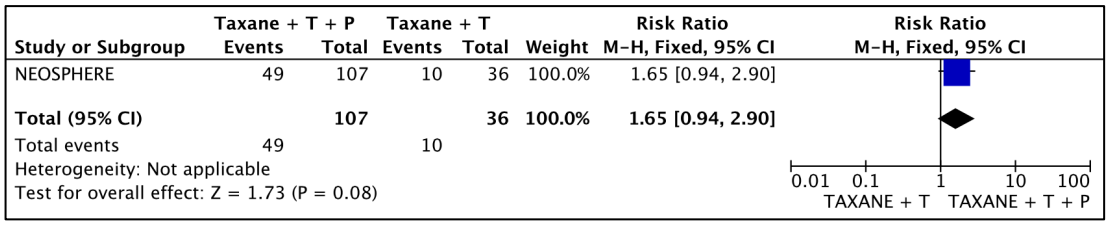
9.23.4. Comparison 4: CHEMO (taxane) plus TRASTUZUMAB (arm 2) vs CHEMO (taxane) plus TRASTUZUMAB plus LAPATINIB (arm 6)

Study or Subgroup	Taxane + T + L Events	Total	Taxane + T Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CALGB40601	60	118	24	60	51.8%	1.27 [0.89, 1.82]
NEOALTTO	78	152	22	74	48.2%	1.73 [1.18, 2.53]
Total (95% CI)		**270**		**134**	**100.0%**	**1.49 [1.15, 1.94]**
Total events	138		46			

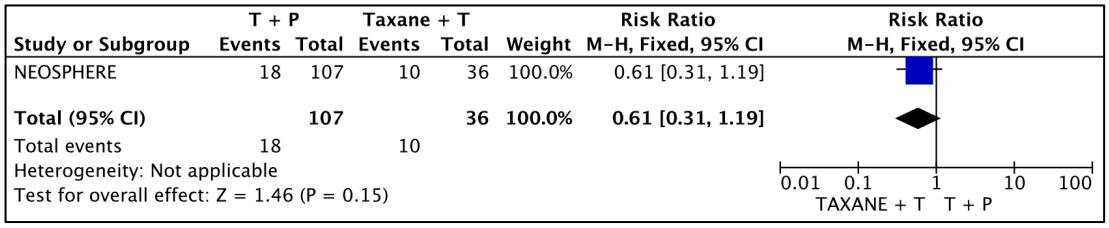
Heterogeneity: $Chi^2 = 1.33$, df = 1 (P = 0.25); $I^2 = 25\%$
Test for overall effect: Z = 2.99 (P = 0.003)



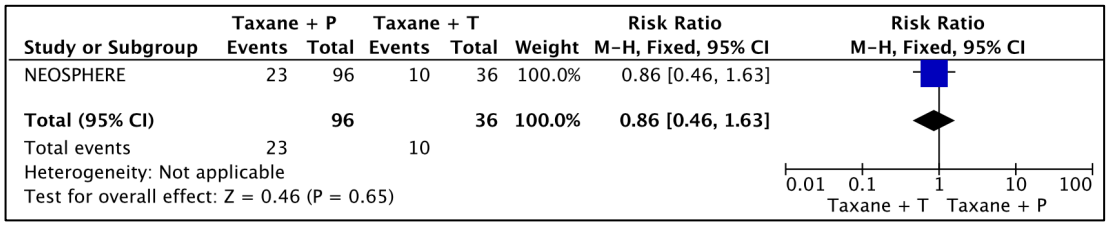
9.23.5. Comparison 5: CHEMO (taxane) plus TRASTUZUMAB (arm 2) vs CHEMO (taxane) plus TRASTUZUMAB plus PERTUZUMAB (arm 7)



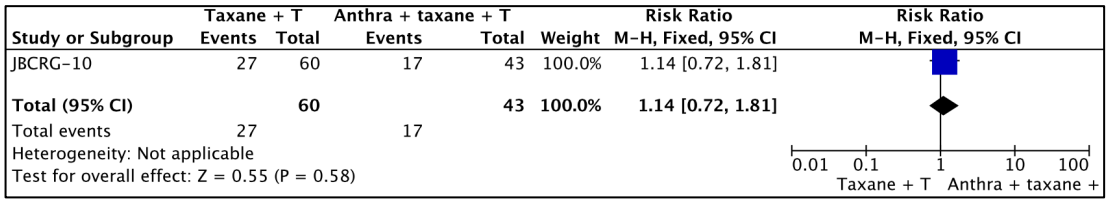
9.23.6. Comparison 6: CHEMO (taxane) plus TRASTUZUMAB (arm 2) vs TRASTUZUMAB plus PERTUZUMAB (no chemo) (arm 10)



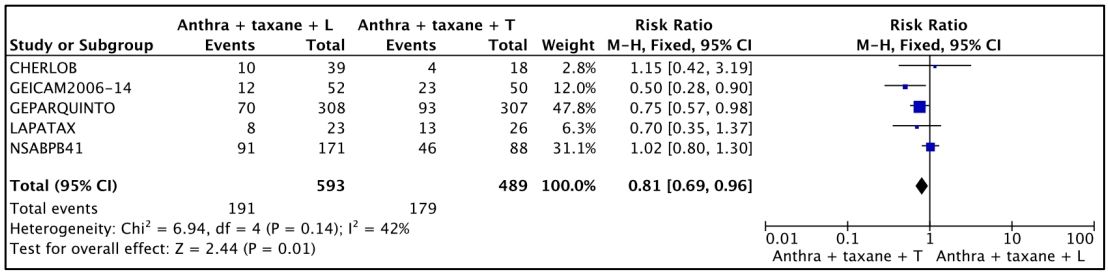
9.23.7. Comparison 7: CHEMO (taxane) plus TRASTUZUMAB (arm 2) vs CHEMO (taxane) plus PERTUZUMAB (arm 11)



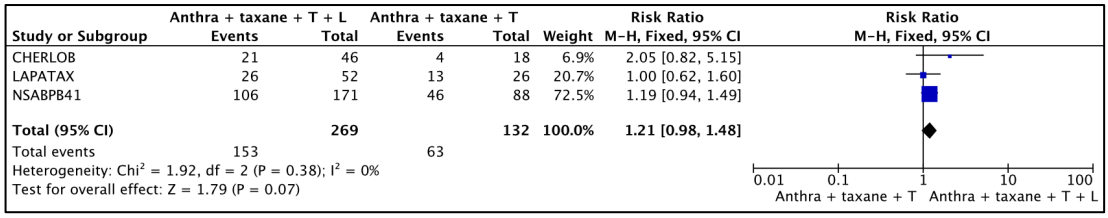
9.23.8. Comparison 8: CHEMO (anthra + taxane) plus TRASTUZUMAB (arm 3) vs CHEMO (taxane) plus TRASTUZUMAB (arm 2)



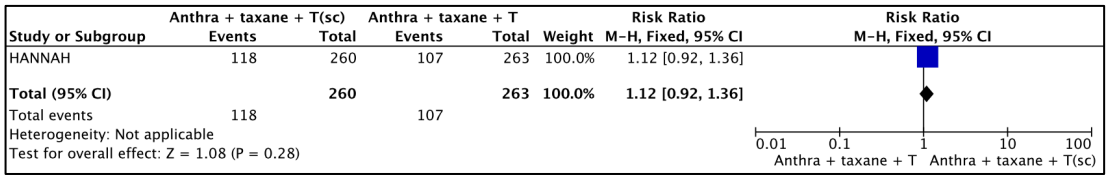
9.23.9. Comparison 9: CHEMO (anthra + taxane) plus TRASTUZUMAB (arm 3) vs CHEMO (anthra + taxane) plus LAPATINIB (arm 5)



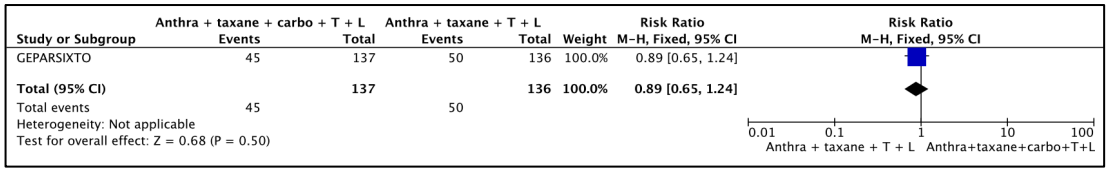
9.23.10. Comparison 10: CHEMO (anthra + taxane) plus TRASTUZUMAB (arm 3) vs CHEMO (anthra + taxane) plus TRASTUZUMAB plus LAPATINIB (arm 12)



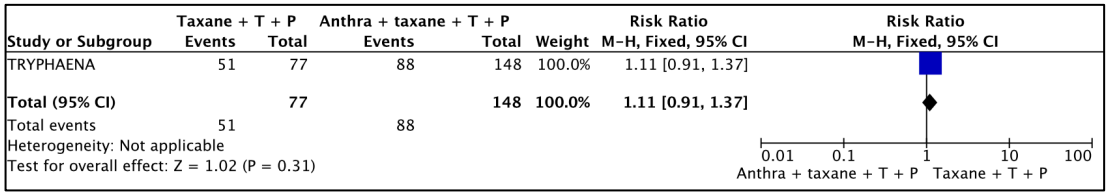
9.23.11. Comparison 11: CHEMO (anthra + taxane) plus TRASTUZUMAB (arm 3) vs CHEMO (anthra + taxane) plus TRASTUZUMABsc (arm 8)



9.23.12. Comparison 12: CHEMO (anthra + taxane) plus TRASTUZUMAB plus LAPATINIB (arm 12) vs CHEMO (anthra + taxane + CARBO) plus TRASTUZUMAB plus LAPATINIB (arm 9)



9.23.13. Comparison 13: CHEMO (anthra + taxane) plus TRASTUZUMAB plus PERTUZUMAB (arm 13) vs CHEMO (taxane) plus TRASTUZUMAB plus PERTUZUMAB (arm 7)



9.26. REDE 3: RESPOSTA PATOLÓGICA COMPLETA – RANQUEAMENTO

	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Arm 7	Arm 8	Arm 9	Arm 10	Arm 11	Arm 12	Arm 13	Arm 14
Rank 1	0.0%	0.0%	0.01%	0.0%	0.0%	15.73%	24.01%	0.42%	0.42%	0.0%	0.01%	0.21%	5.34%	53.88%
Rank 2	0.0%	0.09%	0.02%	0.01%	0.0%	29.12%	40.40%	1.93%	1.52%	0.0%	0.05%	1.27%	20.41%	5.20%
Rank 3	0.0%	1.00%	0.12%	0.10%	0.0%	26.71%	25.22%	3.53%	2.22%	0.01%	0.46%	3.02%	32.05%	5.62%
Rank 4	0.0%	12.29%	0.62%	0.64%	0.02%	22.73%	6.03%	7.39%	4.47%	0.13%	4.16%	6.73%	25.83%	8.97%
Rank 5	0.0%	29.83%	2.14%	3.83%	0.04%	2.90%	1.71%	15.70%	8.26%	0.57%	10.21%	15.10%	5.95%	3.76%
Rank 6	0.0%	16.88%	5.84%	9.43%	0.34%	1.30%	1.18%	17.20%	9.15%	1.41%	10.60%	20.91%	3.31%	2.99%
Rank 7	0.01%	10.61%	14.01%	9.46%	0.97%	0.89%	0.81%	17.09%	10.72%	2.48%	8.20%	19.86%	2.54%	2.32%
Rank 8	0.05%	10.21%	21.49%	7.84%	3.29%	0.45%	0.45%	14.58%	12.04%	2.98%	6.76%	15.90%	1.98%	1.99%
Rank 9	0.16%	10.13%	22.67%	9.21%	9.42%	0.15%	0.14%	10.95%	12.71%	2.87%	7.68%	10.41%	1.50%	2.00%
Rank 10	0.78%	7.07%	18.88%	12.77%	18.80%	0.02%	0.04%	6.57%	12.61%	4.00%	10.64%	4.85%	0.71%	2.25%
Rank 11	3.42%	1.75%	10.95%	19.11%	24.23%	0.01%	0.01%	3.26%	11.72%	7.05%	14.39%	1.50%	0.31%	2.30%
Rank 12	9.64%	0.19%	3.22%	17.64%	26.95%	0.0%	0.0%	1.18%	9.12%	12.86%	15.90%	0.25%	0.04%	3.00%
Rank 13	29.45%	0.01%	0.06%	8.18%	15.61%	0.0%	0.0%	0.19%	4.56%	29.58%	9.09%	0.0%	0.01%	3.27%
Rank 14	56.49%	0.01%	0.0%	1.78%	0.33%	0.0%	0.0%	0.01%	0.47%	36.08%	2.40%	0.0%	0.0%	2.45%

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. CHEMO (taxane) plus TRASTUZUMAB
03. CHEMO (anthra + taxane) plus TRASTUZUMAB
04. CHEMO (taxane) plus LAPATINIB
05. CHEMO (anthra + taxane) plus LAPATINIB
06. CHEMO (taxane) plus TRASTUZUMAB plus LAPATINIB
07. CHEMO (taxane) plus TRASTUZUMAB plus PERTUZUMAB
08. CHEMO (anthra + taxane) plus TRASTUZUMABsc
09. CHEMO (anthra + taxane + CARBO) plus TRASTUZUMAB
10. TRASTUZUMAB plus PERTUZUMAB (no chemo)
11. CHEMO (taxane) plus PERTUZUMAB
12. CHEMO (anthra + taxane) plus TRASTUZUMAB plus LAPATINIB
13. CHEMO (anthra + taxane) plus TRASTUZUMAB plus PERTUZUMAB
14. CHEMO (taxane + CARBO) plus TRASTUZUMAB

9.27. REDE 3: RESPOSTA PATOLÓGICA COMPLETA – RISCOS RELATIVOS GERAIS

1	**2.00** (1.20-3.50)	**1.70** (1.30-2.20)	1.50 (0.85-2.90)	**1.40** (1.00-2.00)	**2.90** (1.60-5.30)	**3.10** (1.60-6.00)	**1.90** (1.30-2.60)	**1.70** (1.10-2.70)	1.10 (0.53-2.30)	1.60 (0.78-3.30)	**1.90** (1.40-5.50)	**2.80** (1.40-5.50)	3.50 (0.93-25.00)
2.00 (1.20-3.50)	**2**	0.86 (0.52-1.30)	**0.78** (0.59-1.00)	0.72 (0.43-1.20)	**1.50** (1.20-1.80)	**1.50** (1.10-2.20)	0.95 (0.56-1.50)	0.86 (0.47-1.50)	**0.56** (0.59-0.93)	0.81 (0.50-1.30)	0.95 (0.57-1.50)	1.40 (0.92-2.10)	1.80 (0.42-13.00)
1.70 (1.30-2.20)	0.86 (0.52-1.30)	**3**	0.91 (0.54-1.60)	**0.85** (0.73-0.98)	**1.70** (1.10-2.90)	**1.80** (1.00-3.30)	1.10 (0.91-1.40)	1.00 (0.70-1.40)	0.66 (0.33-1.30)	0.94 (0.49-1.80)	1.10 (0.96-1.30)	1.60 (0.89-3.10)	2.10 (0.54-15.00)
1.50 (0.85-2.90)	**0.78** (0.59-1.00)	0.91 (0.54-1.60)	**4**	0.93 (0.51-1.60)	1.90 (1.50-2.40)	**2.00** (1.30-3.20)	1.20 (0.67-2.10)	1.10 (0.56-2.10)	0.72 (0.40-1.30)	1.00 (0.60-1.80)	1.20 (0.68-2.10)	**1.80** (1.10-3.00)	2.30 (0.53-18.00)
1.40 (1.00-2.00)	0.72 (0.43-1.20)	**0.85** (0.73-0.98)	0.93 (0.51-1.60)	**5**	**2.00** (1.20-3.50)	**2.10** (1.20-4.00)	**1.30** (1.00-1.70)	1.20 (0.82-1.70)	0.78 (0.38-1.60)	1.10 (0.57-2.20)	**1.30** (1.10-1.60)	**1.90** (1.00-3.70)	2.50 (0.63-18.00)
2.90 (1.60-5.30)	**1.50** (1.20-1.80)	**1.70** (1.10-2.90)	1.90 (1.50-2.40)	**2.00** (1.20-3.50)	**6**	1.10 (0.70-1.60)	0.65 (0.37-1.10)	0.58 (0.31-1.10)	**0.38** (0.22-0.66)	**0.55** (0.33-0.90)	0.65 (0.37-1.10)	0.95 (0.60-1.50)	1.20 (0.28-9.20)
3.10 (1.60-6.00)	**1.50** (1.10-2.20)	**1.80** (1.00-3.30)	**2.00** (1.30-3.20)	**2.10** (1.20-4.00)	1.10 (0.70-1.60)	**7**	0.61 (0.32-1.10)	0.55 (0.27-1.10)	**0.36** (0.22-0.57)	**0.52** (0.33-0.77)	0.61 (0.32-1.10)	0.90 (0.73-1.10)	1.20 (0.26-8.90)
1.90 (1.30-2.60)	0.95 (0.56-1.50)	1.10 (0.91-1.40)	1.20 (0.67-2.10)	**1.30** (1.00-1.70)	0.65 (0.37-1.10)	0.61 (0.32-1.10)	**8**	0.90 (0.60-1.40)	0.59 (0.29-1.20)	0.85 (0.43-1.70)	1.00 (0.78-1.30)	1.50 (0.77-2.90)	1.90 (0.48-14.00)
1.70 (1.10-2.70)	0.86 (0.47-1.50)	1.00 (0.70-1.40)	1.10 (0.56-2.10)	1.20 (0.82-1.70)	0.58 (0.31-1.10)	0.55 (0.27-1.10)	0.90 (0.60-1.40)	**9**	0.66 (0.30-1.40)	0.94 (0.45-2.00)	1.10 (0.80-1.50)	1.60 (0.80-3.40)	2.10 (0.50-15.00)
1.10 (0.53-2.30)	**0.56** (0.59-0.93)	0.66 (0.33-1.30)	0.72 (0.40-1.30)	0.78 (0.38-1.60)	**0.38** (0.22-0.66)	**0.36** (0.22-0.57)	0.59 (0.29-1.20)	0.66 (0.30-1.40)	**10**	1.40 (0.83-2.50)	1.70 (0.82-3.40)	**2.50** (1.50-4.20)	3.20 (0.69-25.00)
1.60 (0.78-3.30)	0.81 (0.50-1.30)	0.94 (0.49-1.80)	1.00 (0.60-1.80)	1.10 (0.57-2.20)	**0.55** (0.33-0.90)	**0.52** (0.33-0.77)	0.85 (0.43-1.70)	0.94 (0.45-2.00)	1.40 (0.83-2.50)	**11**	1.20 (0.59-2.30)	**1.70** (1.10-2.80)	2.20 (0.49-18.00)
1.90 (1.40-5.50)	0.95 (0.57-1.50)	1.10 (0.96-1.30)	1.20 (0.68-2.10)	**1.30** (1.10-1.60)	0.65 (0.37-1.10)	0.61 (0.32-1.10)	1.00 (0.78-1.30)	1.10 (0.80-1.50)	1.70 (0.82-3.40)	1.20 (0.59-2.30)	**12**	1.50 (0.79-2.80)	1.90 (0.48-14.00)
2.80 (1.40-5.50)	1.40 (0.92-2.10)	1.60 (0.89-3.10)	**1.80** (1.10-3.00)	**1.90** (1.00-3.70)	0.95 (0.60-1.50)	0.90 (0.73-1.10)	1.50 (0.77-2.90)	1.60 (0.80-3.40)	**2.50** (1.50-4.20)	**1.70** (1.10-2.80)	1.50 (0.79-2.80)	**13**	1.30 (0.28-10.00)
3.50 (0.93-25.00)	1.80 (0.42-13.00)	2.10 (0.54-15.00)	2.30 (0.53-18.00)	2.50 (0.63-18.00)	1.20 (0.28-9.20)	1.20 (0.26-8.90)	1.90 (0.48-14.00)	2.10 (0.50-15.00)	3.20 (0.69-25.00)	2.20 (0.49-18.00)	1.90 (0.48-14.00)	1.30 (0.28-10.00)	**14**

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. CHEMO (taxane) plus TRASTUZUMAB
03. CHEMO (anthra + taxane) plus TRASTUZUMAB
04. CHEMO (taxane) plus LAPATINIB
05. CHEMO (anthra + taxane) plus LAPATINIB
06. CHEMO (taxane) plus TRASTUZUMAB plus LAPATINIB
07. CHEMO (taxane) plus TRASTUZUMAB plus PERTUZUMAB
08. CHEMO (anthra + taxane) plus TRASTUZUMABsc
09. CHEMO (anthra + taxane + CARBO) plus TRASTUZUMAB
10. TRASTUZUMAB plus PERTUZUMAB (no chemo)
11. CHEMO (taxane) plus PERTUZUMAB
12. CHEMO (anthra + taxane) plus TRASTUZUMAB plus LAPATINIB
13. CHEMO (anthra + taxane) plus TRASTUZUMAB plus PERTUZUMAB
14. CHEMO (taxane + CARBO) plus TRASTUZUMAB

9.28. REDE 3: RESPOSTA PATOLÓGICA COMPLETA – RISCOS RELATIVOS CONTRA QUIMIOTERAPIA ISOLADA

	ANY CHEMOTHERAPY ALONE
CHEMO (taxane) plus TRASTUZUMAB	**2.00 (1.20-3.50)**
CHEMO (anthra + taxane) plus TRASTUZUMAB	**1.70 (1.30-2.20)**
CHEMO (taxane) plus LAPATINIB	1.50 (0.85-2.90)
CHEMO (anthra + taxane) plus LAPATINIB	**1.40 (1.00-2.00)**
CHEMO (taxane) plus TRASTUZUMAB plus LAPATINIB	**2.90 (1.60-5.30)**
CHEMO (taxane) plus TRASTUZUMAB plus PERTUZUMAB	**3.10 (1.60-6.00)**
CHEMO (anthra + taxane) plus TRASTUZUMABsc	**1.90 (1.30-2.60)**
CHEMO (anthra + taxane + CARBO) plus TRASTUZUMAB	**1.70 (1.10-2.70)**
TRASTUZUMAB plus PERTUZUMAB (no chemo)	1.10 (0.53-2.30)
CHEMO (taxane) plus PERTUZUMAB	1.60 (0.78-3.30)
CHEMO (anthra + taxane) plus TRASTUZUMAB plus LAPATINIB	**1.90 (1.40-5.50)**
CHEMO (anthra + taxane) plus TRASTUZUMAB plus PERTUZUMAB	**2.80 (1.40-5.50)**
CHEMO (taxane + CARBO) plus TRASTUZUMAB	3.50 (0.93-25.00)

9.29. REDE 3: RESPOSTA PATOLÓGICA COMPLETA – AVALIAÇÃO DA INCONSISTÊNCIA

Nesta rede, todas as "alças fechadas" são decorrentes de estudos com pelo menos 3 braços, de modo que não se aplica o cálculo da estimativa da inconsistência na rede.

9.30. REDE 4: CARDIOTOXICIDADE

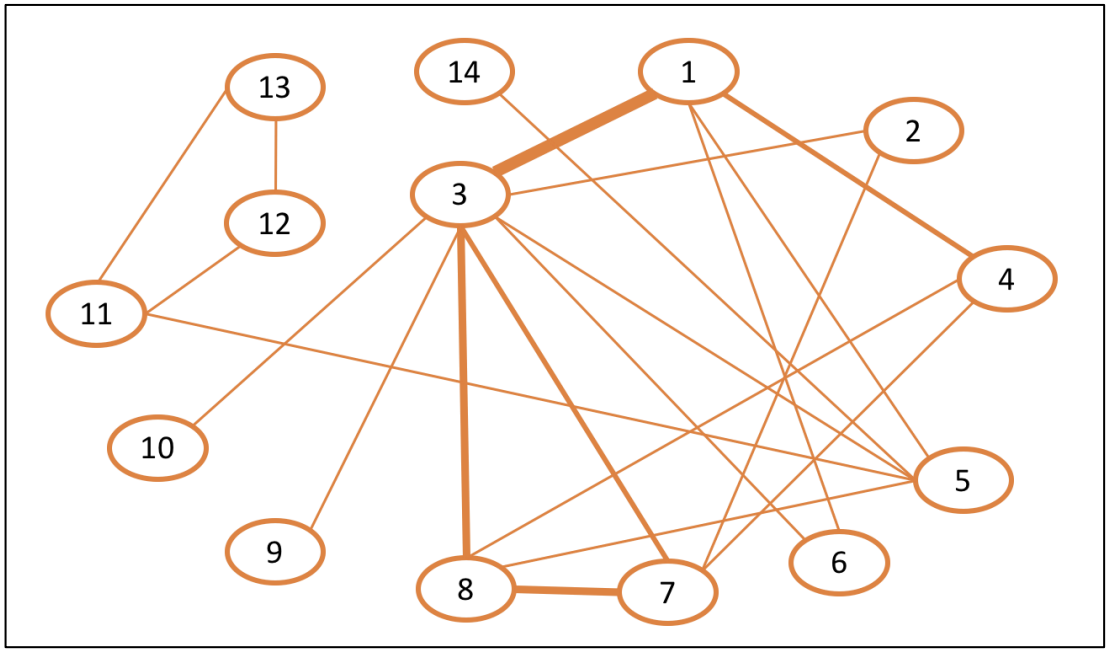
Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB ≤6 mo (sequential, if anthracycline)
03. ANY CHEMO / TRASTUZUMAB 12 mo (sequential, if anthracycline)
04. ANY CHEMO / TRASTUZUMAB ≤6 mo (concomitant with, if anthracycline)
05. ANY CHEMO / TRASTUZUMAB 12 mo (concomitant with, if anthracycline)
06. TAXANE (no anthracycline)/ TRASTUZUMAB 12 mo
07. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB
08. ANY CHEMO / TRASTUZUMAB / LAPATINIB
09. PLD (peg_lipos_doxo) + TAXANE / TRASTUZUMAB 12 mo (concomitant with PLD)
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (sequential, if anthracycline)
12. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (concomitant, if anthracycline)
13. TAXANE (no athracycline) / TRASTUZUMAB 12 mo / PERTUZUMAB
14. ANTHRA + TAXANE / TRASTUZUMAB SC12 mo (concomitant with Anthracycline)

STUDY*	COMPARISON	RR	COMPARISON	RR
BCIRG006	3 vs. 1	1.70 (1.29-2.24)	6 vs. 1	1.18 (0.86-1.61)
HERA/BIG01-01	3 vs. 1	3.42 (2.50-4.67)	--------	--
NCCTG N9831	3 vs. 1	1.61 (1.03-2.51)	--------	--
NSABP B31	3 vs. 1	1.98 (1.65-2.37)	--------	--
PACS	3 vs. 1	2.50 (1.78-3.50)	--------	--
ABCSG-24	4 vs. 1	3.35 (0.36-31.00)	--------	--
BUZDAR	4 vs. 1	1.16 (0.44-3.06)	--------	--
NOAH	5 vs. 1	1.55 (0.93-2.59)	--------	--
PHARE	3 vs. 2	1.33 (1.01-1.79)	--------	--
GEICAM2006-14	7 vs. 2	0.48 (0.04-5.14)	--------	--
ACOSOG_Z1041	5 vs. 3	1.62 (0.99-2.64)	--------	--
ALTTO	7 vs. 3	0.77 (0.67-0.89)	8 vs. 3	1.00 (0.88-1.12)
NEOALTO	7 vs. 3	0.48	8 vs. 3	0.49

		(0.03-7.58)		(0.03-7.68)
NSABPB41	8 vs. 3	0.76 (0.47-1.22)	--------	--
CONSORT	9 vs. 3	0.19 (0.07-0.51)	--------	--
EXTENET	10 vs. 3	1.20 (0.61-2.37)	--------	--
CHERLOB	7 vs. 4	0.31 (0.01-7.34)	8 vs. 4	0.26 (0.01-6.26)
GEPARQUINTO	8 vs. 5	0.25 (0.03-2.22)	--------	--
NEOSPHERE	11 vs. 5	1.73 (0.20-14.65)	--------	--
HANNAH	14 vs. 5	1.17 (0.40-3.44)	--------	--
TRYPHAENA	12 vs. 11	0.71 (0.31-1.60)	13 vs. 11	0.49 (0.20-1.19)

Network design for Cardiotoxicity



Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB ≤6 mo (sequential, if anthracycline)
03. ANY CHEMO / TRASTUZUMAB 12 mo (sequential, if anthracycline)
04. ANY CHEMO / TRASTUZUMAB ≤6 mo (concomitant with, if anthracycline)
05. ANY CHEMO / TRASTUZUMAB 12 mo (concomitant with, if anthracycline)
06. TAXANE (no anthracycline)/ TRASTUZUMAB 12 mo
07. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB
08. ANY CHEMO / TRASTUZUMAB / LAPATINIB
09. PLD (peg_lipos_doxo) + TAXANE / TRASTUZUMAB 12 mo (concomitant with PLD)
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (concomitant with anthracycline)
12. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (sequential with anthracycline)
13. TAXANE (no athracycline) / TRASTUZUMAB 12 mo / PERTUZUMAB
14. ANTHRA + TAXANE / TRASTUZUMAB SC12 mo (concomitant with Anthracycline)

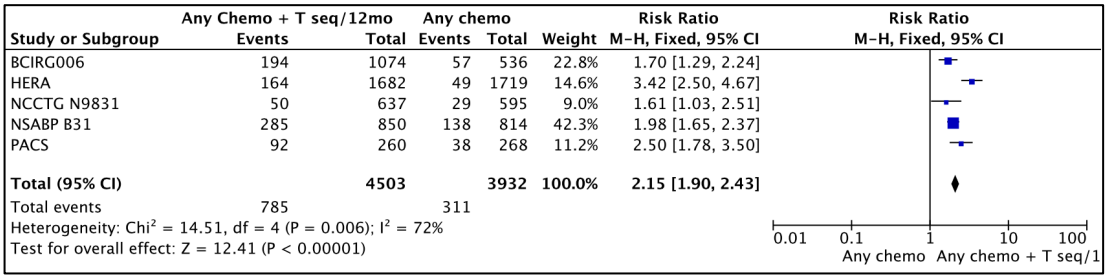
9.31. REDE 4: CARDIOTOXICIDADE – DEFINIÇÕES

Verificou-se bastante variação nas definições utilizadas pelos diferentes estudos incluídos nesta metanálise para definir evento cardíaco. Todavia, queda da fração de ejeção para valores abaixo do limiar da normalidade (55%) ou queda maior ou igual a 10 pontos percentuais absolutos a partir da medida basal aferida antes do inicio do tratamento utilizando-se ecocardiografia ou radiocardiografia foi defecho reportado na maior parte dos estudos. Por isso, esta foi a definição utilizada para contabilizar evento adverso de cardiotoxicidade nesta análise.

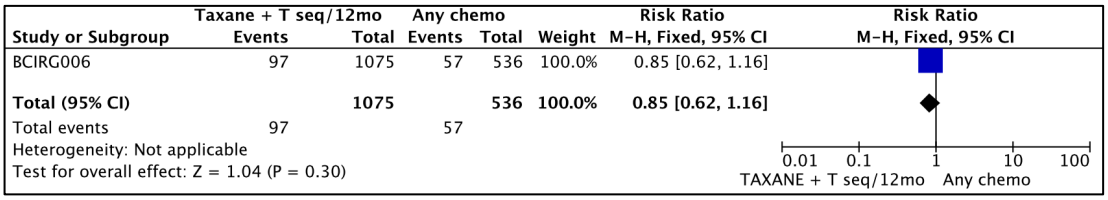
Além disso, esse é um critério com relevância clínica, posto que determina suspensão temporária do uso de trastuzumabe tanto nos cenários adjuvante quanto no neoadjuvante do câncer de mama.

9.32. REDE 4: CARDIOTOXICIDADE – COMPARAÇÕES "*PAIRWISE*"

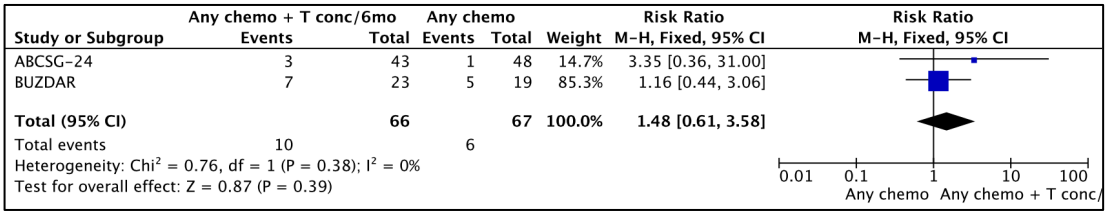
9.29.1. Comparison 1: ANY CHEMO ALONE (arm 1) vs ANY CHEMO / TRASTUZUMAB 12 months (sequential, if anthracycline) (arm 3)



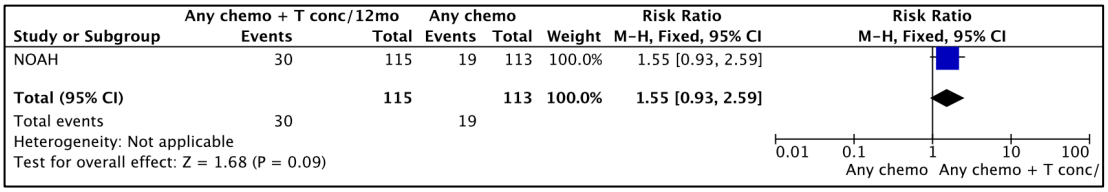
9.29.2. Comparison 2: ANY CHEMO ALONE (arm 1) vs TAXANE (no anthracycline)/ TRASTUZUMAB 12 months (arm 6)



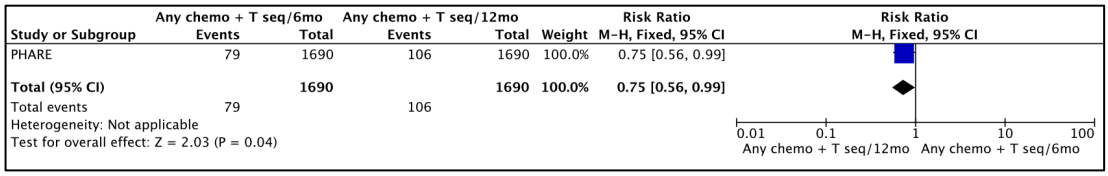
9.29.3. Comparison 3: ANY CHEMO ALONE (arm 1) vs ANY CHEMO / TRASTUZUMAB ≤ 6 months (concomitant with, if anthracycline) (arm 4)



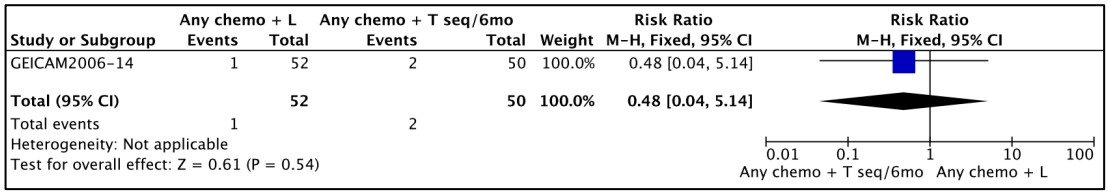
9.29.4. Comparison 4: ANY CHEMO ALONE (arm 1) vs ANY CHEMO / TRASTUZUMAB 12 months (concomitant with, if anthracycline) (arm 5)



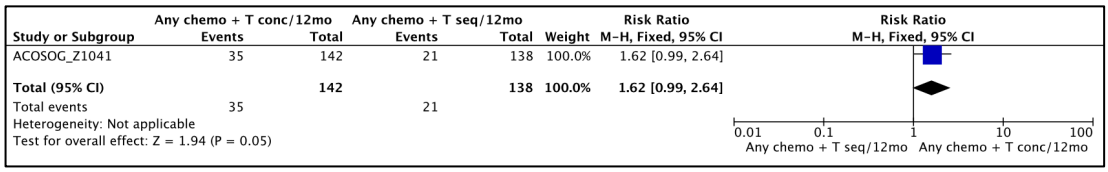
9.29.5. Comparison 5: ANY CHEMO / TRASTUZUMAB ≤ 6 months (sequential, if anthracycline) (arm 2) vs ANY CHEMO / TRASTUZUMAB 12 months (sequential, if anthracycline) (arm 3)



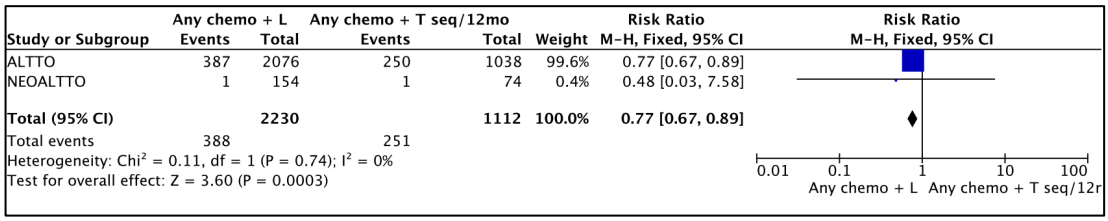
9.29.6. Comparison 6: ANY CHEMO / TRASTUZUMAB ≤ 6 months (sequential, if anthracycline) (arm 2) vs ANY CHEMO / NO TRASTUZUMAB / LAPATINIB (arm 7)



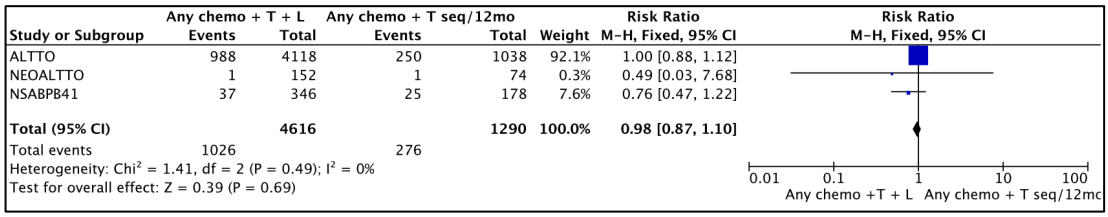
9.29.7. Comparison 7: ANY CHEMO / TRASTUZUMAB 12 months (sequential, if anthracycline) (arm 3) vs ANY CHEMO / TRASTUZUMAB 12 months (concomitant with, if anthracycline) (arm 5)



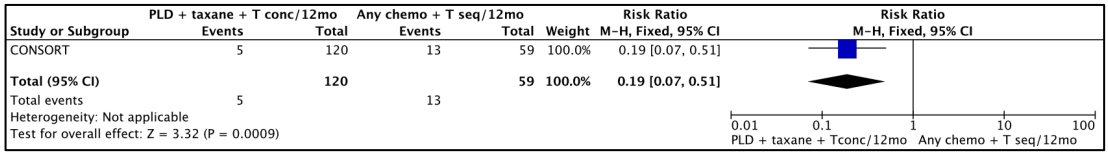
9.29.8. Comparison 8: ANY CHEMO / TRASTUZUMAB 12 months (sequential, if anthracycline) (arm 3) vs ANY CHEMO / NO TRASTUZUMAB / LAPATINIB (arm 7)



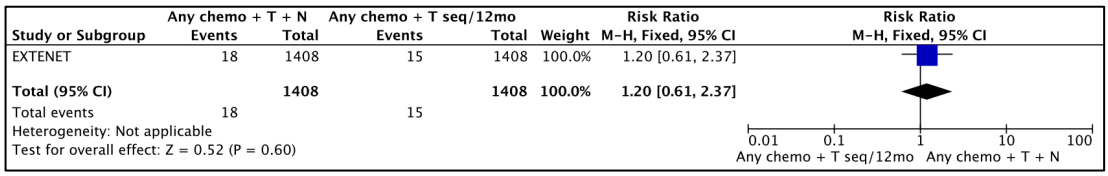
9.29.9. Comparison 9: ANY CHEMO / TRASTUZUMAB 12 months (sequential, if anthracycline) (arm 3) vs ANY CHEMO / TRASTUZUMAB / LAPATINIB (arm 8)



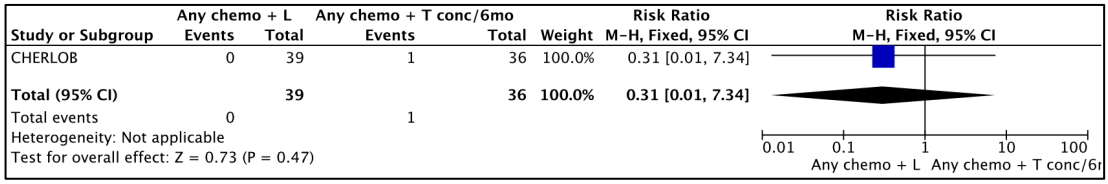
9.29.10. Comparison 10: ANY CHEMO / TRASTUZUMAB 12 months (sequential, if anthracycline) (arm 3) vs PLD (peg_lipos_doxo) + TAXANE / TRASTUZUMAB 12 months (concomitant with PLD) (arm 9)



9.29.11. Comparison 11: ANY CHEMO / TRASTUZUMAB 12 months (sequential, if anthracycline) (arm 3) vs ANY CHEMO / TRASTUZUMAB 12 months / NERATINIB 12 months (arm 10)

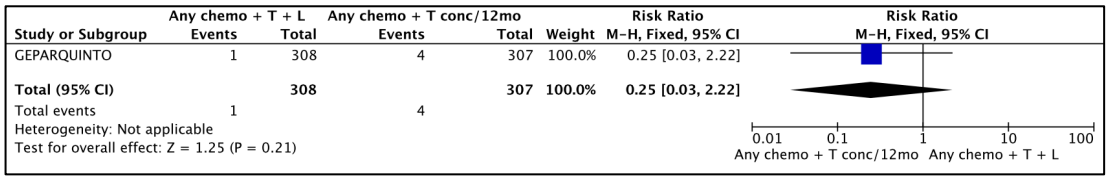


9.29.12. Comparison 12: ANY CHEMO / TRASTUZUMAB ≤ 6 months (concomitant with, if anthracycline) (arm 4) vs ANY CHEMO / NO TRASTUZUMAB / LAPATINIB (arm 7)

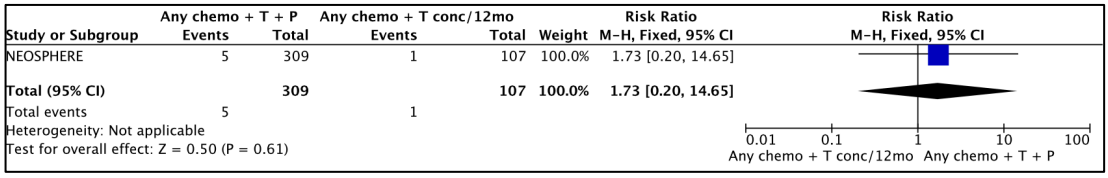


9.29.13. Comparison 13: ANY CHEMO / TRASTUZUMAB ≤ 6 months (concomitant with, if anthracycline) (arm 4) vs ANY CHEMO / TRASTUZUMAB / LAPATINIB (arm 8)

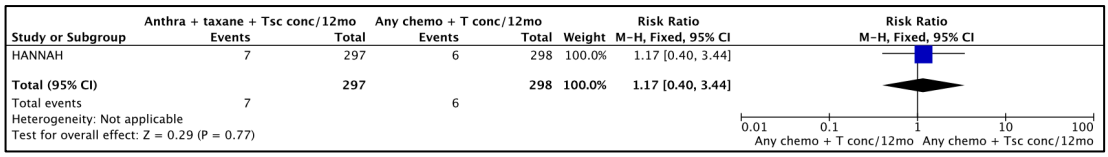
9.29.14. Comparison 14: ANY CHEMO / TRASTUZUMAB 12 months (concomitant with, if anthracycline) (arm 5) vs ANY CHEMO / TRASTUZUMAB / LAPATINIB (arm 8)



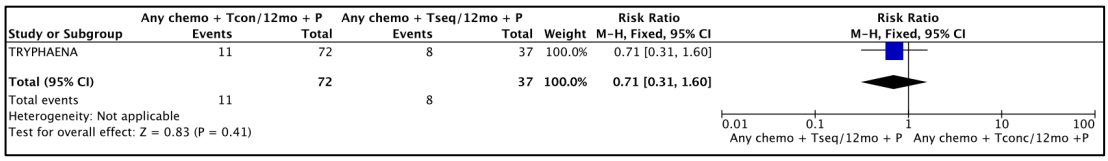
9.29.15. Comparison 15: ANY CHEMO / TRASTUZUMAB 12 months (concomitant with, if anthracycline) (arm 5) vs ANY CHEMO / TRASTUZUMAB 12 months / PERTUZUMAB (sequential, if anthracycline) (arm 11)



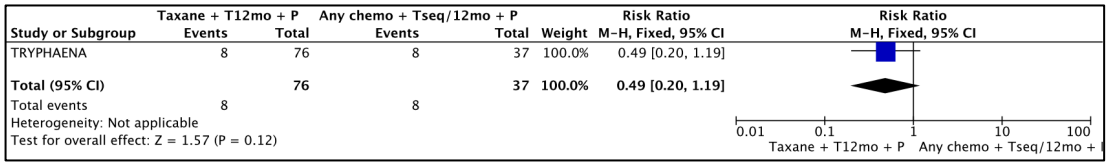
9.29.16. Comparison 16: ANY CHEMO / TRASTUZUMAB 12 months (concomitant with, if anthracycline) (arm 5) vs ANTHRA + TAXANE / TRASTUZUMAB SC 12 months (concomitant with Anthracycline) (arm 14)



9.29.17. Comparison 17: ANY CHEMO / TRASTUZUMAB 12 months / PERTUZUMAB (sequential, if anthracycline) (arm 11) vs ANY CHEMO / TRASTUZUMAB 12 months / PERTUZUMAB (concomitant, if anthracycline) (arm 12)



9.29.18. Comparison 18: ANY CHEMO / TRASTUZUMAB 12 months / PERTUZUMAB (sequential, if anthracycline) (arm 11) vs TAXANE (no athracycline) / TRASTUZUMAB 12 months / PERTUZUMAB (arm 13)



9.33. REDE 4: CARDIOTOXICIDADE – RANQUEAMENTO

	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Arm 7	Arm 8	Arm 9	Arm 10	Arm 11	Arm 12	Arm 13	Arm 14
Rank 1	0.0%	0.40%	0.80%	4.17%	7.64%	0.0%	0.0%	0.40%	0.0%	14.98%	7.39%	40.48%	0.78%	22.95%
Rank 2	0.0%	1.48%	4.18%	4.56%	17.22%	0.0%	0.0%	2.23%	0.0%	12.59%	25.68%	15.15%	6.13%	10.79%
Rank 3	0.0%	2.91%	10.94%	4.47%	17.43%	0.0%	0.01%	6.33%	0.0%	11.14%	13.31%	6.68%	17.49%	9.01%
Rank 4	0.0%	5.07%	16.85%	5.27%	19.37%	0.0%	0.13%	12.24%	0.50%	12.93%	6.24%	3.83%	6.72%	11.37%
Rank 5	0.0%	9.63%	19.02%	5.32%	19.02%	0.0%	0.97%	17.36%	0.0%	11.13%	3.86%	2.59%	4.05%	7.06%
Rank 6	0.01%	15.17%	20.12%	6.25%	10.12%	0.0%	5.16%	19.66%	0.01%	8.92%	3.19%	2.94%	3.02%	5.46%
Rank 7	0.12%	16.80%	17.90%	6.85%	4.69%	0.11%	12.60%	19.16%	0.01%	6.40%	4.10%	3.87%	2.49%	4.92%
Rank 8	1.55%	18.28%	8.12%	9.68%	2.66%	1.03%	16.54%	15.42%	0.07%	6.95%	5.50%	4.94%	3.60%	5.66%
Rank 9	6.86%	18.36%	1.90%	9.79%	1.40%	4.22%	21.83%	6.25%	0.14%	6.06%	6.88%	5.74%	4.99%	5.58%
Rank 10	9.81%	9.66%	0.18%	12.91%	0.38%	8.86%	27.99%	0.96%	0.29%	4.94%	6.95%	3.24%	7.73%	6.12%
Rank 11	22.38%	2.26%	0.0%	16.35%	0.07%	14.90%	14.78%	0.0%	1.51%	3.12%	5.52%	5.05%	8.72%	5.35%
Rank 12	42.16%	0.01%	0.0%	5.50%	0.0%	30.85%	0.01%	0.0%	1.93%	0.49%	8.08%	3.96%	5.06%	1.94%
Rank 13	16.86%	0.0%	0.0%	8.30%	0.0%	39.04%	0.0%	0.0%	7.06%	0.34%	2.97%	1.13%	20.87%	3.43%
Rank 14	0.26%	0.0%	0.0%	0.58%	0.0%	0.98%	0.0%	0.0%	88.98%	0.02%	0.34%	0.12%	8.36%	0.37%

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB ≤6 mo (sequential, if anthracycline)
03. ANY CHEMO / TRASTUZUMAB 12 mo (sequential, if anthracycline)
04. ANY CHEMO / TRASTUZUMAB ≤6 mo (concomitant with, if anthracycline)
05. ANY CHEMO / TRASTUZUMAB 12 mo (concomitant with, if anthracycline)
06. TAXANE (no anthracycline)/ TRASTUZUMAB 12 mo
07. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB
08. ANY CHEMO / TRASTUZUMAB / LAPATINIB
09. PLD (peg_lipos_doxo) + TAXANE / TRASTUZUMAB 12 mo (concomitant with PLD)
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (concomitant with anthracycline)
12. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (sequential with anthracycline)
13. TAXANE (no athracycline) / TRASTUZUMAB 12 mo / PERTUZUMAB
14. ANTHRA + TAXANE / TRASTUZUMAB SC12 mo (concomitant with Anthracycline)

9.34. REDE 4: CARDIOTOXICIDADE – RISCOS RELATIVOS GERAIS

1	**1.80** (1.40-2.30)	**2.00** (1.80-2.30)	1.50 (0.68-2.30)	**2.40** (1.70-3.40)	0.95 (0.75-1.20)	**1.50** (1.30-1.80)	**2.00** (1.70-2.30)	**0.35** (0.11-0.89)	**2.30** (1.1-4.5)	2.30 (0.45-19.00)	3.00 (0.22-14.00)	1.50 (0.22-14.00)	2.40 (0.75-7.50)
1.80 (1.40-2.30)	**2**	1.10 (0.89-1.50)	0.85 (0.36-2.20)	1.30 (0.87-2.10)	**0.53** (0.38-0.74)	**0.86** (0.66-1.10)	1.10 (0.86-1.40)	**0.20** (0.06-0.51)	1.30 (0.62-2.70)	1.30 (0.25-11.00)	1.70 (0.28-16.00)	0.83 (0.12-7.80)	1.30 (0.41-4.30)
2.00 (1.80-2.30)	1.10 (0.89-1.50)	**3**	0.75 (0.33-1.80)	1.20 (0.82-1.70)	**0.47** (0.37-0.58)	**0.75** (0.67-0.85)	0.97 (0.89-1.10)	**0.17** (0.06-0.44)	1.10 (0.57-2.20)	1.10 (0.22-9.30)	1.50 (0.25-14.00)	0.73 (0.11-6.90)	1.20 (0.37-3.70)
1.50 (0.68-2.30)	0.85 (0.36-2.20)	0.75 (0.33-1.80)	**4**	1.60 (0.60-3.80)	0.63 (0.25-1.40)	1.00 (0.41-2.30)	1.30 (0.53-2.90)	**0.23** (0.05-0.79)	1.50 (0.50-4.40)	1.50 (0.24-14.00)	2.00 (0.28-21.00)	0.97 (0.12-11.00)	1.60 (0.37-6.30)
2.40 (1.70-3.40)	1.30 (0.87-2.10)	1.20 (0.82-1.70)	1.60 (0.60-3.80)	**5**	**0.40** (0.26-0.60)	**0.64** (0.44-0.93)	0.83 (0.57-1.20)	**0.15** (0.05-0.40)	0.96 (0.45-2.10)	0.97 (0.20-7.70)	1.30 (0.23-11.00)	0.62 (0.10-5.70)	1.00 (0.33-3.00)
0.95 (0.75-1.20)	**0.53** (0.38-0.74)	**0.47** (0.37-0.58)	0.63 (0.25-1.40)	**0.40** (0.26-0.60)	**6**	**1.60** (1.30-2.10)	**2.10** (1.60-2.60)	**0.37** (0.12-0.95)	**2.40** (1.20-4.90)	2.40 (0.47-20.00)	3.20 (0.54-30.00)	1.50 (0.23-15.00)	2.50 (0.78-7.90)
1.50 (1.30-1.80)	0.86 (0.66-1.10)	**0.75** (0.67-0.85)	1.00 (0.41-2.30)	**0.64** (0.44-0.93)	**1.60** (1.30-2.10)	**7**	0.61 (0.32-1.10)	0.55 (0.27-1.10)	**0.36** (0.22-0.57)	**0.52** (0.33-0.77)	0.61 (0.32-1.10)	0.90 (0.73-1.10)	1.20 (0.26-8.90)
2.00 (1.70-2.30)	1.10 (0.86-1.40)	0.97 (0.89-1.10)	1.30 (0.53-2.90)	0.83 (0.57-1.20)	**2.10** (1.60-2.60)	0.61 (0.32-1.10)	**8**	0.90 (0.60-1.40)	0.59 (0.29-1.20)	0.85 (0.43-1.70)	1.00 (0.78-1.30)	1.50 (0.77-2.90)	1.90 (0.48-14.00)
0.35 (0.11-0.89)	**0.20** (0.06-0.51)	**0.17** (0.06-0.44)	**0.23** (0.05-0.79)	**0.15** (0.05-0.40)	**0.37** (0.12-0.95)	0.55 (0.27-1.10)	0.90 (0.60-1.40)	**9**	0.66 (0.30-1.40)	0.94 (0.45-2.00)	1.10 (0.80-1.50)	1.60 (0.80-3.40)	2.10 (0.50-15.00)
2.30 (1.1-4.5)	1.30 (0.62-2.70)	1.10 (0.57-2.20)	1.50 (0.50-4.40)	0.96 (0.45-2.10)	**2.40** (1.20-4.90)	**0.36** (0.22-0.57)	0.59 (0.29-1.20)	0.66 (0.30-1.40)	**10**	1.40 (0.83-2.50)	1.70 (0.82-3.40)	**2.50** (1.50-4.20)	3.20 (0.69-25.00)
2.30 (0.45-19.00)	1.30 (0.25-11.00)	1.10 (0.22-9.30)	1.50 (0.24-14.00)	0.97 (0.20-7.70)	2.40 (0.47-20.00)	**0.52** (0.33-0.77)	0.85 (0.43-1.70)	0.94 (0.45-2.00)	1.40 (0.83-2.50)	**11**	1.20 (0.59-2.30)	**1.70** (1.10-2.80)	2.20 (0.49-18.00)
3.00 (0.22-14.00)	1.70 (0.28-16.00)	1.50 (0.25-14.00)	2.00 (0.28-21.00)	1.30 (0.23-11.00)	3.20 (0.54-30.00)	0.61 (0.32-1.10)	1.00 (0.78-1.30)	1.10 (0.80-1.50)	1.70 (0.82-3.40)	1.20 (0.59-2.30)	**12**	1.50 (0.79-2.80)	1.90 (0.48-14.00)
1.50 (0.22-14.00)	0.83 (0.12-7.80)	0.73 (0.11-6.90)	0.97 (0.12-11.00)	0.62 (0.10-5.70)	1.50 (0.23-15.00)	0.90 (0.73-1.10)	1.50 (0.77-2.90)	1.60 (0.80-3.40)	**2.50** (1.50-4.20)	**1.70** (1.10-2.80)	1.50 (0.79-2.80)	**13**	1.30 (0.28-10.00)
2.40 (0.75-7.50)	1.30 (0.41-4.30)	1.20 (0.37-3.70)	1.60 (0.37-6.30)	1.00 (0.33-3.00)	2.50 (0.78-7.90)	1.20 (0.26-8.90)	1.90 (0.48-14.00)	2.10 (0.50-15.00)	3.20 (0.69-25.00)	2.20 (0.49-18.00)	1.90 (0.48-14.00)	1.30 (0.28-10.00)	**14**

Legend for treatment arms

01. ANY CHEMO ALONE (NO ANTI-HER2 THERAPY)
02. ANY CHEMO / TRASTUZUMAB ≤6 mo (sequential, if anthracycline)
03. ANY CHEMO / TRASTUZUMAB 12 mo (sequential, if anthracycline)

04. ANY CHEMO / TRASTUZUMAB ≤6 mo (concomitant with, if anthracycline)
05. ANY CHEMO / TRASTUZUMAB 12 mo (concomitant with, if anthracycline)
06. TAXANE (no anthracycline)/ TRASTUZUMAB 12 mo
07. ANY CHEMO / NO TRASTUZUMAB / LAPATINIB
08. ANY CHEMO / TRASTUZUMAB / LAPATINIB
09. PLD (peg_lipos_doxo) + TAXANE / TRASTUZUMAB 12 mo (concomitant with PLD)
10. ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo
11. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (concomitant with anthracycline)
12. ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (sequential with anthracycline)
13. TAXANE (no athracycline) / TRASTUZUMAB 12 mo / PERTUZUMAB
14. ANTHRA + TAXANE / TRASTUZUMAB SC12 mo (concomitant with Anthracycline)

9.35. REDE 4: CARDIOTOXICIDADE – RISCOS RELATIVOS CONTRA QUIMIOTERAPIA ISOLADA

	ANY CHEMOTHERAPY ALONE
ANY CHEMO / TRASTUZUMAB ≤6 mo (sequential, if anthracycline)	**1.80 (1.40-2.30)**
ANY CHEMO / TRASTUZUMAB 12 mo (sequential, if anthracycline)	**2.00 (1.80-2.30)**
ANY CHEMO / TRASTUZUMAB ≤6 mo (concomitant with, if anthracycline)	1.50 (0.68-2.30)
ANY CHEMO / TRASTUZUMAB 12 mo (concomitant with, if anthracycline)	**2.40 (1.70-3.40)**
TAXANE (no anthracycline)/ TRASTUZUMAB 12 mo	0.95 (0.75-1.20)
ANY CHEMO / NO TRASTUZUMAB / LAPATINIB	**1.50 (1.30-1.80)**
ANY CHEMO / TRASTUZUMAB / LAPATINIB	**2.00 (1.70-2.30)**
PLD (peg_lipos_doxo) + TAXANE / TRASTUZUMAB 12 mo (concomitant with PLD)	**0.35 (0.11-0.89)**
ANY CHEMO / TRASTUZUMAB 12 mo / NERATINIB 12mo	**2.30 (1.1-4.5)**
ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (concomitant with anthracycline)	2.30 (0.45-19.00)
ANY CHEMO / TRASTUZUMAB 12 mo / PERTUZUMAB (sequential with anthracycline)	3.00 (0.22-14.00)
TAXANE (no athracycline) / TRASTUZUMAB 12 mo / PERTUZUMAB	1.50 (0.22-14.00)
ANTHRA + TAXANE / TRASTUZUMAB SC12 mo (concomitant with Anthracycline)	2.40 (0.75-7.50)

9.36. REDE 4: CARDIOTOXICIDADE – AVALIAÇÃO DA INCONSISTÊNCIA

Não foi observada qualquer evidência de inconsistência na rede utilizando-se o método de "*split node*", conforme descrito na tabela abaixo. O valor de "p" apresentado na coluna da direita refere-se a um teste cuja hipótese nula é a não existência de inconsistência na rede. Para que esse teste aceite globalmente 5% de erro alfa, deve-se corrigir o limiar de significância para as 12 comparações procedidas, tendo-se como limiar de significância corrigido 0.004. Portanto, todo valor de "p" acima de 0.004 é considerado não significativo na tabela abaixo.

COMPARISON	SOURCE OF EVIDENCE – logRR	P-VALUE
1 vs. 3	- direct: 0.90 (0.76 – 1.00) - indirect: 0.32 (-0.46 – 1.10) - network: 0.88 (0.75 – 1.00)	0.16
1 vs. 4	- direct: 0.54 (-0.62 – 1.80) - indirect: -1.4 (-4.7 – 0.47) - network: 0.03 (-0.90 – 0.91)	0.10
1 vs. 5	- direct: 0.57 (-0.08 – 1.20) - indirect: 1.6 (0.99 – 2.20) - network: 1.1 (0.70 – 1.60)	0.03
2 vs. 3	- direct: 0.31 (0.01 – 0.62) - indirect: -0.61 (-4.1 – 2.00) - network: 0.30 (0.01 – 0.60)	0.49
2 vs. 7	- direct: -0.94 (-4.4 – 1.70) - indirect: -0.02 (-0.35 – 0.31) - network: -0.03 (-0.36 – 0.30)	0.49
3 vs. 5	- direct: 0.61 (0.02 – 1.20) - indirect: -0.15 (-0.76 – 0.51) - network: 0.26 (-0.18 – 0.69)	0.01
3 vs. 7	- direct: -0.33 (-0.48 – -0.18) - indirect: -0.09 (-1.30 – 1.1) - network: -0.33 (-0.48 – -0.19)	0.68
3 vs. 8	- direct: -0.02 (-0.14 – 0.10) - indirect: -0.33 (-1.70 – 0.97) - network: -0.02 (-0.14 – 0.10)	0.64
4 vs. 7	- direct: 2.2 (0.14 – 5.50) - indirect: 0.01 (-1.20 – 1.20) - network: 0.52 (-0.38 – 1.50)	0.08
4 vs. 8	- direct: 2.00 (-0.06 – 5.30) - indirect: 0.32 (-0.92 – 1.50) - network: 0.83 (-0.06 – 1.80)	0.18
5 vs. 8	- direct: -1.70 (-5.10 – 0.41) - indirect: -0.21 (-0.68 – 0.25) - network: -0.28 (-0.73 – 0.17)	0.20
7 vs. 8	- direct: 0.31 (0.18 – 0.45) - indirect: 0.89 (-1.80 – 4.50) - network: 0.31 (0.18 – 0.44)	0.67

9.37. REDE 5: TOXICIDADES GRAUS 3 E 4

Em virtude da grande heterogeneidade entre os efeitos adversos reportados entre os estudos, não foi possível construir uma rede para a análise desse desfecho.

9.38. BOLSA CNPQ

Este projeto recebeu fomento do Programa Ciência Sem Fronteiras na forma de bolsa para doutorado sanduíche via Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).