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名古屋市立大学学位論文

悪性腫瘍領域における第 III 相臨床試験の成功確率が低い原因の探索：Systematic review による検討

平成 30 年度（2019 年 3 月）

大学院薬学研究科博士後期課程創薬生命科学専攻

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① 本論文は、平成 30 年度（2019 年 3 月）名古屋市立大学大学院薬学研究科において審査されたものである。

主査　鈴木　匡　教授
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② 本論文は、学術情報雑誌に収載された次の報文を基礎とするものである。

1. Mitsugu Ikeda, Tatsuya Ochibe, and Masahiro Tohkin: Possible causes of failing to meet primary endpoints: a systematic review of randomized controlled phase 3 clinical trials in patients with non-small-cell-lung cancer. Therapeutic Innovation & Regulatory Science 2018 Aug 8:first published online
2. Mitsugu Ikeda, Tatsuya Ochibe, and Masahiro Tohkin: Success rate and possible causes of failures of phase 3 clinical trials in patients with breast cancer: A systematic review. Journal of Clinical Trials 8, 349, 2018.

③ 本論文の基礎となる研究は、頭金　正博　教授の指導の下に名古屋市立大学大学院薬学研究科において行われた。

目次

1. 緒言

医薬品開発の後期では、一般的に、有効性と安全性を検証するための第 3 相臨床試験が計画される [1]。第 3 相臨床試験では、対照群に対する優越性または非劣性を検証するための統計解析によって、被験薬の有効性が評価される。このため、効果の大きさの見積もり値の正確性は、第 3 相臨床試験結果に影響を及ぼす重大な要素である。一般的に、第 3 相臨床試験の被験薬の効果の大きさは、第 2 相臨床試験結果を基に推定される。しかし、第 3 相臨床試験が大規模なイベント評価試験の場合、比較的小規模な第 2 相臨床試験から得られた結果に基づく推定精度には限界がある。このため、第 2 相臨床試験で得られた良好なシグナルが、第 3 臨床相試験で同様に認められるとは限らない。

実際に、第 3 相臨床試験で事前に推定した被験薬の効果の大きさを検証できなかった事例が数多く存在する。悪性腫瘍領域では、他の疾患領域と比較して第 3 相臨床試験の成功確率が最も低く、40-46%と報告されている [2-4]。特に、悪性腫瘍領域においては、癌種ごとに標準治療が異なるため、癌種ごとに臨床試験が実施されるが、特定の癌種で事前に推定した被験薬の効果の大きさを第 3 相臨床試験で検証できたとしても、別の癌種においても第 3 相臨床試験で同様に検証できるとは限らない。

第 3 相臨床試験の成功確率が低い原因の一つとして、第 2 相臨床試験における false positive が考えられる。すなわち、何等かの原因により、第 2 相臨床試験の結果が、見かけ上、本来の被験薬の効果よりも大きく検出されたため、第 2 相臨床試験の結果を基に推定した被験薬の効果が、第 3 相臨床試験で再現できなかったものと考えられる。第 2 相臨床試験において false positive が認められる割合は、約 20～40%との報告がある [5]。また、対照群との比較を行わない single arm 試験では、randomized 試験と比較して、false positive が認められる割合が 2～4 倍増加することが報告されている [6]。

抗悪性腫瘍薬の臨床評価方法に関するガイドラインによると [7]、一般的に、第 2 相臨床試験では腫瘍縮小率を主要評価項目とし、第 3 相臨床試験では progression-free survival（PFS）や overall survival（OS）などの生存期間が主要評価項目として評価される。第 2 相臨床試験においても、PFS や OS などの生存期間は評価されるが、探索的な位置づけでの評価であり、第 3 相臨床試験での効果の見積もりに十分な評価ができているとは限らない。

以上のことから、悪性腫瘍領域では、特に、第 3 相臨床試験の主要評価項目の事前の見積もりが容易ではないため、その正確性が臨床試験の成否に大きな影響を与えている可能性が考えられる。

悪性腫瘍による死亡原因として最も多い癌種が肺癌である。このうち、非小細胞肺癌が肺癌による死亡の約 80%を占めている [8]。非小細胞肺癌に対する治療オプションは増えているものの、依然として、大きなアンメット・ニーズが存在する [9]。また、乳癌は女性の中で最も多い罹患数が多い癌種である。初期の乳癌では、過去 20 年間で生存率が大幅に向上しているものの、乳癌の発症率は上昇している [10]。病期や治療ラインに応じた治療が求められるようになり、特に、転移性乳癌の場合、治療薬に対する抵抗性を獲得することで、その生物学的機序は益々複雑になっており [11]、大きなアンメット・ニーズが存在する。このため、非小細胞肺癌および乳癌は、悪性腫瘍の中で最も医薬品開発が盛んな癌種であり、第 3 相臨床試験の実施件数が多い [4]。

そこで、今回、非小細胞肺癌と乳癌を対象とした第 3 相臨床試験において、事前に推定した対照薬および被験薬の効果の大きさと実際に得られた結果の差異を分析し、抗悪性腫瘍領域の第 3 相臨床試験の成功確率が低い原因が、主要評価項目の見積もりの正確性に起因しているかどうかを検討した。また、その原因を解決するための対策として、試験実施計画書策定における留意点について考察した。

本検討では、systematic review の手法を用いた。Systematic review は、エビデンスレベルが高い手法であり、診療ガイドラインの作成にも用いられる [12]。Research question に答えるために、再現性があり、かつ、バイアスを最小限に抑えた基準をあらかじめ定めた上で、文献の網羅的な調査を行い、系統的な分析および評価を行う手法であり [12]、今回の検討に適した手法である。

2. 方法

2.1 オンライン・データベース検索

罹患数が多く、アンメット・ニーズが高く、かつ、医薬品開発が最も活発に行われている癌種として、非小細胞肺癌および乳癌を選択し、これらを対象とした第 3 相臨床試験の systematic review を実施した。本研究は、systematic review の実施におけるガイドラインとして最も汎用されている PRISMA guideline に準拠して実施した[13]。

2011 年 1 月から 2017 年 6 月の間に試験結果が公表された非小細胞肺癌および乳癌を対象とした第 3 相臨床試験を MEDLINE/PubMed、Cochrane Central Register of Controlled Trials（CENTRAL）、および EMBASE より収集した。

各オンライン・データベースで設定した検索条件を表 1 に示した。各オンライン・データベースで設定した検索条件は、癌種（非小細胞肺癌又は乳癌）以外、同一とした。

表 1. オンライン・データベースの検索条件（1/2）

データベース	MEDLINE/PubMed	CENTRAL	EMBASE
検索実施日	2017 年 12 月 28 日	2017 年 12 月 29 日	2017 年 12 月 29 日
検索条件　非小細胞肺癌	・Article types: Clinical trial, phase 3 ・Full-text available ・Publication dates: January 1st in 2011 to June 30st in 2017 ・Search terms: “randomized [randomised]” “non-small-cell lung cancer” in titles or abstracts ・Language: English	・Search items include “phase 3” “randomized” “non-small-cell lung cancer” in title, abstract, and keywords. ・Publication type: article ・Publication dates: January 1st in 2011 to June 30st in 2017	・Population: “non small cell lung cancer” in titles or abstracts ・Study design: “randomized controlled trial” in titles or abstracts ・Study types: phase 3 clinical trial ・Publication types: Article or Article in Press ・Publication dates: January 1st in 2011 to June 30st in 2017

表 1. オンライン・データベースの検索条件（2/2）

データベース	MEDLINE/PubMed	CENTRAL	EMBASE
検索実施日	2017 年 12 月 28 日	2017 年 12 月 29 日	2017 年 12 月 29 日
検索　乳癌条件	・Article types: Clinical trial, phase 3 ・Full-text available ・Publication dates: January 1st in 2011 to June 30st in 2017 ・Search terms: “randomized [randomised]” “breast cancer” in titles or abstracts ・Language: English	・Search items include “phase 3” “randomized” “breast cancer” in title, abstract, and keywords. ・Publication type: article ・Publication dates: January 1st in 2011 to June 30st in 2017	・Population: “breast cancer” in titles or abstracts ・Study design: “randomized controlled trial” in titles or abstracts ・Study types: phase 3 clinical trial ・Publication types: Article or Article in Press ・Publication dates: January 1st in 2011 to June 30st in 2017

2.2　選択・除外基準

収集した試験の選択・除外基準を表 2 に示した。研究対象は、主要評価項目に対する被験薬の有効性を評価した無作為割付第 3 相臨床試験とし、全文が英語で公開されている論文を網羅的に収集した。

事前に推定した対照薬および被験薬の効果の大きさと実際に得られた結果の差異を分析することを目的としているため、優越性試験だけでなく、非劣性試験も研究対象に含めた。

オンライン・データベースの検索条件に、”phase 3”を設定しても、検索範囲である title or abstract に”phase 3”が含まれている文献は、第 2 相臨床試験結果の報告であったとしても抽出される。従って、本研究の目的に合致した対象文献を厳密に選定するため、2.3 項に記載する手順にて、第 2 相臨床試験結果の報告、試験実施計画書の報告、総説、サブグループ解析、追加解析あるいは探索的解析などの主要評価項目以外の結果を主体とした報告、メタ解析結果の報告、バイオマーカー探索結果の報告、抗悪性腫瘍薬以外の臨床試験結果の報告を研究対象から除外

した。また、後発医薬品（バイオシミラーを含む）の臨床試験や製剤変更のための臨床試験、さらに、3 群比較試験や 2 つ以上の治療法を組み合わせた要因試験についても、本研究の目的に合致しないため、除外した。

表 2. Systematic review で収集した臨床試験の選択・除外基準

選択基準	・ 主要評価項目に対する被験薬の有効性を評価した無作為割付第 3 相臨床試験
	・ 全文が公開された英語論文
除外基準	・ 第 2 相臨床試験
	・ 試験実施計画書の報告
	・ 総説
	・ 主要評価項目以外の結果を主体とした報告
	・ メタ解析結果の報告
	・ バイオマーカー探索結果の報告
	・ 抗悪性腫瘍薬の被験薬以外の臨床試験
	・ 後発医薬品（バイオシミラーを含む）の臨床試験
	・ 製剤変更のための臨床試験
	・ 3 群比較試験
	・ 2 つ以上の治療法を組み合わせた要因試験

2.3　研究対象試験選択手順

選択バイアスを排除するため、2 名の独立したレビューアにより、選択・除外基準に合致した臨床試験を抽出した。2 名の見解が異なる場合は、両者の合意に基づき選択した。

まず、MEDLINE/PubMed、CENTRAL、および EMBASE の検索で抽出された文献のうち、重複している文献を除外し、abstract review 対象文献を選定した。

選択・除外基準の多くは、abstract review で判断可能と考えられたため、abstract review 対象文献について、表 2 で示した選択・除外基準に従い、非対象試験を特定し、full-text review 対象文献を選定した。Abstract review で判断できなかった文献は full-text review 対象文献に含めた。

Full-text review 対象文献について、表 2 で示した選択・除外基準に従って full-text review を実施し、非対象試験を除外した後、本研究対象試験を特定した。

2.4　データの抽出および解析方法

それぞれの癌種ごとに、主要評価項目を抽出し、試験結果を Positive （主要評価項目を達成した）と Negative（主要評価項目を達成しなかった）に振り分け、主要評価項目別に集計した。

非小細胞肺癌対象試験では、対象患者、試験デザインなどの特性を抽出して Positive 試験と Negative 試験に振り分け、その分布をカイ二乗検定を用いて検定した。なお、分割表の中で、期待度数 5 未満のセルが全体の 20%を超えた場合にはフィッシャーの直接確率計算法を用いて検定した。

また、それぞれの癌種で主要評価項目ごとに、試験計画時点での見積もり値と実際に得られた試験結果を抽出し､その差について paired t-test を用いて検定した。さらに、Positive 試験と Negative 試験の特徴的傾向を検討し、見出された特徴的傾向については、公表論文を精査することにより、その原因について検討した。また、その原因検討を踏まえて、第 3 相臨床試験計画を立案する際の留意点について考察した。

全ての統計解析には、JMP Pro13（SAS Institute Japan Ltd., Tokyo Japan）を用いた。

2.5　バイアスに対する評価

本研究におけるバイアスの混入リスクに対する評価として、公表論文に試験計画時点での見積もり値の記載が不十分であった場合に解析結果に及ぼす影響を検討した。また、パブリケーションバイアスに対する評価も行った。

3. 結果

3.1 対象試験の選択結果

2011 年 1 月から 2017 年 6 月の間に試験結果が公表された第 3 相臨床試験のうち、本研究の対象となる試験の選択結果を、非小細胞肺癌および乳癌のそれぞれについて、図 1 および 2 に示す。

3.1.1 非小細胞肺癌対象試験の選択結果

2011 年 1 月 1 日から 2017 年 6 月 30 日までに試験結果が公表された非小細胞肺癌を対象とした無作為化第 3 相臨床試験は、MEDLINE/PubMed で 222 件、EMBASE または CENTRAL で 227 件であり、このうち、重複していた 160 件を除く 334 件が abstract review 対象となった。Abstract review の結果、222 件が除外対象であり、112 件が full-text review の対象となった。Full-text review の結果、6 件が除外対象であり、106 件が本研究対象試験として選定された。このうち、Positive は 40 件、Negative は 66 件であり、Positive 試験の割合は 38%であった。

106 件の非小細胞肺癌を対象とした第 3 相臨床試験について、文献から抽出したデータの一覧を Positive 40 試験および Negative 66 試験に分けて、それぞれ、付録 1 および 2 に示した。

3.1.2 乳癌対象試験の選択結果

2011 年 1 月 1 日から 2017 年 6 月 30 日までに試験結果が公表された乳癌を対象とした無作為化第 3 相臨床試験は、MEDLINE/PubMed で 393 件、EMBASE または CENTRAL で 519 件であり、このうち、重複していた 272 件を除く 640 件が abstract review 対象となった。Abstract review の結果、507 件が除外対象であり、133 件が full-text review の対象となった。Full-text review の結果、20 件が除外対象であり、113 件が本研究対象試験として選定された。このうち、Positive は 39 件、Negative は 74 件であり、Positive 試験の割合は 35%であった。

113 件の乳癌を対象とした第 3 相臨床試験について、文献から抽出したデータの一覧を Positive 39 試験および Negative 74 試験に分けて、それぞれ、付録 3 および 4 に示した。

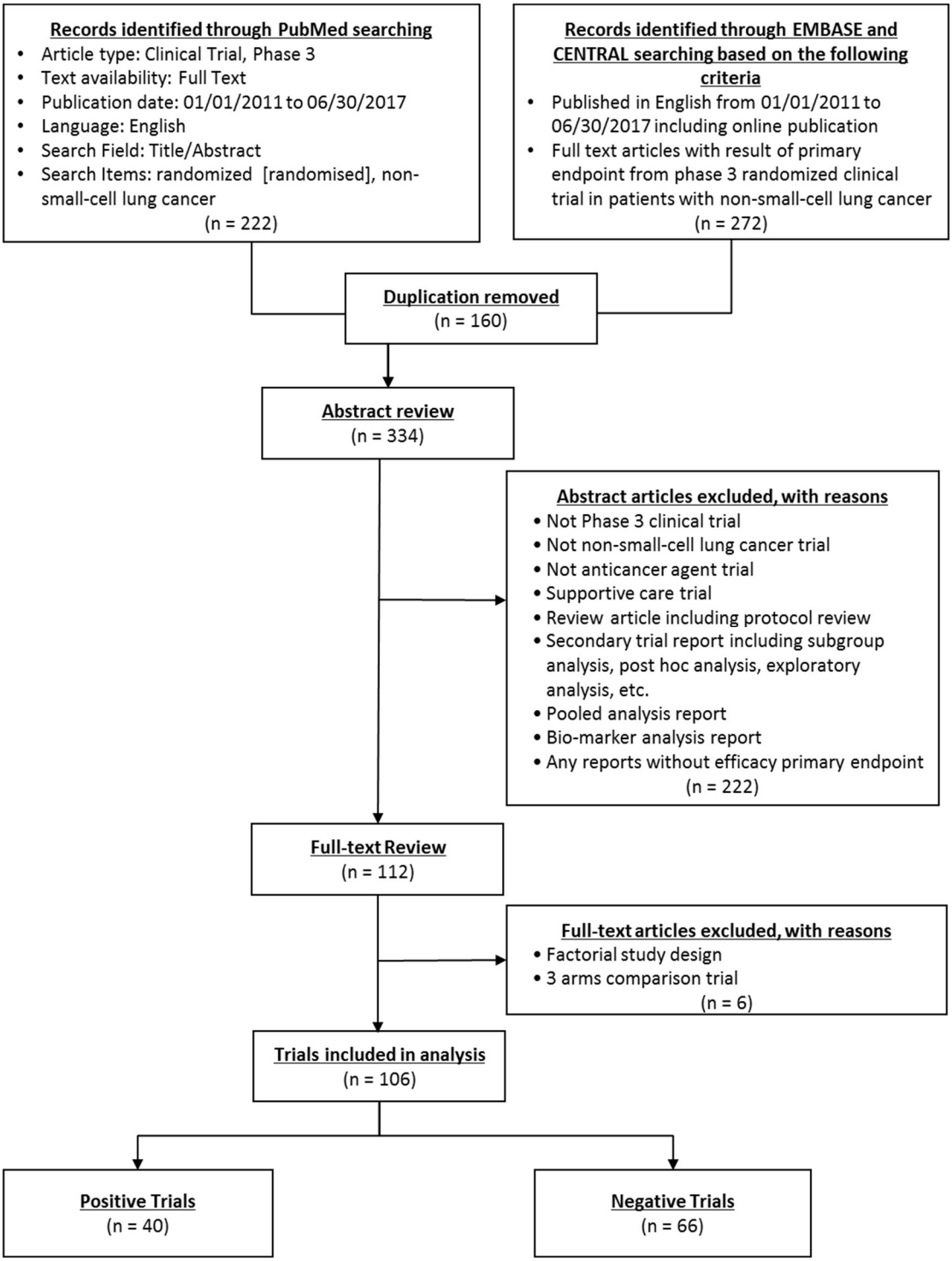

図 1. 研究対象試験選択フロー（非小細胞肺癌）

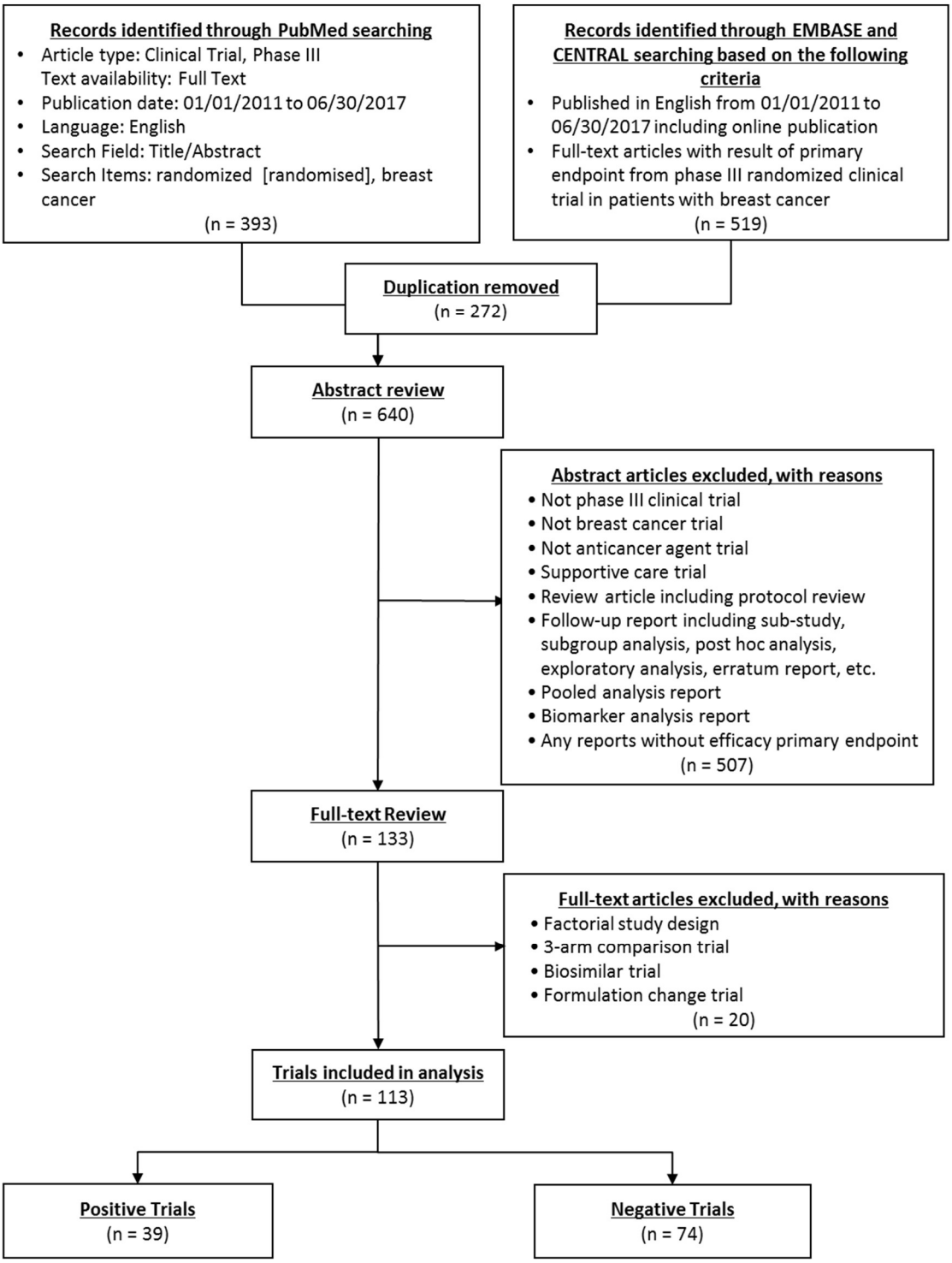

図 2. 研究対象試験選択フロー（乳癌）

3.2　非小細胞肺癌における検討

3.2.1　第 3 相臨床試験の特性（非小細胞肺癌）

非小細胞肺癌を対象とした 106 件の第 3 相臨床試験の特性を表 3 にまとめた。

Positive 試験と Negative 試験の割合について、癌のステージ、performance status、試験デザイン、および被験薬の種類で有意な違いは認められなかった。

表 3. 非小細胞肺癌を対象とした第 3 相臨床試験の特性（1/2）

特性項目	合計	Positive 試験 n (%)	Negative 試験 n (%)	p 値
合計	106	40 (38)	66 (62)	
癌のステージ				
IIIB または IV	69	29 (42)	40 (58)	0.262
その他	29	10 (34)	19 (66)	
不明	8	1 (13)	7 (88)	
Performance status				
0-1	49	19 (39)	30 (61)	0.630
0-2	53	21 (40)	32 (60)	
その他	3	0 (0)	3 (100)	
不明	1	0 (0)	1 (100)	
試験デザイン				
Double-blind	41	12 (29)	29 (71)	0.234
Open	55	25 (45)	30 (55)	
不明	10	3 (30)	7 (70)	
被験薬の種類				
化学療法	22	10 (45)	12 (55)	0.875
放射線化学療法	9	2 (22)	7 (78)	
血管新生阻害剤	18	7 (39)	11 (61)	
EGFR 阻害剤	28	11 (39)	17 (61)	
免疫療法	13	5 (38)	8 (62)	
その他	16	5 (31)	11 (69)	

EGFR: epidermal growth factor receptor

P values were calculated by the Chi-squared test or Fisher’s exact test.

表 3. 非小細胞肺癌を対象とした第 3 相臨床試験の特性（2/2）

特性項目	合計	Positive 試験 n (%)	Negative 試験 n (%)	p 値
対象被験者数				
< 200	18	10 (56)	8 (44)	0.078
200–400	37	17 (46)	20 (54)	
400–600	22	6 (27)	16 (73)	
> 600	29	7 (24)	22 (76)	
対象患者集団				
All comer	87	29 (33)	58 (67)	0.045
Enriched population	19	11 (58)	8 (42)	
主要評価項目				
OS	56	14 (25)	42 (75)	0.007
PFS	44	24 (55)	20 (45)	
その他	6	2 (33)	4 (67)	

OS: overall survival, PFS: progression-free survival

P values were calculated by the Chi-squared test or Fisher’s exact test.

対象被験者数については、Positive 試験と Negative 試験の割合が異なる傾向が認められ（p = 0.078）、対象被験者数が 200 例未満では、Positive 試験が多い傾向が認められた（Positive：10 件［56%］、Negative：8 件［44%］）。第 3 相臨床試験の対象被験者数設計においては、被験薬と対照薬の効果の見積もり値の差が大きいほど、被験者数が少なくなり、被験薬と対照薬の効果の見積もり値の差が小さいほど、被験者数が多くなる。このため、第 3 相臨床試験計画時に、対照薬と比べて効果の見積もり値の差が大きいと推定できた被験薬では、被験者数が少なく、成功確率が高い可能性が考えられた。

癌細胞のターゲット分子に選択的に作用する薬剤の場合、そのターゲット分子の特異的な発現が認められる患者を選別して（enriched population）臨床試験を実施する場合がある。そこで、対象患者集団の選別を行っていない（all comer）臨床試験との間で Positive 試験と Negative 試験の割合について検討したところ、有意な差が認められ（p＝0.045）、Enriched population では、Positive 試験が多く認めら

れた（Positive：11 件［58%］、Negative：8 件［42%］）

Enriched population の臨床試験では、ターゲット分子の特異的な発現が認められる患者に限定するため、より高い効果が期待でき、より少ない被験者数で第 3 相臨床試験を実施することが可能であると予想されたが、対象患者集団が enriched population の Positive 試験 11 件のうち、対象被験者数が 200 例未満であった第 3 相臨床試験は 2 件であった[14,15]。

主要評価項目が overall survival（OS）または progression-free survival（PFS）においても、Positive 試験と Negative 試験の割合に違いが認められた（$p = 0.007$）。非小細胞肺癌を対象とした第 3 相臨床試験では、ほとんどの主要評価項目が OS または PFS であり、その成功確率は OS で 25%（14/56）、PFS で 55%（24/44）であった。

3.2.2　試験計画時と得られた試験結果の比較（非小細胞肺癌）

非小細胞肺癌を対象とした第 3 相臨床試験について、試験計画時と得られた試験結果の OS 中央値を比較した（図 3）。

被験薬群では（図 3A）、Positive 試験 9 件および Negative 試験 27 件のいずれにおいても、試験計画時と得られた試験結果の OS 中央値に有意な差は認められなかった（それぞれ、$p = 0.291$ および $p = 0.799$）。このことから、被験薬の有効性の事前の見積もりは、Positive 試験および Negative 試験のいずれにおいても、比較的正確であったと考えられる。

一方、コントロール群では（図 3B）、Positive 試験 9 件の試験計画時と得られた試験結果の OS 中央値に有意な差は認められなかったものの（$p = 0.372$）、Negative 試験 27 件の試験計画時と得られた試験結果の OS 中央値には有意な差が認められた（$p < 0.001$）。このことから、Positive 試験では、コントロール群の事前の見積もりは、比較的正確であったものの、Negative 試験では、コントロール群の事前の見積もりが正確ではなかったと考えられる。

以上のように、OS を主要評価項目とした場合、Positive 試験では、被験薬およびコントロール群のいずれにおいても、事前の見積もりが比較的正確であり、事前に正確な見積もり値を算出することができれば、第 3 相臨床試験の成功確率が高まることが示唆される。一方、Negative 試験の場合、被験薬の事前の見積もりは比較的正確であったものの、コントロール群の事前の見積もりが正確でなかっ

たため、計画していた効果の差を検出できなかった可能性が考えられる。

コントロール群の事前の見積もりが正確でなかった主な原因について、Negative 試験の公表論文を精査したところ、OS は引き続き行われる治療の影響を受け易いとの考察が多く認められた[16-24]。OS を評価する臨床試験では、被験者が試験から離脱した場合であっても、解析に必要と設定された死亡イベント数に到達するまで、追跡調査が実施される。例えば、被験者の病態が進行し、他の治療薬への切り替え、あるいは、他の臨床試験に参加することになったとしても、死亡イベントの追跡調査は継続される。従って、コントロール群の被験者の病態が進行したとしても、引き続き行われる治療の影響で死亡イベント到達までの期間が延長する可能性がある。Senan ら[16]は、PET scan の普及により、病態進展に関する診断が進み、より早期に治療の変更が行われていること、およびコントロール群の被験者でより多くの後治療への変更が行われていることを報告している。また、Miller ら[23]は、副次評価項目とした PFS では有意な延長が認められたものの、コントロール群でより多くの被験者が後治療を受けており、主要評価項目である OS では有意な延長が認められなかったことを報告している。このように、非小細胞肺癌を対象とした第 3 相臨床試験で OS を主要評価項目としたとき、引き続き行われる治療が影響し、試験計画時と比較してコントロール群の OS を延長させ、多くの Negative な結果を導いた原因になっていると考えられた。

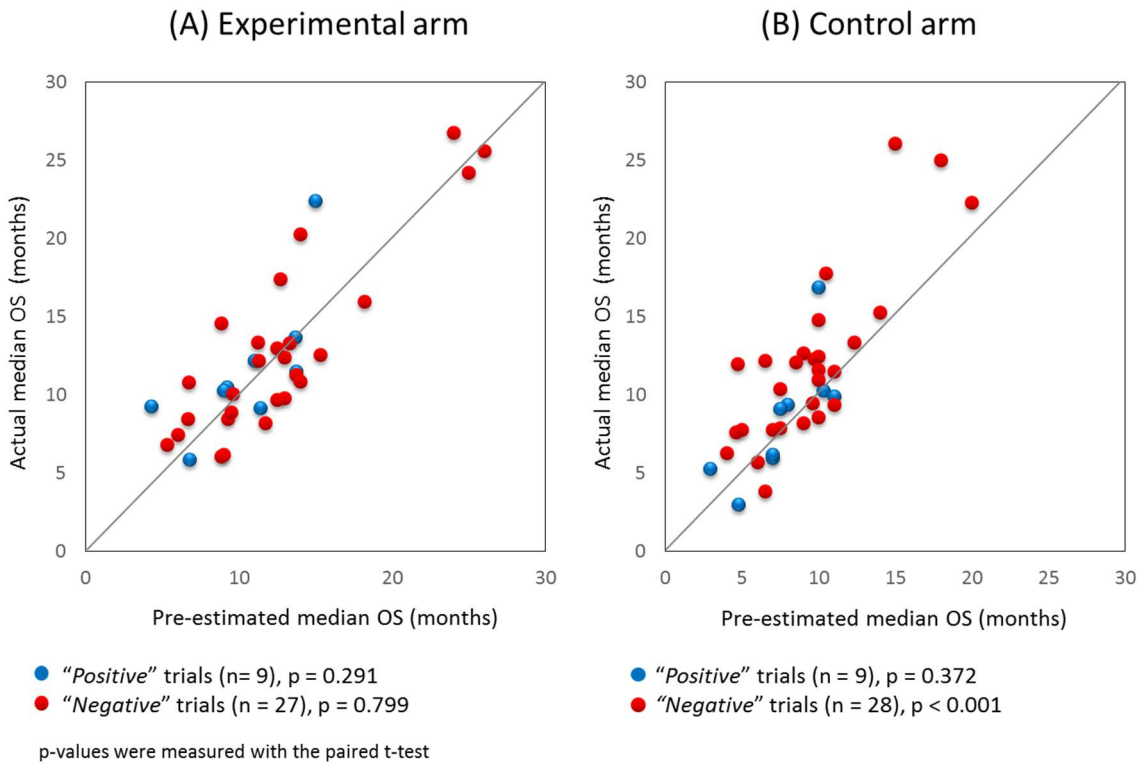

図 3. 試験計画時と実際に得られた試験結果の OS 中央値の比較（非小細胞肺癌）

同様に、試験計画時と得られた試験結果の PFS 中央値を比較した（図 4）。

被験薬群では（図 4A）、Positive 試験 12 件の試験結果の PFS 中央値は事前の見積もりよりも有意に高い値を示しており（$p = 0.027$）、Negative 試験 16 件の試験結果の PFS 中央値は事前の見積もり値よりも有意に低い値を示していた（$p = 0.035$）。

コントロール群では（図 4B）、Positive 試験 16 件および Negative 試験 16 件のいずれにおいても、試験計画時と得られた試験結果の PFS 中央値に有意な差は認められなかった（それぞれ、$p = 0.061$ および $p = 0.576$）。

以上のことから、PFS を主要評価項目とした場合、コントロール群の事前の見積もりは比較的正確であり、被験薬の効果が見積もりどおり（あるいはそれ以上）であった場合は Positive、被験薬の効果が見積もり未満であった場合は Negative となる傾向が認められた。PFS の場合、病態の進展が認められた時点で評価されるため、治験薬に引き続き行われる治療の影響を受けない。したがって、被験薬の効果を正確に見積もることができれば、第 3 相臨床試験の成功確率が高まること

が示唆される。

COX-2 阻害剤である celecoxib と標準化学療法との併用治療の効果を標準化学療法と比較した第 3 相臨床試験では、コントロール群の事前の PFS の中央値の見積もりが 6 ヵ月、実際に得たれた試験結果が 5.26 ヵ月であり、ほぼ一致していたのに対し、被験薬群の PFS の中央値の見積もりは 9.2 ヵ月、実際に得られた試験結果は 5.16 ヵ月であり、事前の見積もりを大きく下回り、Negative な結果であった [25]。この第 3 相臨床試験は、第 2 相臨床試験が Negative な結果であったものの、COX-2 が高発現していた被験者集団に限定した解析結果に基づいて設計された。第 3 相臨床試験は、COX-2 が高発現した被験者を対象に実施されたが、第 2 相臨床試験における COX-2 が高発現した被験者集団に限定した解析結果を再現できなかった。一般的に、部分集団解析では背景因子のばらつきが大きくなるため、得られた結果の解釈には注意が必要である。本事例では、第 2 相臨床試験の部分集団解析における false positive が、第 3 相臨床試験の見積もりに影響を及ぼした可能性があると考えられる。

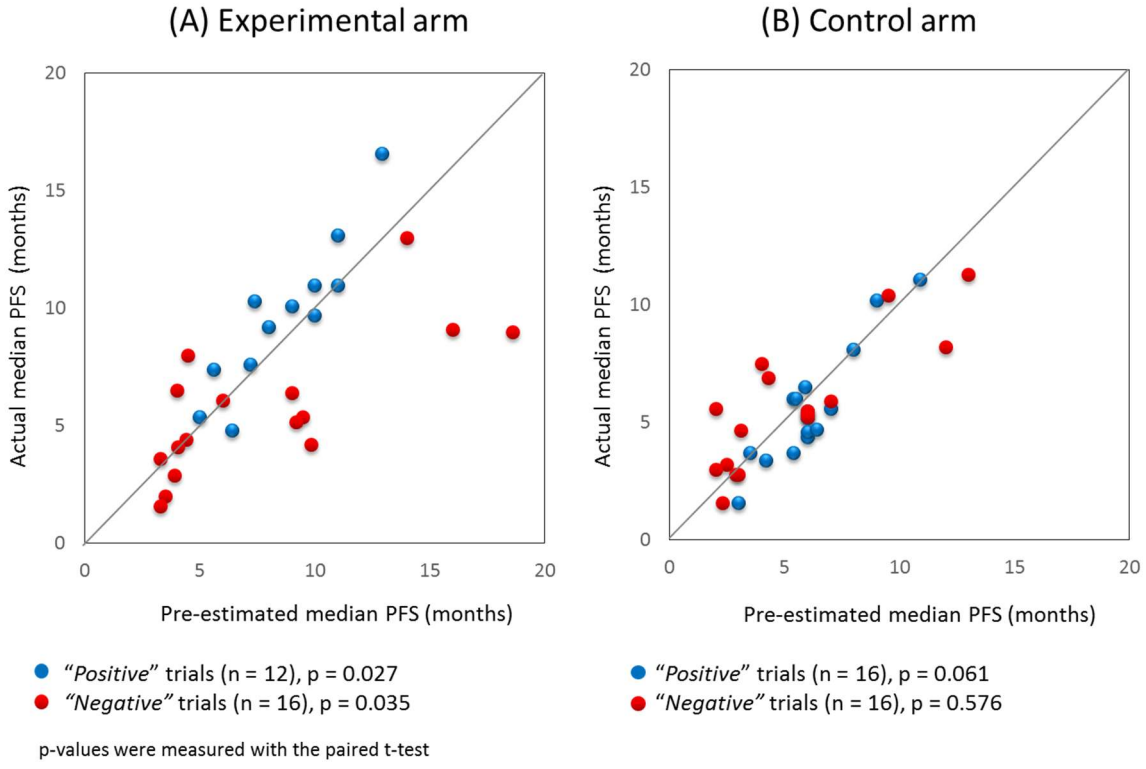

図 4. 試験計画時と実際に得られた試験結果の PFS 中央値の比較（非小細胞肺癌）

3.3　乳癌における検討

3.3.1　第 3 相臨床試験の特性（乳癌）

乳癌を対象とした 113 件の第 3 相臨床試験では、癌のステージ、治療ライン、対象被験者数など多岐に渡っており、特性項目の分類が困難であったため、主要評価項目の分類のみ実施し、Positive および Negative の内訳を表 4 に示した。

なお、主要評価項目の種類も多岐に渡っていた。このため、腫瘍縮小率を評価した response rate、全生存期間を評価した OS、PFS のような病態の進展を評価した progression-related endpoint、recurrence-free survival（RFS）や disease-free survival（DFS）のような再発を評価した recurrence-related endpoint に分類し、それぞれの分類に含めた主要評価項目を表 5 に示した。

乳癌を対象とした第 3 相臨床試験では、response rate や OS を評価した試験は少なく（それぞれ 13 件）、病態の進展を評価した progression-related endpoint（51 件）または再発を評価した recurrence-related endpoint（36 件）が多くを占めた。

主要評価項目別の成功確率は、response rate で 54%、OS で 46%、progression-related endpoint で 39%、recurrence-related endpoint で 17%であった。

表 4. Positive および Negative の内訳（主要評価項目別）

	試験数			成功確率
	計	Positive	Negative	
乳癌				
Response rate	13	7	6	54%
OS	13	6	7	46%
Progression-related endpoint	51	20	31	39%
Recurrence-related endpoint	36	6	30	17%
計	113	39	74	35%

OS: overall survival

表 5. 主要評価項目の分類の内訳

主要評価項目の分類	内訳
Response rate	• Pathological complete response rate • Clinical complete response rate • Objective response rate • Clinical benefit rare
OS	• Co-primary endpoint with PFS • Co-primary endpoint with TTP
Progression-related endpoint	• PFS • TTP
Recurrence-related endpoint	• DFS • Invasive DFS • RFS • Breast cancer RFS • Breast cancer-free interval • EFS • Incidence of distant metastases • Rate of invasive breast cancer events

OS: overall survival, PFS: progression-free survival, TTP: time-to-progression, DFS: disease-free survival, RFS: recurrence-free survival, EFS: event-free survival

3.3.2　試験計画時と得られた試験結果の比較（乳癌）

乳癌を対象とした第 3 相臨床試験では、response rate または OS を主要評価項目としたときの成功確率がそれぞれ 54%または 46%と、その他の評価項目よりも高かったが、対象試験数が少ないため（いずれも 13 件）、試験計画時点での見積もり値と実際に得られた試験結果の比較検討は行わず、Negative な結果となった原因について公表論文を精査し、表 6 にまとめた。

表 6. Negative 結果の主な原因（乳癌対象、response rate または OS 評価試験）

主要評価項目	主な原因
Response rate	• 薬効不十分 • 減量または頻回な投与中断による曝露量不足 • 検出力不足
OS	• 投与期間または頻度の不足におる薬効不足 • 適格患者選択不十分 • 検出力不足 • 共変量間の交絡因子の影響 • 後治療の影響

OS: overall survival

Response rate を主要評価項目とした第 3 相臨床試験の Negative な結果の原因として、いずれも、被験薬の効果あるいは安全性に対する予測が不十分なまま試験計画が策定された可能性が考えられる。

OS を主要評価項目とした第 3 相臨床試験の Negative な結果の原因として、被験薬の効果あるいは安全性に対する予測が不十分なまま（薬効不足・検出力不足）、適格患者の選定が不十分なまま（適格患者選択不十分）、あるいは、患者背景の不均衡を最小化する方策が不十分なまま（共変量間の交絡）、試験計画が策定された可能性が考えられる。また、後治療の影響については、3.2.2 項で検討したように、被験薬に引き続き行われる治療の影響を受けた可能性が考えられる。

乳癌を対象とした第 3 相臨床試験では、progression-related endpoint および recurrence-related endpoint の Positive 試験数が少なかったため、それぞれ、Negative 試験における試験計画時の見積もりと得られた試験結果の比較から、その原因を検討した（それぞれ、図 5 および図 6）。

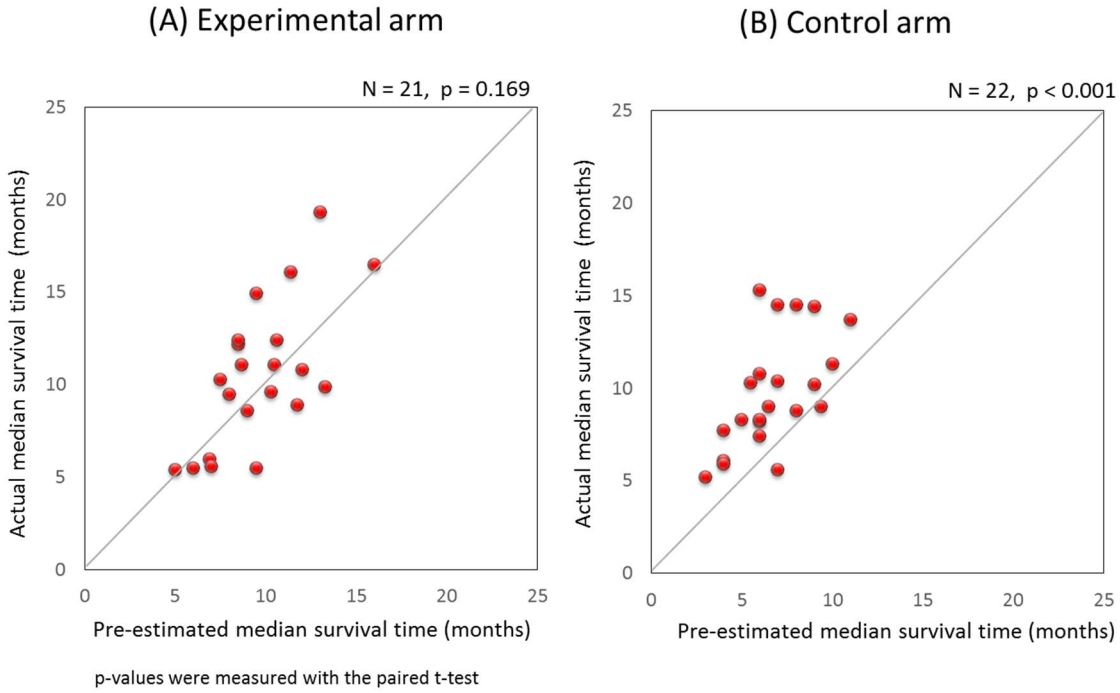

図 5. 試験計画時と実際に得られた試験結果の progression-related endpoint の比較（乳癌 Negative 試験）

Progression-related endpoint を対象とした Negative 試験の被験薬群では（図 5A）、試験計画時と得られた試験結果に有意な差は認められなかった（p＝0.169）。一方、コントロール群では（図 5B）、試験計画時と比較して試験結果では有意に長い survival time が認められた（p＜0.001）。このことから、Negative 試験では、コントロール群の事前の見積もりが正確ではなかったと考えられる。

Recurrence-related endpoint を対象とした Negative 試験では、被験薬群（図 6A）およびコントロール群（図 6B）のいずれにおいても、試験計画時と比較して試験結果では有意に高い survival rate が認められた（それぞれ、p = 0.034 および p < 0.001）。このことから、Negative 試験では、被験薬群およびコントロール群のいずれにおいても、事前の見積もりが正確ではなかったと考えられるが、有意差検定で得られた p 値から、コントロール群でその傾向がより顕著であったと考えられる。

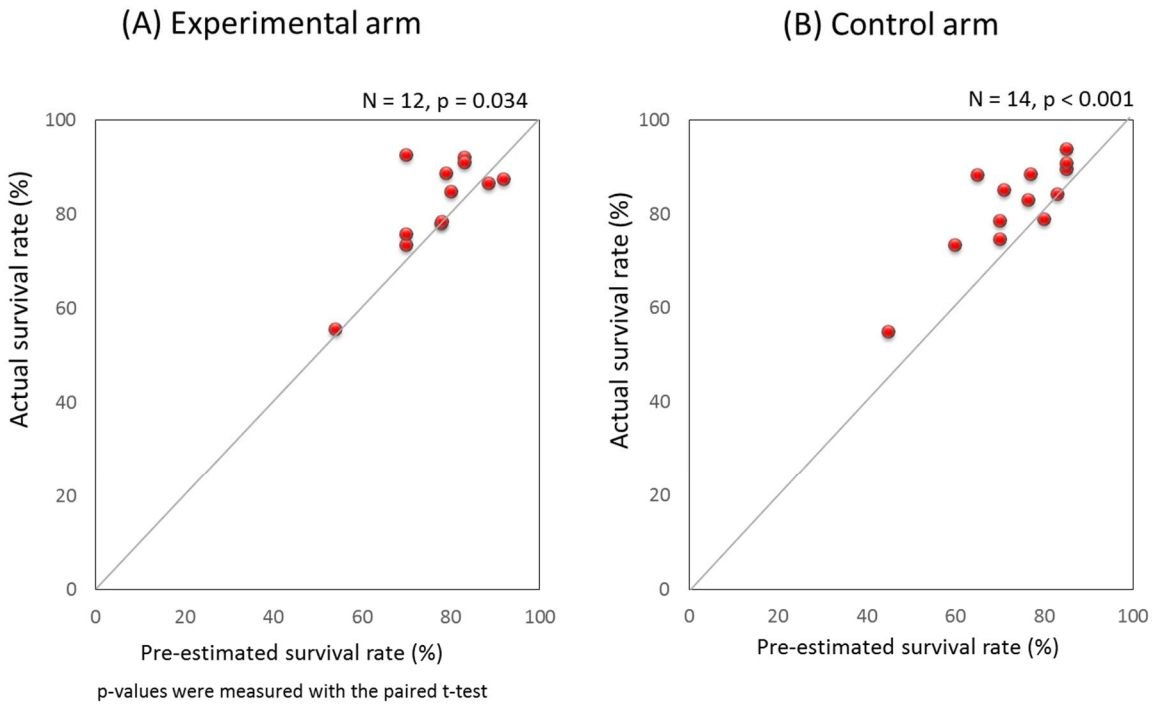

図 6. 試験計画時と実際に得られた試験結果の recurrence-related endpoint の比較
（乳癌 Negative 試験）

その主な原因について、Negative 試験の公表論文を精査したところ、試験計画時と比較して、試験実施時の治療水準が向上しており、このことが、乳癌を対象とした第 3 相臨床試験で progression-related endpoint または recurrence-related endpoint を主要評価項目としたときに、試験計画時のコントロール群の推定値の設定を困難にしており[26-41]、Negative 試験が多い原因となっていると考えられた。

3.4　バイアスのリスクに対する評価

本研究において、論文中に試験計画時の見積もり値の記載が確認できなかった試験は、試験計画時と得られた試験結果の比較検討には含まれていないため、そのバイアスの影響について検討した。

非小細胞肺癌の Negative 試験の公表論文を精査したところ、引き続き行われる治療による交絡や診断あるいは標準治療の向上が OS を主要評価項目とした試験の Negative な結果の原因として考えられており[16-24]、このことは、図 3 で認められたコントロール群の OS の延長を裏付けるものと考えられる。また、PFS を主要評価項目とした場合は、disease progression が認められた時点で endpoint に達し、その後に引き続き行われる治療の影響を受けないため、試験計画時に予測した PFS を再現できる可能性が高く、図 4 で認められたコントロール群の PFS の再現性を裏付けていると考えられる。

同様に、乳癌の Negative 試験の公表論文を精査したところ、試験計画時と比較して、試験実施時の治療水準が向上していることが、コントロール群の progression-related endpoint および recurrence-related endpoint の改善に繋がっており[26-41]、図 4 および 5 で認められた結果を裏付けるものと考えられる。

以上のことから、本研究において、論文中に試験計画時の見積もり値の記載が確認できなかったことによるバイアスは最小限であると考えられる。

また、一般的に Negative な結果は Positive な結果より公表され難いとされているが、悪性腫瘍を対象とした第 3 相臨床試験の場合、その結果が及ぼす社会的影響を考慮すると、Negative な結果も積極的に公表されるため、パブリケーションバイアスはほとんどないと考えられる。実際、本研究で確認できた第 3 相臨床試験の成功確率（35-38%）は、過去に報告されている悪性腫瘍を対象とした第 3 相臨床試験の成功確率（40-46%）と類似していた[2-4]。

今回の systematic review では、2011 年 1 月から 2017 年 6 月の間に試験結果が公表された第 3 相臨床試験を収集したが、収集対象期間が本研究に及ぼす影響を検討するために、期間別の成功確率を算出した（表 7）。非小細胞肺癌および乳癌のいずれを対象とした第 3 相臨床試験においても、期間別の成功確率はばらついており、一定の傾向は認められなかった。収集対象期間によって、全体の成功確率に違いが生じる可能性はあるが、期間別の成功確率のばらつきは本研究の目的である第 3 相臨床試験の成功確率が低い原因の検討に影響を及ぼさないと考えら

れた。

表 7. 期間別の第 3 相臨床試験の成功確率

期間	非小細胞肺癌を対象とした第 3 相臨床試験の成功確率 Positive/対象試験 (%)	乳癌を対象とした第 3 相臨床試験の成功確率 Positive/対象試験 (%)
2011 年	2/13 (15)	4/17 (24)
2012 年	6/21 (29)	2/13 (15)
2013 年	6/11 (55)	3/18 (17)
2014 年	4/13 (31)	8/13 (62)
2015 年	8/21 (38)	5/15 (33)
2016 年	4/11 (36)	11/22 (50)
2017 年	10/16 (63)	6/15 (40)

4. 考察

近年、悪性腫瘍の増殖等の生物学的メカニズムの解明が進んでおり、新規ターゲット分子を標的とした新薬の開発が活発化している。これらの臨床試験では、より効果が期待できるエンリッチされた患者対象集団が選択される傾向にあるため、第 3 相臨床試験の成功確率は向上することが期待される。

一方、第 3 相臨床試験の成功確率を高めるためには、より再現性が高い評価項目で、より精度が高い Effect size の見積もりを得ることが求められる。

FDA は 2015 年に Guidance for Industry Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics を発出した[42]。これによると、非小細胞肺癌では、OS は臨床的ベネフィットを評価する上で、標準的な評価項目であるとされている。しかし、本研究で明らかになったように、引き続き行われる治療による交絡の影響を受けやすく、試験計画時の効果の見積もりを再現することが容易ではない。一方、FDA のガイダンスでは、Hazard ratio および PFS の中央値で十分な規模の改善が示せるようデザインされた試験であれば、PFS は主要評価項目となり得るとされている。本研究で示したように、PFS を主要評価項目とした非小細胞肺癌の第 3 相臨床試験の成功確率は高い。これは、PFS は病態の進展が認められた時点で評価されるため、引き続き行われる治療の影響を受け難く、臨床試験計画時、比較的正確な見積もりが可能であることを反映したものと考えられる。ただし、PFS には主観的要素が含まれるため、OS の延長が予測可能なほど、または肺癌の Stage やその他の治療法を考慮の上、薬剤の毒性を上回る臨床的ベネフィットが示せるほど、十分なかつ統計的に頑健な PFS を示すことが求められる。EGFR 遺伝子変異陽性の非小細胞肺癌を対象に開発された osimertinib の第 3 相臨床試験は、FDA との事前の協議を踏まえて PFS を主要評価項目として実施された[43]。この試験では、PFS の中央値をコントロール群で 6 ヵ月および被験薬群で 10 ヵ月と見積もり、実際に得られた結果は、コントロール群で 4.4 ヵ月および被験薬群で 10.1 ヵ月であり（ハザード比 : 0.30、95%信頼区間［0.23、0.41］、$p < 0.001$）、Positive な結果であった。コントロール群の PFS を保守的に見積もり、被験薬群の PFS を確実に再現することで成功した事例であると考えられる。

本研究では、乳癌を対象とした第 3 相臨床試験で response rate を主要評価項目とした場合、高い成功確率が示唆された。FDA は、2014 年に発出した Guidance for Industry Pathological Complete Response in Neoadjuvant Treatment of High-Risk

Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval の中で、リスクが高い初期乳癌の術前補助療法を対象とした加速承認のために、病理的完全奏功（pathological Complete Response ; pCR）を主要評価項目とすることを推奨している [44]。腫瘍増殖メカニズムのターゲット分子を標的とし、高い腫瘍縮小効果が期待できる場合は、そのターゲット分子が高発現した患者集団を対象とした臨床試験で pCR を主要評価項目とすることにより、高い成功確率が期待できる。

乳癌を対象とした試験計画時に、recurrence-related endpoint である disease-free survival の見積もり値を得ることの難しさは、閉経前の初期乳癌患者を対象とした Tamoxifen and Exemestane Trial（TEXT）および Suppression of Ovarian Function Trial（SOFT）の試験デザインの考察で述べられている [45]。TEXT および SOFT 試験の試験デザイン検討の際には、タモキシフェン治療を受けた閉経前ホルモン受容体陽性乳癌患者の臨床試験データが限られていた。このため、TEXT および SOFT 試験の 5-year disease-free survival（DFS）は、タモキシフェン未治療患者の臨床試験データに基づいて見積もられた。このように、過去の臨床試験結果に基づく effect size の見積もりは、10-20 年前の標準治療や腫瘍評価方法に依存することとなり、結果として、effect size の overestimation の原因となっている。さらに、医療水準の向上により DFS イベント発現までの期間が長くなり、統計学的検出力が低下するだけでなく、臨床試験実施期間が長期化することにより、試験の完遂が困難となる。

興味深いことに、本研究では、非小細胞肺癌を対象とした第 3 相臨床試験では PFS の成功確率は高く、コントロール群の試験結果は事前の見積もり値とよく一致していたが、乳癌を対象とした第 3 相臨床試験では progression-related endpoints の成功確率は低く、コントロール群の試験結果は事前の見積もり値と比較して有意に延長していた。上述の如く、非小細胞肺癌では PFS は比較的正確な見積もりが可能なエンドポントと考えられるが、乳癌では TEXT および SOFT 試験の DFS の見積もりの難しさの考察と同様に、PFS においても見積もりの根拠となる過去の臨床試験時の医療水準が大きく異なっていた可能性が考えられる。同様の現象は、別の癌種でも起こる可能性がある。非小細胞肺癌のように病態の進展が早い癌種では、コントロール群の見積もりに必要なデータを直近の臨床試験結果から得ることができる可能性があるが、乳癌のように病態の進展が比較的緩徐な癌種では、コントロール群の見積もりに必要なデータを得るためには、数年以上前の

臨床試験結果まで遡る必要があるかもしれない。

また、2007 年に発出された FDA ガイダンスでは、DFS を主要評価項目とする際には、最新の標準治療のデータに基づき被験薬の effect size を推定することを推奨している [46]。また、潜在的バイアスの排除と事前の推定値の再現性保持のためには、臨床試験の対象患者および腫瘍評価スケジュールについて、effect size の推定に用いた根拠データと一貫性を確保することが重要であると述べられている。

以上のように、第 3 相臨床試験の成功確率を高めるためには、第 2 相臨床試験計画策定の段階から、将来の第 3 相臨床試験計画を想定して、第 3 相臨床試験計画時に必要となる Effect size の見積もりの根拠となるデータを取得できるよう試験計画を設計することが重要である。特に、コントロール群の見積もりに用いることができる最新のデータが存在しない場合には、第 2 相臨床試験にコントロール群を設けて見積もりに必要となるデータを取得することを考慮するべきである。また、Real World Data を活用することにより、最新の標準治療を反映したコントロール群の見積もり値を取得することも検討する必要がある。このように、精度が高い最新のコントロール群の見積もり値を得ることができれば、第 3 相臨床試験に進む価値がある被験薬であるかどうかを判断することが容易となり、真に成功確率が高いと予測し得る被験薬だけが、第 3 相臨床試験を実施することができるようになる。このことは、臨床試験実施者だけなく、臨床試験に参加する被験者に対しても大きな福音となる。

本研究には、以下に示す限界が存在する。癌のステージ、治療ライン、performance status、対象被験者数、あるいは被験薬の作用機序の違いは、主要評価項目の結果に影響を与える可能性がある因子である。しかし、本研究では、事前の見積もり値と実際の試験結果の違いを検討できる十分な試験数を確保するため、これらの違いを考慮せず解析を行った。また、本研究では、地域あるいは人種のデータを収集することができなかった。これらの要因が試験の成功確率に及ぼす影響を検討するためには、さらなる研究対象試験数の確保が必要である。

さらに、本研究では、対象とした第 3 相臨床試験の事前の見積もり値が第 2 相臨床試験結果に基づくものであるかどうかを特定することが困難であった。第 2 相臨床試験結果からの見積もりの正確性を検討することで、第 3 相臨床試験の成功確率を高めるための新たな知見が得られる可能性がある。

5. 結論

非小細胞肺癌を対象とした第 3 相臨床試験では、OS を主要評価項目とした場合、Negative な結果のほうが多く、PFS を主要評価項目とした場合、Positive な結果のほうが多い傾向が認められた。この原因として、OS を主要評価項目とした場合、引き続き行われる治療による交絡を受け易いことが考えられた（例えば、first line を対象とした試験では、second line の治療効果により対照群との差が縮まるなど)。一方で、PFS を主要評価項目とした場合は、disease progression が認められた時点で endpoint に達し、その後に引き続き行われる治療の影響を受けないため、試験計画時に予測した PFS を再現できる可能性が高いと考えられた。

乳癌を対象とした第 3 相臨床試験では、progression-related endpoint および recurrence-related endpoint のいずれを主要評価項目とした場合においても、Negative な結果のほうが多い傾向が認められた。この原因として、試験計画時と比較して試験実施時の治療水準が向上しており、試験計画時に予測した主要評価項目の見積もりを再現することが困難であることが示唆された。

第 3 相臨床試験の成功確率を高めるためには、より再現性が高い評価項目で、より精度が高い Effect size の見積もりを得ることが求められる。第 2 相臨床試験計画策定の段階から、将来の第 3 相臨床試験計画を想定して、第 3 相臨床試験計画時に必要となる Effect size の見積もりの根拠となるデータを取得できるよう試験計画を設計することが重要である。また、有効性の高い再現性を得るためには、対象患者、診断基準、標準治療などの一貫性を堅持可能な試験計画を設計することが重要であると考えられた。

また、精度が高い Effect size の見積もりを得ることができれば、第 3 相臨床試験に進む価値がある被験薬であるかどうかを判断することが容易となり、真に成功確率が高いと予測し得る被験薬だけが、第 3 相臨床試験を実施することができるようになる。このようにして、第 3 相臨床試験の成功確率を高めることができれば、臨床試験実施者だけなく、臨床試験に参加する被験者に対しても大きな福音となり、医療への貢献に繋がると考えられた。

さらに、最新の科学水準に照らして出来る限り精度が高い Effect size の見積もりを得ることは、臨床試験に参加する被験者に対する倫理的な観点においても重要であり、本研究で得られた知見が、精度が高い Effect size の見積もりの一助となることを期待する。

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付録 1　非小細胞肺癌を対象とした第 3 相臨床試験の一覧（Positive 40 試験）

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Rittmeyer A, et al. (1)	OS	stage IIIB or IV	0-1 (ECOG)	Open	atezolizumab vs. docetaxel	425 vs. 425	anti-PD-L1 antibody	PD-L1 positive	13.8 M vs 9.6M, HR = 0.73 (95% CI = 0.62 - 0.87, p = 0.0003)	Median survival: not found, HR: not found
Liang J, et. el (2)	OS	unresectable stage III	< = 2 (ECOG)	Open	etoposide/cisplatin vs. carboplatin/paclitaxel	95 vs 96	Chemo-radiation	All comer	23.3 M vs. 20.7 M, HR = 0.76 (95% CI = 0.55 – 1.05, p = 0.095)	Median survival: not found, but 3-year OS of 35% vs. 17%, HR = 0.83
Borghaei H, et al (3)	OS	stage IIIB or IV or recurrent nonsquamous	0-1 (ECOG)	Open	nivolumab vs. docetaxel	292 vs. 290	anti-PD1 antibody	All comer	12.2 M vs. 9.4 M, HR = 0.73 (96% CI = 0.59 - 0.89, p = 0.002)	11 M vs. 8 M, HR = 0.72
Brahmer J, et al (4)	OS	stage IIIB or IV recurrent squamous-cell	0-1 (ECOG)	Open	nivolumab vs. docetaxel	135 vs. 137	anti-PD1 antibody	All comer	9.2 M vs. 6.0 M, HR = 0.59 (95% CI = 0.44 - 0.79, p < 0.001)	11.4 M vs. 7 M, HR = 0.61
Kubota K, et al (20)	OS	stage IIIB or IV or postoperative recurrence	0-1 (ECOG)	Open	S-1 + cisplatin vs. docetaxel + cisplatin	303 vs. 305	Chemotherapy	All comer	16.1 M vs. 17.1 M HR = 1.013 (96.4% CI = 0.837 – 1.227)	Median survival: not found, but 1-year OS of 60 % in docetaxel + cisplatin group and the noninferiority margin of ~ 10%,(corresponds to HR = 1.322)

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Ma X, et al (6)	OS	stage IIIB or IV	0-1 (ECOG)	Double -blind	docetaxel + carboplatin/cisplatin + Recombinant Mutated Human TNF vs. docetaxel + carboplatin/cisplatin alone	265 vs. 264	anti-angiogenic agent	All comer	13.7 M vs. 10.3 M, HR = 0.75 (95% CI = 0.63 – 0.89, p = 0.001)	Not found exp. arm vs 10.3 M, HR = 0.75 (exp. arm: 13.7 M is calculated)
Thatcher N, et al (7)	OS	stage IV squamous first line	0-2 (ECOG)	Open	necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin alone	545 vs. 548	anti-EGFR antibody	All comer	11·5 M vs. 9·9 M, HR = 0·84 (95% CI = 0·74 – 0·96, p = 0.01)	13.75 M vs. 11.0 M, HR = 0.8
Alfonso S, et al (8)	OS	stage IIIB or IV at least stable disease after first-line chemotherapy	0-2 (ECOG)	Double -blind	racotumomab-alum vs. placebo	87 vs. 89	anti-NeuGcGM3 antibody	All comer	8.23 M vs. 6.80 M, HR = 0.63 (95% CI = 0.46 - 0.87, p = 0.004)	Median survival: not found, HR = 0.56
Kimura H, et al (9)	OS	stage IB-IV	0-1 (ECOG)	Open	chemo-immunotherapy (autologous activated killer T cells and dendritic cells) vs. chemotherapy	50 vs. 51	chemo-immunotherapy	All comer	Not reached vs. 47.5 M , HR = 0.229 (95%CI = 0.093 - 0.564, p = 0.0013)	Median survival: not found, HR: not found
Zukin M, et al (10)	OS	stages IIIB (malignant effusion) or IV 1st line	2 (ECOG)	Open	carboplatin + pemetrexed vs. pemetrexed alone	108 vs. 109	Chemotherapy	All comer	9.3 M vs. 5.3 M, HR = 0.62 (95% CI = 0.46 - 0.83, p = 0.001)	4.3 M vs. 2.9 M, HR = 0.674
Morabito A, et al (11)	OS	stage IIIB or IV 1st line	2 (ECOG)	Open	gemcitabine + cisplatin vs. gemcitabine alone	28 vs. 28	Chemotherapy	All comer	5.9 M vs. 3.0 M, HR = 0.52 (95% CI = 0.28 - 0.98, p = 0.039)	6.8 M vs. 4.8 M, HR = 0.71

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Garon EB, et al (12)	OS	stage IV 2nd line	0-1 (ECOG)	Double -blind	ramucirumab + docetaxel vs. placebo + docetaxel	628 vs. 625	anti-VEGF antibody	All comer	10.5 M vs. 9.1 M, HR = 0.86 (95% CI = 0.75 - 0.98; p = 0.023)	9.2 M vs. 7.5 M, HR = 0.816
Atagi S, et al (13)	OS	unresectable stage IIIA/B	0-2 (ECOG)	Open	carboplatin + radiotherapy vs. radiotherapy alone	100 vs. 100	Chemo-radiation	All comer	22.4 M vs. 16.9 M, HR = 0.68 (95% CI = 0.47 - 0.98; p = 0.0179)	15 M vs. 10 M, HR: not found (calculated HR = 0.67)
Quoix E, et al (14)	OS	stage III or IV	0-2 (WHO)	Open	carboplatin + paclitaxel vs. vinorelbine or gemcitabine monotherapy	225 vs. 226	Chemotherapy	All comer	10.3 M vs. 6.2 M, HR = 0.64 (95% CI = 0.52 - 0.78, p < 0.0001)	9 M vs. 7 M, HR: not found (calculated HR = 0.78)
Hida T, et al. (15)	PFS	stage IIIB, stage IV, or postoperative recurrent	0-2 (ECOG)	Open	alectinib vs. crizotinib	103 vs. 104	ALK inhibitor	ALK-positive	Not reached vs. 10.2 M, HR = 0.34 (99.7% CI = 0.17 - 0.71, p < 0.0001)	14.0 M vs. 9.0 M, HR = 0·643
Baggstrom MQ, et al. (16)	PFS	stage IIIB/IV	0-1 (ECOG)	Double -blind	sunitinib vs. placebo	106 vs. 104	VEGFR-TKI	All comer	4.3 M vs. 2.6 M, HR = 0.62 (95% CI = 0.47 - 0.82, p = 0.0006)	Median survival: not found, HR: not found
Wang Y, et al. (17)	PFS	stage II to IV	0-2 (ECOG)	not found	erlotinib + bevacizumab + panitumumab vs. erlotinib + placebo	150 vs. 147	anti-VEGF antibody	All comer	4.6 M vs. 1.9 M, HR: not found (p = 0.003)	Median survival: not found, HR: not found

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Park C-K, et al. (18)	PFS	stage IIIB or IV	0-2 (ECOG)	Open	docetaxel + cisplatin vs. pemetrexed + cisplatin	71 vs. 77	chemotherapy	All comer	4.4 M (95% CI = 3.7 - 5.1) vs. 4.7 M (95% CI = 4.4 - 5.0) the lower limit of the CI (3.7 M) in the experimental arm was greater than the lower limit of noninferior margin (2.9 M) in the control arm.	median PFS of 6.4 M in the control arm is expected, a noninferiority margin of 1.5 M (HR of 1.3)
Reck M, et al. (19)	PFS	stage IV	0-1 (ECOG)	Open	pembrolizumab vs. chemotherapy	154 vs. 151	anti-PD-1 antibody	PD-L1 positive	10.3 M vs. 6.0 M, HR = 0.50 (95% CI = 0.37 - 0.68, p < 0.001).	7.4/7.5 M vs. 5.5 M, HR = 0.55
Soria J-C, et al. (20)	PFS	stage IIIB/IV	0-2 (WHO)	Open	ceritinib vs. chemotherapy	189 vs. 187	ALK inhibitor	ALK-positive	16.6 M vs. 8.1 M, HR = 0.55 (95% CI = 0.42 - 0.73, p < 0·00001)	12.94 M vs. 8 M, HR = 0.62
Peters S, et al. (21)	PFS	untreated, stage IIIB or IV	0-2 (ECOG)	Open	alectinib vs. crizotinib	152 vs. 151	ALK inhibitor	ALK-positive	Not reached vs. 11.1 M, HR = 0.47 (95% CI = 0.34 - 0.65, p < 0.001)	16.8 M vs. 10.9 M, HR = 0.65

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Hanna NH, et al. (22)	PFS	stage IIIB/IV or recurrent	0-1 (ECOG)	Double -blind	nintedanib + pemetrexed vs. placebo + pemetrexed	353 vs. 360	anti-angiogenic agent	All comer	4.4 M vs. 3.6 M, HR = 0.83 (95% CI = 0.70 –0.99, p = 0.0435)	Median survival: not found, HR = 0.78
Shaw AT, et al. (23)	PFS	stage IIIB or IV	0-2 (WHO)	Open	ceritinib vs. chemotherapy (pemetrexed or docetaxel)	115 vs. 116	ALK inhibitor	ALK-positive	5.4 M vs. 1.6 M, HR = 0.49 (95% CI = 0.36 – 0.67, p < 0.0001)	Not found experimental arm vs 3 M, HR = 0.60 (experimental arm: 5 M is calculated)
Mok TS, et al (24)	PFS	Locally advanced or metastatic	0-1 (WHO)	Open	osimertinib vs. pemetrexed + carboplatin or cisplatin	279 vs. 140	EGFR-TKI	T790M positive	10.1 M vs. 4.4 M, HR = 0.30 (95% CI = 0.23 - 0.41, p < 0.001)	9 M vs. 6M, HR = 0.67
Schuler M, et al (25)	PFS	stage IIIb (wet) or IV, resistance to erlotinib/ gefitinib and afatinib monotherapy	0-2 (ECOG)	Open	afatinib + paclitaxel vs. investigator's choice of single-agent chemotherapy	134 vs. 68	EGFR-TKI	All comer	5.6 M vs. 2.8 M, HR = 0.60 (95% CI = 0.43 – 0.85, p = 0.003)	Median survival: not found, HR = 0.67
Wu YL, et al (26)	PFS	stage IIIB or IV	0-2 (ECOG)	Open	erlotinib vs. gemcitabine/cisplatin	110 vs. 107	EGFR-TKI	EGFR mutation positive	11.0 M vs. 5.5 M, HR = 0.34 (95% CI = 0.22 – 0.51, p < 0.0001)	10M vs. 6M, HR: not found (calculated HR = 0.6)
Zhou C, et al (27)	PFS	stage IIIb or Stage IV), or recurrent non-squamous-cell	0-1 (ECOG)	Double -blind	carboplatin/paclitaxel + bevacizumab vs. carboplatin/paclitaxel + placebo	138 vs. 138	anti-VEGF antibody	All comer	9.2 M vs. 6.5 M, HR= 0.40 (95% CI = 0.29 - 0.54, p < .001)	8.0 M vs. 5.9 M, HR < 0.83

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Johnson BE, et al (28)	PFS	stage IIIB with malignant pleural effusion or stage IV or recurrent	0-1 (ECOG)	Double -blind	erlotinib + bevacizumab vs. placebo + bevacizumab	370 vs. 373	EGFR-TKI	All comer	4.8 M vs. 3.7 M, HR = 0.71 (95% CI = 0.58 - 0.86, p < 0.001)	6.4 M vs. 5.4 M, HR = 0.79
Barlesi F, et al (29)	PFS	stage IIIB or IV maintenance	0-2 (ECOG)	Open	bevacizumab + pemetrexed vs. bevacizumab alone	128 vs. 125	Chemotherapy	All comer	7.4 M vs. 3.7 M, HR = 0.48 (95% CI = 0.35 - 0.66, p < 0.0001)	24 W vs. 15 W, HR = 0.68
Scagliotti GV, et al (30)	PFS	stages IB, II, or IIIA	0-1 (ECOG)	not found	preoperative cisplatin + gemcitabine + surgery vs. surgery alone	129 vs. 141	Chemotherapy	All comer	4.0 Y vs. 2.9 Y, HR =0.70 (95% CI = 0.50 - 0.97, p = 0.003)	Median survival: not found, HR = 0.75
Wu YL, et al (31)	PFS	treatment-naïve stage IIIB or IV	0-1 (ECOG)	Open	afatinib vs. cisplatin + gemcitabine	242 vs. 122	EGFR-TKI	EGFR mutation positive	11.0 M vs. 5.6 M, HR = 0.28 (95% CI = 0.20 - 0.39, p < 0.001)	11 M vs. 7 M, HR = 0.64
Reck M, et al (32)	PFS	stage IIIB or IV recurrent	0-1 (ECOG)	Double -blind	docetaxel + nintedanib vs. docetaxel + placebo	655 vs. 659	multikinase inhibitor	All comer	3.4 M vs. 2.7 M, HR = 0.79 (95% CI = 0.68 - 0.92; p = 0.019)	Median survival: not found, HR = 0.78
Shi Y, et al (33)	PFS	stage IIIB or IV	0-2 (ECOG)	Double -blind	icotinib vs. gefitinib	199 vs. 196	EGFR-TKI	All comer	4.6 M vs 3.4 M, HR = 0.84 (95% CI = 0.67 - 1.05, p = 0.13); non-inferiority test	Not found exp. arm vs. 4.2 M, non-inferiority margin of 87.5% (HR = 1.14) (exp. arm: at least 3.68 M is calculated)

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Wu YL, et al (34)	PFS	untreated stage IIIB or IV	0-1 (ECOG)	Double -blind	erlotinib + gemcitabine + platinum vs. placebo + gemcitabine + platinum	226 vs. 225	EGFR-TKI	All comer	7.6 M vs 6.0 M, HR = 0.57 (95% CI = 0.47 - 0.69, p < 0.0001)	Not found exp. arm vs. 5.4 M, HR = 0.75 (exp. arm: 7.2 M is calculated)
Zhang L, et al (35)	PFS	stage IIIB or IV	0-2 (WHO)	Double -blind	gefi tinib vs. placebo	148 vs. 148	EGFR-TKI	All comer	4.8 M vs. 2.6 M, HR = 0.42 (95% CI = 0.33 - 0.55, p < 0.0001)	Median survival: not found, HR = 0.70
Paz-Ares L, et al (36)	PFS	advanced non-squamous stage IIIB or IV	0-1 (ECOG)	Double -blind	pemetrexed + BSC vs. placebo + BSC	359 vs. 180	Chemotherapy	All comer	4.1 M vs. 2.8 M, HR = 0.62 (95% CI = 0.49 - 0.79, p < 0.0001)	Median survival: not found, HR = 0.65
Rosell R, et al (37)	PFS	stage IIIB or IV 1st line	0-2 (ECOG)	Open	erlotinib vs. standard chemotherapy (cisplatin + docetaxel or cisplatin + gemcitabine)	86 vs. 87	EGFR-TKI	EGFR mutation positive	9.7 M vs. 5.2 M, HR = 0.37 (95% CI = 0.25 – 0.54, p < 0.0001)	10 M vs. 6 M, HR: not found (calculated HR = 0.6)
Zhou C, et al (38)	PFS	advanced or recurrent stage IIIB or IV	0-2 (ECOG)	Open	erlotinib vs. chemotherapy (gemcitabine + carboplatin)	82 vs.72	EGFR-TKI	EGFR mutation positive	13.1 M vs. 4.6 M, HR = 0.16 (95% CI = 0.10 - 0.26, p < 0.0001)	11 M vs. 6 M, HR = 0.54
Lin H, et al. (39)	Respons e rate	stage IIIA or IIIB	0-1 (ECOG)	Open	paclitaxel at 15 mg/m2, three times per week for 6 weeks vs. weekly paclitaxel at 45 mg/m2 for 6 weeks	74 vs. 60	chemotherapy	All comer	83.1% vs. 54.2%,, HR: not found, p = 0.001	Response rate: not found, HR: not found

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Kim K-S, et al (40)	Respons e rate	stage IIIB or IV	0-2 (ECOG)	not found	docetaxel 60 mg/m2 + cisplatin 60 mg/m2 vs. docetaxel 75 mg/m2 + cisplatin 60 mg/m2	67 vs. 65	chemotherapy	All comer	40.3% vs. 38.5%, 95% CI = −14.8 to 18.5%	Response rate: not found, HR: not found, -15% of non-inferiority margin

OS: overall survival, PFS: progression-free survival, WHO: World Health Organization, ECOG: Eastern Cooperative Oncology Group, PS: performance status, exp.: experimental, BSC: best supportive care, EGFR: epidermal growth factor receptor, TKI: tyrosine kinase inhibitor, PD1: programmed cell death 1, VEGF: vascular endothelial growth factor, CI: Confidence Interval, HR: Hazard Ratio, M: Months, W: Weeks, Y: Years

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付録 2　非小細胞肺癌を対象とした第 3 相臨床試験の一覧（Negative 66 試験）

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Karampeazis A, et al. (1)	OS	inoperable stage IIIB/IV	0-2 (ECOG)	Open	docetaxel + gemcitabine vs. gemcitabine	54 vs. 52	chemotherapy	All comer	14.6 M vs. 12.2 M, HR: not found (p = 0.121)	38 W vs. 28 W, HR: not found (calculated HR = 0.74) (35% inclease in median OS)
Rodriguez PC, et al. (2)	OS	stage IIIB/IV	0-2 (ECOG)	not found	CIMAvax-EGF vs. best supportive care	270 vs. 135	EGF vaccine	All comer	10.83 M vs. 8.86 M, HR = 0.82 (95% CI = 0.661 – 1.03, p = 0.100)	Median survival: not found, HR = 0.7
Debus J, et al. (3)	OS	stage III	0-2 (WHO)	Open	epoetin + radiochemotherapy vs. radiochemotherapy	195 vs. 190	epoetin	All comer	2-year survival rate: 28.5% vs. 20.6%, HR: not found (p = 0.2278)	2-year survival rate: not found, HR: not found
Cicènas S, et al. (4)	OS	stage IIIB or IV	0-1 (ECOG)	Double -blind	erlotinib vs. placebo	322 vs. 321	EGFR-TKI	EGFR mutation positive	9.7 M vs. 9.5 M, HR = 1.02 (95% CI = 0.85 - 1.22)	12.5 M vs. 9.6 M, HR = 0.77
Spigel DR, et al. (5)	OS	stage IIIB to IV locally advanced or metastatic	0-1 (ECOG)	Double -blind	onartuzumab + erlotinib vs. placebo + erlotinib	250 vs. 249	anti-MET antibody	MET positive	6.8 M vs. 9.1 M, HR = 1.27 (95% CI = 0.98 - 1.65, p = 0.067)	Median survival: not found, HR = 0.73
Senan S, et al (6)	OS	unresectable nonsquamous stage IIIA/B	0-1 (ECOG)	Open	pemetrexed-cisplatin and thoracic radiation therapy (TRT) followed by consolidation pemetrexed, vs. etoposide-cisplatin and TRT followed by	301 vs. 297	Chemo-radiation	All comer	26.8 M vs. 25.0 M, HR = 0.98 (95% CI = 0.79 - 1.20, p = 0.831)	24 M vs. 18 M. HR = 0.74

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
					nonpemetrexed doublet consolidation					
Paz-Ares L, et al (7)	OS	3rd or 4th line	0-1 (ECOG)	Double -blind	sorafenib vs. placebo	350 vs. 353	multikinase inhibitor	All comer	8.2 M vs. 8.3 M, HR = 0.99 (95% CI = 0.84 – 1.17, p = 0.47)	Median survival: not found, HR: not found (33% increase in median OS)
Scagliotti G, et al (8)	OS	surgically unresectable locally advanced or metastatic stage IIIb to IV	0-1 (ECOG)	Double -blind	erlotinib + tivantinib vs. erlotinib + placebo	526 vs. 522	MET receptor -TKI	All comer	8.5 M vs. 7.8 M, HR = 0.98 (95% CI = 0.84 - 1.15, p = 0.81)	9.3 M vs. 7 M, HR = 0.75 (33% increase in median OS)
Abe T, et al (9)	OS	stage III or IV or recurrent	0-1 (ECOG)	Open	weekly docetaxel + cisplatin vs. docetaxel monotherapy	139 vs. 137	Chemotherapy	All comer	13.3 M vs. 14.8 M, HR = 1.18 (95% CI = 0.83 - 1.69)	13.3 M vs. 10 M, HR: not found (calculated HR = 0.75) (33% increase in median OS)
Giaccone G, et al (10)	OS	stage III or IV	0-2 (ECOG)	Double -blind	belagenpumatucel-L vs. placebo	270 vs. 262	allogeneic whole tumour cell vaccine	All comer	20.3 M vs. 17.8 M, HR = 0.94, p = 0.594	14 M vs. 10.5 M. HR: not found (calculated HR = 0.75)

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
O'Brien ME, et al (11)	OS	stage IIIB or IV or recurrent	0-2 (WHO)	Double -blind	pazopanib vs. placebo	50 vs. 52	multikinase inhibitor	All comer	17.4 M vs. 12.3 M, HR = 0.72 (95% CI = 0.40 – 1.28, p = 0.257)	Not found exp. arm vs 9.7 M, HR = 0.764 (exp. arm: 12.7 M is calculated)
Paz-Ares L, et al (12)	OS	stage IV non-squamous 1st line	0-2 (ECOG)	Open	necitumumab + pemetrexed + cisplatin vs. pemetrexed + cisplatin alone	315 vs. 318	anti-EGFR antibody	All comer	11.3 M vs. 11.5 M, HR = 1.01 (95% CI = 0.84 – 1.21, p = 0.96)	13.75 M vs. 11.0 M, HR = 0.8
Scagliotti GV, et al (13)	OS	stage IIIB or IV or recurrent	0-2 (ECOG)	Open	figitumumab + erlotinib vs. erlotinib alone	289 vs. 290	anti-IGF-1R antibody	All comer	6.2 M vs. 5.7 M, HR = 1.09 (95% CI = 0.91 - 1.31, p = 0.35)	8 M vs. 6 M, HR = 0.75
Novello S, et al (14)	OS	stage IIIB or IV or recurrent squamous	0-2 (ECOG)	Double -blind	motesanib vs. placebo	182 vs. 178	multikinase inhibitor	All comer	11.1 M vs. 10.7 M, HR = 0.89 (95% CI = 0.71 - 1.12, p = 0.3306)	Median survival: not found, HR: not found
Langer CJ, et al (15)	OS	stage IIIB or IV or recurrent	0-1 (ECOG)	Open	figitumumab + paclitaxel + carboplatin vs. paclitaxel + carboplatin alone	338 vs. 333	anti-IGF-1R antibody	All comer	9.8 M vs. 8.6 M, HR = 1.18 (95% CI = 0.99 - 1.40, p = 0.06)	13 M vs. 10 M, HR = 0.77 (30% increase in median OS)
Patel JD, et al (16)	OS	stage IIIB or IV nonsquamous	0-1 (ECOG)	Open	pemetrexed + carboplatin + bevacizumab followed by pemetrexed + bevacizumab vs. paclitaxel + carboplatin + bevacizumab followed by	472 vs. 467	Chemotherapy	All comer	12.6 M vs. 13.4 M, HR = 1.00 (95% CI = 0.86 - 1.16, p = 0.949)	15.3 M vs. 12.3 M, HR = 0.80

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
					bevacizumab					
Ramalingam S, et al (17)	OS	stage IIIB or IV 3rd or more line	0-2 (ECOG)	Double -blind	talactoferrin alfa vs. placebo	497 vs. 245	dendritic cell-mediated immunotherapy	All comer	7.49 M vs. 7.66 M, HR = 1.04 (95% CI = 0.873 - 1.24, p = 0.6602)	6.0 M vs. 4.6 M, HR = 0.70
Ramlau R, et al (18)	OS	locally advanced or metastatic	0-2 (ECOG)	Double -blind	aflibercept and docetaxel vs. docetaxel alone	456 vs. 457	anti-VEGF antibody	All comer	10.1 M vs. 10.4 M, HR = 1.01 (95% CI = 0.87 - 1.17, p = 0.90)	9.62 M vs 7.5 M, HR = 0.78
Paz-Ares LG, et al (19)	OS	stage IIIb or IV	0-1 (ECOG)	Double -blind	sorafenib + gemcitabine/cisplatin vs. gemcitabine/cisplatin alone	385 vs. 387	multikinase inhibitor	All comer	12.4 M vs. 12.5 M, HR = 0.98 (95% CI = 0.83 - 1.16, p = 0.401)	13 M vs. 10 M, HR = 0.77 (30% increase in median OS)
Gridelli C, et al (20)	OS	stage IIIb or IV	0-1 (ECOG)	Open	first line erlotinib followed by second line cisplatin + gemcitabine vs. first line cisplatin + gemcitabine followed by second line erlotinib	273 vs. 263	EGFR-TKI	All comer	8.7 M vs. 11.6 M, HR = 1.24 (95% CI = 1.04 - 1.47)	median OS of 10 M in control arm is expected, the noninferiority is defined as upper limit 1.25 of 95% CI of HR (corresponds to lower limit of HR = 0.80 in favor of the control arm)
Scagliotti GV, et al (21)	OS	stage IIIB or IV or recurrent nonsquamous	0-1 (ECOG)	Double -blind	motesanib vs. placebo	541 vs. 549	multikinase inhibitor	All comer	13.0 M vs. 11.0 M, HR = 0.90 (95% CI = 0.78 - 1.04, p = 0.14)	12.5 M vs. 10 M, HR = 0.80

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Lee JS, et al (22)	OS	stage IIIB or IV	0-2 （WHO)	Double -blind	vandetanib vs. placeb	617 vs. 307	multikinase inhibitor	All comer	8.5 M vs. 7.8 M, HR = 0.95 (95.2% CI = 0.81 - 1.11, p = 0.527)	6.65 M vs. 5 M, HR = 0.75 (33% increase in median OS)
Hoang T, et al (23)	OS	unresectable stage IIIA/B	0-1 (ECOG)	Open	thalidomide + paclitaxel + carboplatin followed by radiation vs. paclitaxel + carboplatin followed by radiation	271 vs. 275	Chemo-radiation	All comer	16.0 M vs. 15.3 M, HR = 1.00 (95% CI = 0.83 - 1.20, p = 0.99)	18.2 M vs. 14 M, HR = 0.77
Jalal SI, et al (24)	OS	inoperable locally advanced stage IIIA/B	0-1 (ECOG)	not found	docetaxel consolidation after chemoradiation with etoposide + cisplatin vs. no treatment after chemoradiation with etoposide + cisplatin	82 vs. 84	Chemo-radiation	All comer	24.2 M vs. 26.1 M, HR: not found (p = 0.7499)	25 M vs. 15 M, HR: not found (calculated HR = 0.6)
Carter DL, et al (25)	OS	unresectable or inoperable stage IIIA/B	0-1 (ECOG)	Open	paclitaxel consolidation after chemoradiation with paclitaxel + carboplatin vs. no treatment after chemoradiation with paclitaxel + carboplatin	61 vs. 58	Chemo-radiation	All comer	16.1 M vs. 26.9 M (1-year OS of 66% vs. 77%), HR: not found (p = 0.07)	Median survival: not found, but 1-year OS of 60% vs. 42%, HR = 0.60
Groen HJ, et al (26)	OS	stage IIIB or IV	0-2 (ECOG)	Double -blind	celecoxib vs. placebo	281 vs. 280	COX-2 inhibitor	All comer	8.2 M vs. 8.2 M, HR = 0.9 (95% CI = 0.6 - 1.2, p = 0.32)	11.7 M vs. 9.0 M, HR = 0.77

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Ridolfi L, et al (27)	OS	stage IIIB or IV non-operable	0-2 (ECOG)	not found	IL-2 + gemcitabine + cisplatin vs. gemcitabine + cisplatin	127 vs. 114	IL-2	All comer	10.5 M vs. 12.0 M (1-year OS of 45% vs. 51%), HR: not found (p = 0.456)	Median survival: not found, but 1-year OS of 30% vs. 25%, HR: not found (calculated HR = 0.83)
Lara PN Jr, et al (28)	OS	newly-diagnosed stage IIIb or IV	0-1 (WHO)	Double -blind	vadimezan + paclitaxel + carboplatin vs. plasebo + paclitaxel + carboplatin	649 vs. 650	multikinase inhibitor	All comer	13.4 M vs. 12.7 M, HR = 1.01 (95% CI = 0.85 - 1.19, p = 0.535)	11.25 M vs. 9.0 M, HR = 0.80
Karampeazis A, et al (29)	OS	Chemotherapy -naive inoperable stage IIIB or IV	0-2 (ECOG)	not found	docetaxel vs. vinorelbine	66 vs. 64	Chemotherapy	All comer	6.07 M vs. 3.87 M, HR: not found (p = 0.090)	38 W vs. 28 W, HR: not found (calculated HR = 0.74) (35% increase in median OS)
Hirsh V, et al (30)	OS	Chemotherapy -naive stage IIIB or IV	0-1 (ECOG)	Open	PF-3512676 + paclitaxel/carboplatin vs. paclitaxel/carboplatin alone	408 vs. 420	Toll-like receptor 9 agonist	All comer	10.0 M vs. 9.8 M, HR = 0.95 (95% CI = 0.81 - 1.12, p = 0.56)	Median survival: not found, HR = 0.75
Manegold C, et al (31)	OS	Chemotherapy -naive stage IIIB or IV	0-1 (ECOG)	Open	PF-3512676 + gemcitabine/cisplatin vs. gemcitabine/cisplatin alone	416 vs. 423	Toll-like receptor 9 agonist	All comer	11.0 M vs. 10.7 M, HR = 1.0 (95% CI = 0.85 - 1.18, p = 0.98)	Median survival: not found, HR = 0.75
Kosmidis PA, et al (32)	OS	stage IIIB (wet) or IV	0-1 (ECOG)	not found	paclitaxel + gemcitabine vs. paclitaxel + vinorelbine	196 vs. 202	Chemotherapy	All comer	11.1 M vs. 8.6 M, HR: not found (p = 0.147)	Median survival: not found, HR: not found

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Ellis PM, et al (33)	OS	advanced or metastatic	0-3 (ECOG)	Double -blind	dacotinib vs. placebo	480 vs. 240	EGFR-TKI	All comer	6.83 M vs 6.31 M, HR = 1.00 (95% CI = 0.83 - 1.21, p = 0.506)	5.3 M vs. 4.0 M, HR: not found (calculated HR = 0.75) (33% increase in median OS)
Laurie SA, et al (34)	OS	advanced, incurable stage IIIB or IV	0-1 (ECOG)	Double -blind	cediranib vs. placebo	153 vs. 153	VEGFR-TKI	All comer	12.2 M vs 12.1 M, HR = 0.94 (95% CI = 0.69- 1.30, p = 0.72)	11.3 M vs. 8.5 M, HR = 0.75
Butts C, et al (35)	OS	stage IIIA/B	0-1 (ECOG)	Double -blind	tecemotide vs. placebo	829 vs, 410	MUC1 antigen-specific immunotherapy	All comer	25.6 M vs. 22.3 M, HR = 0.88 (95% CI = 0.75- 1.03, p=0.123)	Not found exp. arm vs. 20 M, HR = 0.77 (exp. arm: 26 M is calculated)
Lee SM, et al (36)	OS	stage IIIB or IV 1st line	≥2 ECOG) or presence of several comorbidities	Double -blind	erlotinib vs. plasebo	350 vs. 320	EGFR-TKI	All comer	3.7 M vs. 3.6 M (1-year OS of 15% vs. 14%), HR = 0.94 (95% CI = 0.81 - 1.10, p=0.46)	Median survival: not found, but 1-year OS of 17.5% vs. 10%, HR = 0.75
Fløtten Ø, et al (37)	OS	stage IIIB or IV	0-2 (WHO)	Open	vinorelbine + gemcitabine vs. vinorelbine + carboplatin	215 vs. 222	Chemotherapy	All comer	6.3 M vs. 7.0 M (1-year OS of 30% vs. 27%), HR = 1.025 (95% CI = 0.85 - 1.24, p = 0.802)	Median survival: not found, but 1-year OS of 40% vs. 29%, HR: not found (calculated HR = 0.73)
Miller VA, et al (38)	OS	stage IIIB or IV adenocarcinoma	0-2 (ECOG)	Double -blind	afatinib vs. placebo	390 vs. 195	EGFR-TKI	All comer	10.8 M vs. 12.0 M, HR = 1.08 (95% CI = 0.86- 1.35, p=0.74)	6.7 M vs. 4.7 M, HR = 0.70

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Ciuleanu T, et al (39)	OS	stage IIIB or IV 2nd line	0-2 (ECOG)	Open	erlotinib vs. chemotherapy (docetaxel or pemetrexed)	203 vs. 221	EGFR-TKI	All comer	5.3 M vs. 5.5 M, HR = 0.96 (95% CI = 0.78 - 1.19, p = 0.73)	Median survival: not found, HR = 0.80
Herbst RS, et al (40)	OS	advanced or recurrent stage IIIB or IV	0-2 (ECOG)	Double -blind	bevacizumab + erlotinib vs. erlotinib alone	319 vs. 317	anti-VEGF antibody	All comer	9.3 M vs. 9.2 M, HR = 0.97 (95% CI = 0.80 – 1.18, p=0.7583)	Median survival: not found, HR: not found (33% increase in median OS)
Gaafar RM, et al (41)	OS	stage IIIB or IV	0-2 (WHO)	Double -blind	gefitinib vs. placebo	86 vs. 87	EGFR-TKI	All comer	10.9 M vs. 9.4 M, HR = 0.81 (95% CI = 0.59 - 1.12, p = 0.204)	14 M vs. 11 M, HR = 0.78
Koch A, et al (42)	OS	stage IIIB or IV	0-2 (WHO)	Double -blind	celecoxib vs. placebo	159 vs. 160	COX-2 inhibitor	All comer	8.9 M vs. 7.9 M, HR = 1.00 (95% CI = 0.79 - 1.26, p = 0.97)	9.5 M vs. 7.5 M, HR: not found (calculated HR = 0.79)
Carbone DP, et al. (43)	PFS	untreated stage IV or recurrent	0-1 (ECOG)	Open	nivolumab vs. platinum doublet chemotherapy	271 vs. 270	anti-PD-L1 antibody	PD-L1 positive	4.2 M vs. 5.9 M, HR = 1.15 (95% CI = 0.91 - 1.45, p = 0.25)	Not found experimental arm vs 7 M, HR = 0.71 (experimental arm: 9.86 M is calculated)
Davidson A, et al. (44)	PFS	stage of disease III or IV	0-2 (ECOG)	Open	Chemotherapy + nitroglycerin vs. Chemotherapy alone	187 vs. 185	nitroglycerin	All comer	5.0 M vs. 4.8 M, HR = 1.07 (95% CI = 0.86 – 1.32, p = 0.55)	Median survival: not found, HR = 0.75

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Edelman MJ, et al. (45)	PFS	stage IIIB with pleural effusion or stage IV	0-2 (ECOG)	Double -blind	celecoxib vs. placebo	158 vs. 154	COX-2 inhibitor	COX-2 expression	5.16 M vs. 5.26 M, HR = 1.076 (95% CI = 0.853 - 1.367, p = 0.5346)	9.2 M vs. 6 M, HR = 0.652
Yoshioka H, et al. (46)	PFS	stage IIIB or IV	0-1 (ECOG)	Open	amrubicin vs. docetaxel	101 vs. 101	chemotherapy	All comer	3.6 M vs. 3.0 M, HR = 0.90 (95% CI = 0.65 –1.25, p = 0.54)	3.3 M vs. 2.0 M, HR: not found (calculated HR = 0.606)
Smit EF, et al. (47)	PFS	stage IIIB or IV	0-2 (ECOG)	Double -blind	erlotinib 300 mg vs. erlotinib 150 mg	160 vs. 155	EGFR-TKI	All comer	7.0 W vs. 6.9 W, HR = 1.05 (95% CI = 0.83 – 1.33, p = 0.671)	14 W vs. 10 W, HR = 0.714
Urata Y, et al. (48)	PFS	stage IIIB or IV	0-2 (ECOG)	Open	erlotinib vs. gefitinib	281 vs. 280	EGFR-TKI	All comer	6.5 M vs. 7.5 M, HR = 1.125 (95% CI = 0.940 - 1.347, p = 0.257)	4 M vs, 4 M, noninferiority margin of HR = 1.30
Ahn JS, et al (49)	PFS	locally advanced Stage IIIA/B	0-1 (ECOG)	Open	concurrent chemoradiotherapy followed by consolidation chemotherapy with docetaxel and cisplatin vs. concurrent chemoradiotherapy alone	209 vs. 211	Chemo-radiation	All comer	9.1 M vs. 8.1 M, HR = 0.91 (95% CI = 0.73 - 1.12, p = 0.36)	16 M vs. 12 M, HR = 0.75

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Moro-Sibilot D, et al (50)	PFS	relapsed following initial surgery–chemotherapy	0-1 (ECOG)	Open	docetaxel + cisplatin/carboplatin vs. docetaxel alone	44 vs. 44	Chemotherapy	All comer	8.0 M vs. 5.6 M, HR = 0.71 (95% CI = 0.45 - 1.1, p = 0.15)	4.5 M vs. 3 M, HR: not found (calculated HR = 0.67)
Zinner RG, et al (51)	PFS without grade 4 toxicity	stage IV nonsquamous	0-1 (ECOG)	Open	pemetrexed + carboplatin followed by pemetrexed vs. paclitaxel + carboplatin + bevacizumab followed by bevacizumab	182 vs. 179	Chemotherapy	All comer	3.91 M vs. 2.86 M, HR = 0.85 (90% CI = 0.7 – 1.04, p = 0.176)	Median survival: not found, HR = 0.75
Yang JJ, et al (52)	PFS	stage IV	0-2 (ECOG)	not found	erlotinib vs. gefitinib	128 vs. 128	EGFR-TKI	EGFR mutation positive	13.0 M vs 10.4 M, HR = 0.81 (95% CI = 0.62 - 1.05, p = 0.108).	14.0 M vs. 9.5 M, HR = 0.65
Flentje M, et al (53)	PFS	stage III	not found	Open	Consolidation chemotherapy following concurrent chemoradiotherapy vs. BSC following concurrent chemoradiotherapy	96 vs. 105	Chemo-radiation	All comer	6.4 M vs. 5.5 M, HR = 0.93 (95% CI = 0.69 – 1.26, p = 0.63)	9 M vs. 6 M, HR: not found (calculated HR = 0.67)
Soria JC, et al (54)	PFS	stage IIIB or IV	0-1 (WHO)	Double -blind	gefitinib vs. placebo	133 vs. 132	EGFR-TKI	EGFR mutation positive	5.4 M vs. 5.4 M, HR = 0.86 (95% CI = 0.65 – 1.13, p = 0·27)	9.5 M vs. 6 M, HR = 0.63
Kawaguchi T, et al (55)	PFS	stage IIIB or IV 2nd or 3rd line	0-2 (ECOG)	Open	erlotinib vs. docetaxel	151 vs. 151	EGFR-TKI	All comer	2.0 M vs. 3.2 M, HR = 1.22 (95% CI = 0.97 - 1.55, p = 0.09)	3.5 M vs. 2.5 M, HR: not found (calculated HR = 0.71)

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Bepler G, et al (56)	PFS	stage IIIB (wet) or IV	0-1 (ECOG)	Open	selected chemotherapy based on expression level of RRM1 and ERCC1 vs. gemcitabine/carboplatin	183 vs. 92	Chemotherapy	All comer	6.1 M vs. 6.9 M, HR: not found (p = 0.181)	6.0 M vs. 4.3 M, HR = 0.68
Scagliotti GV, et al (57)	PFS	stage IIIA/B	0-1 (ECOG)	Open	zoledronic acid vs. no treatment	226 vs. 211	Bisphosphonate	All comer	9.0 M vs. 11.3 M, HR = 1.22 (95% CI = 0.96 - 1.54, p = 0.0957)	18.6 M vs. 13 M, HR = 0.70
Weissman CH, et al (58)	PFS	Chemotherapy -naive stage IIIB or IV	0-1 (ECOG)	not found	gemcitabine + oxaliplatin vs. paclitaxel + carboplatin	191 vs. 192	Chemotherapy	All comer	4.44 M vs. 4.67 M, HR: not found	Not found exp. arm vs. 3.1 M, HR = 0.70 (exp. arm: 4.4 M is calculated)
de Boer RH, et al (59)	PFS	stage IIIB to IV	0-2 (WHO)	Double -blind	vandetanib vs. placeb	256 vs. 278	multikinase inhibitor	All comer	17.6 W vs. 11.9 W, HR = 0.86 (97.58% CI = 0.69 - 1.06, p = 0.108)	Not found exp. arm vs. 3.0 M, HR = 0.74 (exp. arm: 4.0 M is calculated)
Ramalingam SS, et al (60)	PFS	locally advanced or metastatic	0-2 (ECOG)	Double -blind	dacomitinib vs. erlotinib	439 vs. 439	EGFR-TKI	All comer	2.6 M vs. 2.6 M, HR = 0.941 (95% CI = 0.802 - 1.04, p = 0.229)	Median survival: not found, HR: not found (33% increase in median PFS)
Yang JC, et al (61)	PFS	locally advanced or metastatic	0-1 (ECOG)	Open	pemetrexed + cisplatin followed by maintenance gefitinib vs. gefitinib monotherapy	118 vs. 118	EGFR-TKI	All comer	8.38 M vs. 9.63 M, HR = 0.85 (95% CI = 0.63 - 1.13, p = 0.261)	Median survival: not found, HR = 0.65

Trial	Primary Endpoint	Stage/Setting	PS	Open/ Double -blind	Arms (exp. vs. control arm)	Sample size (exp. vs. control arm)	Target	Enriched population	Results of median survival (exp. vs. control arm) and HR	Pre-estimations of median survival (exp. vs. control arm) and HR
Kim ES, et al (62)	PFS	recurrent or progressive	60–100 (Karnofsky PS)	Open	cetuximab + pemetrexed vs. pemetrexed	301 vs. 304	anti-EGFR antibody	All comer	2.9 M vs. 2.8 M, HR = 1.03 (95% CI = 0.87 - 1.21, p = 0.76)	3.9 M vs. 2.9 M, HR: not found (calculated HR = 0.74)
Karampeazis A, et al (63)	TTP	stage IIIB (with pleural effusion) or stage IV	0-2 (WHO)	Open	pemetrexed vs. erlotinib	166 vs. 166	Chemotherapy	All comer	3 M vs. 3.9 M, HR: not found (p = 0.195)	3 M vs. 2.2 M, HR: not found (calculated HR = 0.73) (35% increase in median TTP)
Kelly K, et al (64)	DFS	stage IB-IIIA	0-2 (ECOG)	Double -blind	erlotinib vs. placebo	623 vs. 350	EGFR-TKI	EGFR positive	50.5 M vs. 48.2 M, HR = 0.90 (95% CI = 0.74 - 1.10, p = 0.324)	64 M vs. 48 M, HR = 0.75 (33% increase in median DFS)
Vansteenkiste JF, et al (65)	DFS	completely resected stage IB, II, and IIIA MAGE-A3-positive	0-2 (ECOG)	Double -blind	MAGE-A3 immunotherapeutic vs. placebo	1515 vs. 757	MAGE-A3 immunotherapy	MAGE-A3-positive	60·5 M vs. 57·9 M, HR = 1·02 (95% CI = 0·89 – 1·18, p = 0·74)	Median survival: not found, HR: not found, (28% increase in median DFS)
Price A, et al (66)	EFS	inoperable stage I or II	0-2	Open	gemcitabine + radiotherapy vs. radiotherapy alone	22 vs. 21	Chemo-radiation	All comer	42% vs. 46% in 2-year EFS	60% vs. 30% in 2-year FES

DFS: disease-free survival, EFS: event-free survival, OS: overall survival, PFS: progression-free survival, TTP: time to progression, WHO: World Health Organization, ECOG: Eastern Cooperative Oncology Group, PS: performance status, exp.: experimental, BSC: best supportive care, EGFR: epidermal growth factor receptor, TKI: tyrosine kinase inhibitor, PD1: programmed cell death 1, MET: met rproto-oncogene, VEGF: vascular endothelial growth factor, IGF-1R : insulin-like growth factor 1 receptor, IL: interleukin, COX: cyclooxygenase, CI: Confidence Interval, HR: Hazard Ratio, M: Months, W: Weeks, Y: Years

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付録 3　乳癌を対象とした第 3 相臨床試験の一覧（Positive 39 試験）

Trials	Primary endpoint	Exp. Arm vs. control arm	Sample size	Actual result	Pre-estimate
Park IH, et a. [1]	ORR	Genexol-PM vs. Genexol	105 vs. 107	ORR: 39.1% vs. 24.3%, p = 0.021 (non-inferiority), p = 0.016 (superiority)	ORR: not found, non-inferiority margin: absolute difference of 7%
Zhang M, et al [2]	pCR rate	xeloda/epirubicin/cyclophosphamide vs. 5-fluorouracil/epirubicin/cyclophosphamide	61 vs. 70	pCR rate: 18% vs. 6%, p = 0.027	pCR rate: not found
Steger GG, et al. [3]	pCR rate	epirubicin–docetaxel + capecitabine vs. epirubicin–docetaxel	270 vs. 266	pCR rate: 23% vs. 15.4%, p = 0.027	pCR rate: 27% vs. 16%, OR: 1.5
Mohammadianpanah M, et al. [4]	clinical CR rate	chemotherapy (5-fluorouracil + doxorubicin + cyclophosphamide) + letrozole vs. chemotherapy (5-fluorouracil + doxorubicin + cyclophosphamide) alone	50 vs. 51	clinical CR rate: 27.6% vs. 10.2%, p = 0.028	clinical CR rate: 30% vs. 8%, OR: not found
Untch M, et al. [5]	pCR rate	nab-paclitaxel vs. solvent-based paclitaxel	606 vs. 600	pCR: 38% vs. 29%, OR = 1.53 (95% CI = 1.20 – 1.95), unadjusted p = 0.00065, non-inferiority test	pCR: 41% vs. 33%, OR = 1.41, non-inferior if the lower 95% CI for the OR was above 0.858 (or equivalent to pCR 33% - 10% non-inferiority margin [3.3%], 29.7%)
Earl HM, et al. [6]	pCR rate	bevacizumab + docetaxel + fluorouracil + epirubicin + cyclophosphamide vs. docetaxel + fluorouracil + epirubicin + cyclophosphamide	388 vs. 393	pCR rate: 22% vs. 17%, p = 0.03	10% difference in pCR rate
Masuda N, et al. [7]	ORR	anastrozole vs. tamoxifen	98 vs. 99	ORR: 70.4% vs. 50.5%, estimated difference = 19.9% (95% CI = 6.5 – 33.3), p = 0.004	Non-inferiority if the lower limit for the 95% CI is 10% or less.
Guan Z, et al. [8]	OS	lapatinib + paclitaxel vs. placebo + paclitaxel	222 vs. 222	median OS: 27.8 M vs. 20.5 M, HR = 0.74 (95% CI = 0.58 -	median OS: 28.6 M vs. 20 M, HR = 0.70

Trials	Primary endpoint	Exp. Arm vs. control arm	Sample size	Actual result	Pre-estimate
				0.94). P = 0.0124	
Kimura M, et al. [9]	5-year survival	toremifene vs. tamoxifen	123 vs. 120	5-year survival: 97.0% vs. 96.9 %, difference: 0.1% (90 % CI = -3.9 - 4.1)	5-year survival: 90% vs. 90%, non-inferiority margin of 10 %,
Zielinski C, et al. [10]	OS	bevacizumab + capecitabine vs. bevacizumab + paclitaxel	285 vs. 279	median OS: 30.2 M vs. 26.1 M, HR = 1.02 (97.5% RCI -∞ to 1.26), repeated p = 0.0070 indicating non-inferiority	median OS: 24 M vs. 24 M, null hypothesis of inferiority (HR ≥ 1.33)
Takashima T, et al. [11]	OS	S-1 vs. taxane (docetaxel or paclitaxel)	306 vs. 286	median OS: 35.0 M vs. 37.2 M, HR = 1.05 (95% CI: 0.86 – 1.27), p = 0.015 non-inferiority test	event: 190 vs. 190, non-inferiority margin of 1.333 HR
Krop IE, et al. [12]	OS and PFS	trastuzumab emtansine vs. physician's choice	404 vs. 198	median OS: not reached vs. 14.9 M, HR = 0.552 (95% CI = 0.369 – 0.826), p = 0.0034 median PFS: 6.2 M vs. 3.3 M, HR = 0.528 (95% CI = 0.422 – 0.661), p < 0.0001	median OS: 15.8 M vs. 12 M, HR = 0.76 (p < 0.045) median PFS: 6.15 M vs. 4 M, HR = 0.65 (p < 0.005)
Cortes J, et al. [13]	OS	eribulin vs. physician's choice	508 vs. 254	median OS: 13.1 M vs. 10.6 M, HR = 0.81 (95% CI = 0.66 – 0.99), p = 0.041	median OS: not found, HR: not found
Finn RS, et al. [14]	PFS	palbociclib + letrozole vs. placebo + letrozole	444 vs. 222	median PFS: 24.8 M vs. 14.5 M, HR = 0.58 (95% CI = 0.46 - 0.72), p < 0.001	median PFS: 13 M vs. 9 M, HR = 0.69
Turner NC, et al. [15]	PFS	palbociclib + fulvestrant vs. placebo + fulvestrant	347 vs. 174	median PFS: 9.2 M vs. 3.8 M, HR = 0.42 (95% CI = 0.32 - 0.56), p < 0.001	median PFS: 9.38 M vs. 6.00 M, HR = 0.64
Robson M, et al. [16]	PFS	olaparib vs. chemotherapy	205 vs. 97	median PFS: 7.0 M vs. 4.2 M, HR = 0.58 (95% CI = 0.43 - 0.80), p < 0.001	median PFS: 6.25 M vs. 4.0 M, HR = 0.64
Yamamoto D, et al. [17]	PFS	low-dose capecitabine + docetaxel vs. docetaxel	82 vs. 81	median PFS: 10.5 M vs. 9.8 M HR = 0.62 (95% CI = 0.40 -	median PFS: 9.4 M vs. 6.0 M, HR = 0.64

Trials	Primary endpoint	Exp. Arm vs. control arm	Sample size	Actual result	Pre-estimate
				0.97), p = 0.03	
Baselga J, et al. [18]	PFS	buparlisib + fulvestrant vs. placebo + fulvestrant	576 vs. 571	median PFS: 6.9 M vs. 5.0 M, HR = 0.78 (95% CI = 0.67 - 0.89), one-sided p = 0.00021	median PFS: 7.5 M vs. 5M, HR = 0.67
Miles D, et al. [19]	PFS	bevacizumab + paclitaxel vs. placebo + paclitaxel	239 vs. 242	median PFS: 11.0 M vs. 8.8 M, HR = 0.68 (99% CI = 0.51 - 0.91), p = 0.0007	median PFS: 12 M vs. 8 M, HR = 0.67
Hortobagyi GN, et al. [20]	PFS	ribociclib + letrozole vs. placebo + letrozole	334 vs. 334	median PFS: not reached vs. 14.7 M, HR = 0.56 (95% CI = 0.43 - 0.72), p = 3.29×10−6	median PFS: 13.43 M vs. 9.0 M, HR: 0.67
Noguchi S, et al. [21]	PFS	3-monthly goserelin vs. monthly goserelin	109 vs. 113	24-week PFS: 61.5% vs. 60.2%, treatment difference: 1.3 (95 % CI = −11.4 - 13.9)	24-week PFS: 75% vs. 70%, non-inferiority margin of -17.5%
Wang J, et al. [22]	PFS	Docetaxel / capecitabine vs. vinorelbine / capecitabine	104 vs. 102	median PFS: 8.4 M vs 7.1 M, HR = 1.65 (95% CI = 1.18 - 2.3), p = 0.0026	median PFS: 7 M vs. 5.3 M, noninferiority margin of 1.5 M PFS
Yardley DA, et al. [23]	PFS	everolimus + exemestane vs. placebo + exemestane	485 vs. 239	median PFS: 7.8 M vs. 3.2 M, HR = 0.45 (95% CI = 0.38 - 0.54), p < 0.0001	median PSF: 5 M vs. 3.7 M, HR = 0.74
Park YH, et al. [24]	PFS	Paclitaxel / gemcitabine vs. observation	116 vs. 115	6-M PFS rate: 59.7% vs. 36.0%, p < 0.001	6-M PFS rate: 20% longer vs. observation, HR: not found
Brufsky AM, et al. [25]	PFS	chemotherapy + bevacizumab vs. chemotherapy + placebo	459 vs. 225	median PFS: 7.2 M vs. 5.1 M, HR = 0.78 (95% CI = 0.64 - 0.93), p = 0.0072	median PFS: 5.3 M vs. 4 M, HR = 0.75
Robert NJ, et al. [26]	PFS	chemotherapy (capecitabine, taxane, or anthracycline) + bevacizumab vs. chemotherapy (capecitabine, taxane, or anthracycline) + placebo	capecitabine cohort: 409 vs. 206 taxane / anthracycline cohort: 415 vs. 207	capecitabine cohort: 8.6 M vs. 5.7 M, HR = 0.69 (95% CI = 0.56 - 0.84), p < 0.001 taxane / anthracycline cohort: 9.2 M vs. 8.0 M, HR = 0.64 (95% CI = 0.52 - 0.80), p < 0.001	capecitabine cohort: 8 M vs. 6 M, HR = 0.75 taxane / anthracycline cohort: 10 M vs. 7 M, HR = 0.70

Trials	Primary endpoint	Exp. Arm vs. control arm	Sample size	Actual result	Pre-estimate
Zhang P, et al. [27]	PFS	utidelone + capecitabine vs. capecitabine alone	270 vs. 135	median PFS: 8.44 M vs. 4.27 M, HR = 0.46 (95% CI = 0.36 - 0.59), p < 0·0001.	median PFS: 6 M vs. 4 M, HR = 0.67
Robertson JFR, et al. [28]	PFS	fulvestrant vs. anastrozol	230 vs. 232	median PFS: 16.6 M vs. 13.8 M, HR = 0.797 (95% CI = 0.637 - 0.999), p = 0.0486	median PFS: not found, HR = 0.69
Hu XC, et al. [29]	PFS	cisplatin + gemcitabine vs. paclitaxel + gemcitabine	118 vs. 118	median PFS: 7.73 M vs. 6.47 M, HR = 0.692 (95% CI = 0.523 – 0.915), p = 0.009	median PFS: 6.2 M vs. 5.0, HR = 0.806
Gligorov J, et al. [30]	PFS	capecitabine + bevacizumab vs. bevacizumab alone	91 vs. 94	median PFS: 11.9 M vs. 4.3 M, HR = 0.38 (95% CI = 0.27 – 0.55), p < 0.0001	median PFS: 8.3 M vs. 5.8 M, HR = 0.70
von Minckwitz G, et al. [31].	PFS	bevacizumab + chemotherapy vs. chemotherapy alone	247 vs. 247	median PFS: 6.3 M vs. 4.2 M, HR = 0.75 (95% CI = 0.61 – 0.93]), p = 0.0068	median PFS: 9.3 M vs. 7 M, HR = 0.75
André F, et al. [32]	PFS	everolimus vs. placebo	284 vs. 285	median PFS: 7.00 M vs. 5.78 M, HR = 0.78 (95% CI = 0.65 – 0.95), p = 0.0067	median PFS: 8.25 M vs. 6M, HR = 0.73
Lorusso V, et al. [33]	TTP	non-pegylated liposome-encapsulated doxorubicin + cyclophosphamide vs. non-pegylated liposome-encapsulated doxorubicin + vinorelbine	116 vs. 112	median TTP: 41 W vs. 34 W, p = 0.0234	median TTP: not found, HR: not found
Zdenkowski N, et al. [34]	rate of invasive breast cancer events	letrozole vs. observation	181 vs. 179	rate of invasive breast cancer events: 1.1% vs. 9.5%, (difference 8.4%, 95% CI = 3.8% - 13.0%), p = 0.0004	rate of invasive breast cancer events: not found, HR: not found (60% reduction)
Pivot X, et al. [35]	incidence of CNS metastases	lapatinib-capecitabine vs. trastuzumab-capecitabine	271 vs. 269	Incidence of CNS metastases: 3% vs. 5%, treatment differences = −1.6% (95% CI = −2% - 5%), p = 0.360	incidence of CNS: 8% vs. 12%
Nitz U, et al. [36]	EFS	epiribicine + cyclophosphamide followed by docetaxel vs. 5-fluorouracil + epirubicin +	967 vs. 963	5-year EFS: 89.8% vs. 86.6%, HR = 0.74 (95% CI = 0.57 –	5-year EFS: 76.1% vs. 71.1%, HR: not found

Trials	Primary endpoint	Exp. Arm vs. control arm	Sample size	Actual result	Pre-estimate
		cyclophosphamide or cyclophosphamide + methotrexate + 5-fluorouracil		0.97), p = 0.026	
Coombes RC, et al. [37]	DFS	epirubicin followed by docetaxel vs. epirubicin	406 vs. 397	5-year DFS: 79.5% vs. 72.7%, HR = 0.68 (95% CI = 0.52 - 0.91, p = 0.008)	5-year DFS: 80% vs. 70%, HR: not found
Chan A, et al. [38]	IDFS	neratinib vs. placebo	1420 vs. 1420	2-year IDFS: 93.9% vs. 91.6%, HR = 0.67 (95% CI = 0.50 - 0.91), p = 0.0091	2-year IDFS: not found, HR = 0.70
Margolese RG, et al. [39]	breast cancer-free interval	anastrozole vs. tamoxifen	1539 vs. 1538	90 events vs. 122 events, HR = 0.73 (95% CI = 0.56 – 0.96), p = 0.0234	event rate: not found, HR: not found, 33% reduction in breast cancer event rates

pCR: pathological complete response, CR: complete response, ORR: objective response rate, OS: overall survival, PFS: progression-free survival, TTP: time-to-progression, CNS: central nervous system, EFS: event-free survival, DFS: disease-free survival, IDFS: invasive disease-free survival, OR: odds ratio, CI: confidence interval, M: months, HR: hazard ratio, W: weeks

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付録 4　乳癌を対象とした第 3 相臨床試験の一覧（Negative 74 試験）

Trials	Primary endpoint	Exp. Arm vs. control arm	Sample size	Actual result	Pre-estimate
Yamamoto Y, et al. [1]	clinical benefit rate	toremifene vs. exemestane	46 vs. 45	clinical benefit rate: 41.3% vs. 26.7%, p = 0.14	clinical benefit rate: 45% vs. 30%
Vriens BE, et al. [2]	pCR rate	docetaxel + doxorubicin + cyclophosphamide vs. doxorubicin + cyclophosphamide followed by docetaxel	102 vs. 100	pCR rate: 16% vs. 21%, odds ratio = 1.44 (95% CI = 0.67 - 3.10)	pCR rata: 34% vs. 16%
Chen X, et al. [3]	pCR rate	docetaxel + cyclophosphamide vs. docetaxel + anthracycline + cyclophosphamide	45 vs. 51	pCR rate: 6.8% vs. 17.6%, p = 0.113	pCR rate: > 20% vs. 30%
Buzdar AU, et al. [4]	pCR rate	Fluorouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel + trastuzumab (sequential) vs. paclitaxel + trastuzumab followed by FEC-75 + trastuzumab (concurrent)	140 vs. 142	pCR rate: 56.5% vs. 54.2%, OR = 0.90 (95% CI = 0.55 – 1.49)	pCR rate: 25% vs. 45%, OR: not found
Untch M, et al. [5]	pCR rate	lapatinib + chemo vs. trastuzumab + chemo	311 vs. 309	pCR rate: 22.7% vs. 30·3%, OR = 0.68 (95% CI = 0·47 – 0·97), p = 0·04	pCR rate: 37% vs. 26%, OR = 1·67
Arun BK, et al. [6]	pCR rate	dose-intense 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) + G-CSF vs. FAC	99 vs. 100	pCR rate: 13.1% vs. 9%, p = 0.35	CR rate: 35% vs. 15%, OR: not found
Del Mastro L, et al. [7]	OS	epirubicin + paclitaxel　vs. 5-Fluorouracil + epirubicin + cyclophosphamide	535 vs. 520	5-year OS: 88% vs. 89%, 10-year OS: 74% vs. 73%, HR = 0.87 (95% CI = 0.68 - 1.06), p = 0.405	OS: not found, HR = 0.80
O'Shaughnessy J, et al. [8]	OS and PFS	iniparib + gemcitabine + carboplatin vs. gemcitabine + carboplatin	261 vs. 258	median OS: 11.8 M vs. 11.1 M, HR = 0.88 (95% CI =　0.69 - 1.12), p = 0.28 median PFS: 5.1 M vs. 4.1 M, HR = 0.79 (95% CI = 0.65 - 0.98), p = 0.027	median OS: not found, HR = 0.66 median PFS: not found, HR = 0.65

Trials	Primary endpoint	Exp. Arm vs. control arm	Sample size	Actual result	Pre-estimate
Bedognetti D, et al. [9]	OS	concurrent vs. sequential of adjuvant chemotherapy and tamoxifen.	214 vs. 217	10-year OS: 66% vs. 65%, HR = 1.06 (95% CI = 0.78 - 1.44), p = 0.86	OS: not found, HR = 0.64
Miles D, et al. [10]	OS and TTP	sialyl-TN (STn) keyhole limpet hemocyanin(KLH) vaccine + adjuvant (treatment group) vs. KLH + adjuvant	521 vs. 501	median OS: 23.1 M vs. 22.3 M, p = 0.916 median TTP: 3.4 M vs. 3.0 M, p = 0.353	median OS: not found, HR: not found median TTP: not found, HR: not found
Amadori D, et al. [11]	OS	cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) followed by epirubicin vs. adjuvant epirubicin followedby CMF	438 vs. 440	5-year OS: 93% vs. 91%, HR = 0.88 (95% CI = 0.58 – 1.35)	5-year OS: 85% vs. 78%, HR: not found
Perez EA, et al. [12]	OS	etirinotecan pegol vs. physician's choice	429 vs. 423	median OS: 12.4 M vs. 10.3 M, HR = 0.87 (95% CI = 0.75 – 1.02), p = 0.084	median OS: 13 M vs. 10 M, HR = 0.77
Kaufman PA, et al. [13]	OS and PFS	eribulin vs. capecitabine	554 vs. 548	median OS: 15.9 M vs. 14.5 M, HR = 0.88 (95% CI = 0.77 - 1.00), p = 0.056 median PFS: 4.1 M vs. 4.2 M, HR = 1.08 (95% CI = 0.93 - 1.25), p = 0.30	median OS: 15 M vs. 12 M, HR = 0.80 median PFS: not found, HR: not found
Baselga J, et al. [14]	PFS	capecitabine + sorafenib vs. capecitabine + placebo	266 vs. 271	median PFS: 5.5 M vs. 5.4 M, HR = 0.973 (95% CI = 0.779 - 1.217), p = 0.811	median PFS: not found, HR;: not found (66.7% increase)
Gelmon KA, et al. [15]	PFS	lapatinib + taxane vs. trastuzumab + taxane	326 vs. 326	median PFS: 9.0 M vs. 11.3 M, HR = 1.37 (95% CI = 1.13 - 1.65), p = 0.001	median PFS: not found, non-inferiority HR margin of 1.25
Kader YA, et al. [16]	PFS	bevacizumab + carboplatin + paclitaxel vs. carboplatin + docetaxel	20 vs. 21	median PFS: 10 M vs. 10.2 M, p = 0.9	median PFS: not found, HR: not found
Urruticoechea A, et al. [17]	PFS	pertuzumab + trastuzumab + capecitabine vs. trastuzumab + capecitabine	228 vs. 224	median PFS: 11.1 M vs. 9.0 M, HR = 0.82 (95% CI = 0.65 - 1.02), p = 0.0731	median PFS: 8.67 M vs. 6.5 M, HR = 0.75

Trials	Primary endpoint	Exp. Arm vs. control arm	Sample size	Actual result	Pre-estimate
Pagani O, et al. [18]	TTP	trastuzumab alone followed, at disease progression, by the combination with chemotherapy vs. upfront trastuzumab + chemotherapy	86 vs. 87	median TPP: 12.2 M vs. 10.3 M, HR = 0.7 (95% CI = 0.5 – 1.1), p = 0.1	median TPP: 8.5 M vs. 5.5 M, HR: not found (calculated HR = 0.65)
Harbeck N, et al. [19]	TTP	pegylated liposomal doxorubicin vs. capecitabine	105 vs. 105	median TTP: 6.0 M vs. 6.1 M, HR = 1.08 (95 % CI = 0.76 - 1.54), p = 0.67.	median TTP: 6.9 M vs. 4.0 M, HR = 0.65
Trédan O, et al. [20]	PFS	taxane + bevacizumab vs. exemestane + bevacizumab	59 vs. 58	6-month PFS: 67.2% vs. 55.2%, HR = 1.0 (95% CI = 0.7 - 1.5), p = 0.998	6-month PFS: 65% vs. 50%,, HR = 0.62
Leyland-Jones B, et al. [21]	PFS	epoetin alfa vs. best standard of care	1050 vs. 1048	median PFS: 7.4 M vs. 7.4 M, HR = 1.089 (95% CI = 0.988 - 1.200)	median PFS: not found in experimental arm vs. 6 M, noninferiority HR margin of 1.15
Hatschek T, et al. [22]	PFS	capecitabine + epirubicin + paclitaxel vs. epirubicin + paclitaxel	144 vs. 143	median PFS: 12.4 M vs. 10.8 M, HR = 0.84, (95% CI = 0.65 - 1.07), p = 0.16	median PFS: 8.5 M vs. 6 M, HR = 0.7059
Huober J, et al. [23]	TTP	letrozole + trastuzumab vs. letrozole	26 vs. 31	median TTP: 14.1 M vs. 3.3, HR = 0.67 (95% CI = 0.35 - 1.29), p = 0.23	median TTP: not found, HR: not found (50% improvement)
Welt A, et al. [24]	PFS	capecitabine/bevacizumab + vinorelbine vs. capecitabine/bevacizumab alone	300 vs. 300	median PFS: 9.6 M vs. 8.8 M HR = 0.84 (95% CI = 0.70 – 1.01), p = 0.058	median PFS: 10.3 M vs. 8.0 M; HR = 0.78
Martín M, et al. [25]	PFS	bevacizumab + endocrine therapy (letrozole or fulvestrant) vs. endocrine therapy alone	190 vs. 184	median PFS: 19.3 M vs. 14.4 M, HR = 0.83 (95% CI = 0.65 - 1.06). p = 0.126	median PFS: 13 M vs. 9M, HR = 0.692
Lück HJ, et al. [26]	PFS	taxanes (paclitaxel or docetaxel) + bevacizumab + capecitabine vs. taxanes + bevacizumab	111 vs. 116	median PFS: 9.9 M vs. 11.3 M, HR = 1.13 (95 % CI = 0.806 - 1.59), p = 0.474	median PFS: 13.3 M vs. 10M, HR = 0.75
Mackey JR, et al. [27]	PFS	ramucirumab + docetaxel vs. placebo + docetaxel	759 vs. 385	median PFS: 9.5 M vs. 8.2 M, HR = 0.88 (95% CI = 0.75 - 1.01), p = 0.077	median PFS: 8 M vs. 6 M, HR = 0.75

Trials	Primary endpoint	Exp. Arm vs. control arm	Sample size	Actual result	Pre-estimate
Smorenburg CH, et al. [28]	PFS	pegylated liposomal doxorubicin vs. capecitabine	40 vs. 38	median PFS: 5.6 M vs. 7.7 M, HR = 0.68 (95% CI = 0.42 – 1.09), p = 0.11	median PFS: 7 M vs. 4 M, HR = 0.57
Baselga J, et al. [29]	PFS	nonpegylated liposomal doxorubicin + trastuzumab + paclitaxel vs. trastuzumab + paclitaxel	181 vs. 183	median PFS: 16.1 M vs. 14.5 M, HR = 0.84 (95% CI =), p = 0.174	median PFS: 11.4 M vs. 8 M, HR = 0.70
Lück HJ, et al. [30]	PFS	capecitabine + paclitaxel vs. epirubicin + paclitaxel	169 vs. 170	median PFS: 10.4 M vs. 9.2 M, HR =1.012 (95 % CI = 0.785 – 1.304)	median PFS: not found, HR: not found, upper limit of the 95 % CI for HR of 1.205
Iwata H, et al. [31]	TTP	exemestane vs. anastrozole	149 vs. 149	median TTP: 13.8 M 11.1 M HR = 1.007 (95 % CI = 0.771 - 1.317)	median TTP: not found, HR = 0.9, upper limit of the 95 % CI for HR of 1.25
Gianni L, et al. [32]	PFS	bevacizumab + docetaxel + trastuzumab vs. docetaxel + trastuzumab	216 vs. 208	median PFS: 16.5 M vs. 13.7 M, HR = 0.82 (95% CI = 0.65 - 1.02), p = .0775	median PFS: 16 M vs. 11 M, HR = 0.69
Wolff AC, et al. [33]	PFS	letrozole / temsirolimus vs. letrozole / placebo	556 vs. 556	median PFS: 8.9 M vs. 9 M, HR = 0.90 (95% CI = 0.76 - 1.07), p = 0.25	median PFS: 11.75 M vs. 9.4 M, HR = 0.8
Bergh J, et al. [34]	TTP	fulvestrant + anastrozole vs. anastrozole alone	258 vs. 256	median TTP: 10.8 M vs. 10.2 M, HR = 0.99 (95% CI = 0.81 - 1.20), p = 0.91	median TTP: 12 M vs. 9 M, HR = 0.75
Bergh J, et al. [35]	PFS	sunitinib + docetaxel vs. docetaxel alone	296 vs. 297	median PFS: 8.6 M vs. 8.3 M, HR = 0.92 (95% CI = 0.72 - 1.19), p = 0.265	median PFS: 9 M vs. 6 M, HR = 0.67
Nielsen DL, et al. [36]	TTP	gemcitabine + docetaxel vs. docetaxel alone	170 vs. 167	median TTP: 10.3 M vs. 8.3 M, HR = 0.77 (95% CI = 0.59 - 1.01), p = 0.06	median TTP: 7.5 M vs. 5 M, HR = 0.67
Pallis AG, et al. [37]	PFS	vinorelbine / gemcitabine doublet vs. capecitabine monotherapy	74 vs. 74	median PFS: 5.4 M vs. 5.2 M, p = 0.736	median PFS: 5 M vs. 3 M, HR = 0.6

Trials	Primary endpoint	Exp. Arm vs. control arm	Sample size	Actual result	Pre-estimate
Robert NJ, et al. [38]	PFS	sunitinib + paclitaxel vs. bevacizumab + paclitaxel	242 vs. 243	median PFS: 7.4 M vs. 9.2 M, HR = 1.63 (95% CI = 1.18 - 2.25), p = 0.999	median PFS: not found, HR: not found, 30% improve in PFS
Andersson M, et al. [39]	TTP	docetaxel + trastuzumab vs. vinorelbine + trastuzumab	143 vs. 141	median TTP: 12.4 M vs. 15.3 M, HR = 0.94 (95% CI = 0.71 - 1.25), p = 0.67	median TTP: 10.6 M vs. 6 M, HR = 1.77
Valero V, et al. [40]	TTP	docetaxel + carboplatin + trastuzumab vs. docetaxel + trastuzumab	132 vs. 131	median TTP: 11.1 M vs. 10.4 M, HR = 0.914 (95% CI = 0.694 - 1.203), p = 0.57	median TTP: 10.5 M vs. 7 M, HR = 0.67
Harbeck N, et al. [41]	PFS	afatinib + vinorelbine vs. trastuzumab + vinorelbine	339 vs. 169	Median PFS: 5.5 M vs. 5.6 M HR = 1.10 (95% CI = 0.86 – 1.41), p = 0.43	median PFS: 9.5 M vs. 7 M, HR = 0.74
Hurvitz SA, et al. [42]	PFS	everolimus vs. trastuzumab + paclitaxel	480 vs. 239	median PFS: 14.95 M vs. 14·49 M HR = 0.89 (95% CI = 0.73 – 1.08), p = 0.1166	median PFS: 9.5 M vs. 7 M, HR = 0.74 36% improvement in median PFS
Crown JP, et al. [43]	PFS	sunitinib + capecitabine vs. capecitabine alone	221 vs. 221	median PFS: 5.5 M vs. 5.9 M, HR = 1.22 (95% CI = 0.95 - 1.58), p = 0.941	median PFS: 6 M vs. 4 M, HR = 0.67
Xu B, et al. [44]	TTP	fulvestrant vs. anastrozole	121 vs. 113	median TTP: 110 days vs. 159 days, HR = 1.314 (95% CI = 0.948 - 1.822), p = 0.101	median TTP: not found, HR: not found
Yardley DA, et al. [45]	DFS	doxorubicin/cyclophosphamide followed by ixabepilone vs. doxorubicin/cyclophosphamide followed by paclitaxel	306 vs. 308	5-year DFS: 87.1% vs. 84.7%, HR = 0.92	5-year DFS: not found (10% difference)
Ejlertsen B, et al. [46]	DFS	docetaxel + cyclophosphamide vs. epirubicin + cyclophosphamide followed by docetaxel	1011 vs. 1001	5-year DFS: 88.3% vs. 87.9%, HR = 1.00 (95% CI = 0.78 - 1.28), p = 1.00	3-year DFS: not found in experimental arm vs. 82%, HR = 0.64
Smith I, et al. [47]	DFS	letrozole vs. anastrozole	2061 vs. 2075	5-year DFS: 84.9% vs. 82.9%, HR = 0.93 (95% CI = 0.80 - 1.07), p = 0.3150	5-year DFS: 80.0% vs. 76.5%, HR = 0.83

Trials	Primary endpoint	Exp. Arm vs. control arm	Sample size	Actual result	Pre-estimate
Mavroudis D, et al. [48]	DFS	docetaxel + cyclophosphamide vs. epirubicin + 5-fluorouracil + cyclophosphamide, followed by docetaxel with prophylactic G-CSF support	324 vs. 326	3-year DFS: 91.1% vs. 89.5%, HR = 1.147 (95% CI = 0.716 - 1.839), p = 0.568	3-year DFS: not found in experimental arm vs. 85% non-inferiority HR margin of 1.53
Crivellari D, et al. [49]	BCFI	pegylated liposomal doxorubicin vs. low dose, metronomic cyclophosphamide + methotrexate	38 vs. 36	3-year BFCI: 78% vs. 78%	5-year BFCI: 74% vs. 65%, HR = 0.70
Pritchard KI, et al. [50]	EFS	tamoxifen + octreotide LAR vs. tamoxifen	334 vs. 333	EFS event: 108 vs. 112, HR = 0.93 (95% CI = 0.71 - 1.22), p = 0.62	5-year EFS: 81.2% vs. 73%, HR = 1.5
Mavroudis D, et al. [51]	DFS	epirubicin followed by docetaxel vs. epirubicin + docetaxel	329 vs. 329	5-year DFS: 92.6% vs 88.2%, HR = 1.591 (95% CI = 0.990 - 2.556), p = 0.055	5-year DFS: 70% vs. 65%, HR = 0.86
Kerbrat P, et al. [52]	DFS	6 cycles of 5-fluorouracil/epirubicin/cyclophosphamide vs. 4 cycles of 5-fluorouracil/epirubicin/cyclophosphamide	759 vs. 756	5-year DFS: 92.12% vs. 88.4%, HR = 1.18 (95% CI = 0.89 - 1.56), p = 0.24	5-year DFS: 83% vs. 77%, HR = 1.40
Foukakis T, et al. [53]	BCRFS	tailored dose-dense epirubicin + cyclophosphamide followed by tailored dose-dense docetaxel or fluorouracil + epirubicin + cyclophosphamide followed by docetaxel	1001 vs 999	118 events vs. 151 events (5-year BCRFS: 88.7% vs 85.0%), HR = 0.79 (95% CI = 0.61-1.01), p = 0.06	5-year BCRFS: 79% vs. 71%, HR: 0.54
Colleoni M, et al. [54].	DFS	low-dose cyclophosphamide + methotrexate maintenance (CM) vs. no CM	542 vs. 539	5-year DFS: 78.1% vs. 74.7%, HR = 0.84 (95% CI = 0.66 - 1.06), p = 0.14	5-year DFS: 77.9% vs. 70%, HR = 0.70
Gonçalves A, et al. [55]	DFS	dose-intense epirubicin-cyclophosphamide + docetaxel–5-fluorouracil vs. dose-intense epirubicin-cyclophosphamide alone	87 vs. 87	5-year DFS: 55.5% vs. 55%, HR = 0.94 (95% CI = 0.61 - 1.48), p = 0.81	5-year DFS: 54% vs. 45%, HR = 0.54
Kelly CM, et al. [56]	RFS	capecitabine + docetaxel followed by fluorouracil, epirubicin + cyclophosphamide (FEC) vs. paclitaxel followed by FEC	301 vs. 302	RFS: 87.5%; vs. 90.7%, p = 0.51	RFS: 92% vs. 85%, HR: not found

Trials	Primary endpoint	Exp. Arm vs. control arm	Sample size	Actual result	Pre-estimate
Dubsky PC, et al. [57]	RFS	tamoxifen followed by anastrozole vs. tamoxifen alone	1865 vs. 1849	RFS: 124 events vs. 152 events, HR = 0.80 (95% CI = 0.63 - 1.01), p = 0.06	RFS: not found, HR: not found
Vici P, et al. [58]	DFS	epirubicin + cyclophosphamide (EC) vs. docetaxel followed by EC	360 vs. 368	5-year DFS: 73.4% vs. 73.4%, HR = 0.99 (95% CI = 0.75 - 1.31, p = 0.95)	5-year DFS: 70% vs. 60%, HR = 0.70
Untch M, et al. [59]	DFS	epirubicin + cyclophosphamide + paclitaxel vs. epirubicin + paclitaxel + cyclophosphamide / methotrexate / fluorouracil	362 vs. 352	3-year DFS: 75.8% vs. 78.8%, HR = 1.14, p = 0.37	3-year DFS: 70% vs. 80%, HR = 1.4
Rao RD, et al. [60]	DFS	tamoxifen + fenretinide vs. tamoxifen + placebo	206 vs. 213	51 events vs. 44 events, HR = 1.21 (95% CI = 0.81 - 1.81, p = 0.36)	DFS: not found, HR = 0.67
von Minckwitz G, et al. [61]	DFS	zoledronate vs. observation	343 vs. 350	82 events (23.9%) vs. 87 events (24.9%), HR = 0.960 (95% CI = 0.709 - 1.30), p = 0.789	5-year DFS: 67.2% vs. 58%, HR = 0.73
Coleman R, et al. [62]	DFS	zoledronate + standard treatment vs. standard treatment alone	1681 vs. 1678	473 events (28.1%) vs. 493 events (29.4%), HR = 0.94 (95% CI = 0.82 - 1.06, p = 0.30)	3-year DFS: 78.7% vs. 75%, HR = 0.83
Delbaldo C, et al. [63]	DFS	5-fluorouracil + epirubicine + cyclophosphamide (FEC 100) followed by Taxol vs. FEC 100	420 vs. 417	5-year DFS: 78.4% vs. 78.5%, HR = 0.99 (95% CI = 0.77 - 1.26, p = 0.91)	5-year DFS: 78% vs. 70%, HR = 0.70
Cameron D, et al. [64]	Invasive DFS	chemotherapy + bevacizumab vs. chemotherapy	1301 vs. 1290	3-year IDFS: 83.7% vs. 82.7%, HR = 0.87 (95% CI = 0.72 - 1.07, p = 0.18)	5-year IDFS: 78.2% vs. 72.0%, HR = 0.75
Pivot X, et al .[65]	DFS	6 months vs. 12 months of adjuvant trastuzumab	1690 vs. 1690	2-year DFS: 91.1% vs. 93.8%, HR = 1.28 (95% CI = 1.05 - 1.56, p = 0.29); non-inferiority test	2-year DFS: 83% vs. 85%, The non-inferiority HR margin of 1.15
Goss PE, et al. [66]	DFS	lapatinib vs. placebo	1571 vs. 1576	DFS events: 13% vs. 17%, HR = 0.83 (95% CI = 0.70 - 1.00, p = 0.053)	Yearly recurrence: Not found in experimental arm vs. 9.6%, HR = 0.769
van de Velde	DFS	tamoxifen + exemestane vs. exemestane	4875 vs. 4904	5-year DFS: 86% vs. 85%, HR =	DFS: not found, HR =

Trials	Primary endpoint	Exp. Arm vs. control arm	Sample size	Actual result	Pre-estimate
CJ, et al .[67]		alone		0.97 (95% CI = 0.88 - 1.08, p = 0.60)	0.78
Perrone F, et al. [68]	DFS	weekly docetaxel vs. cyclophosphamide + methotrexate + fluorouracil	147 vs. 152	5-year DFS: 65% vs. 69%, HR = 1.21 (95% CI = 0.83 - 1.76, p = 0.32)	DFS: not found, HR = 0.65
Goss PE, et al. [69]	EFS	exemestane vs. anastrozole	3789 vs. 3787	4-year EFS: 91% vs. 91.2%, HR = 1.02 (95% CI = 0.87 - 1.18), p = 0.85	5-year EFS: 89.9% vs. 87.5%, HR = 0.80
Gogas H, et al. [70]	DFS	epirubicin + paclitaxel (sequential) vs. epirubicin + paclitaxel (concomitant)	551 vs. 535	5-year DFS 74% vs. 74%, HR: not found (p = 0.78)	3-year DFS 85% vs. 80%, HR: not found
Piccart-Gebhart M, et al. [71]	DFS	lapatinib + trastuzumab vs. trastuzumab	2093 vs. 2097	4-year DFS: 88% vs. 86%, HR = 0.84 (97.5% CI = 0.70 - 1.02), p = 0.048	2-year DFS: not found experimental arm vs. 85.55%, HR = 0.80
O'Shaughnessy J, et al. [72]	DFS	doxorubicin + cyclophosphamide + docetaxel + capecitabine vs. doxorubicin + cyclophosphamide + docetaxel	1307 vs. 1304	140 events (10.7%) vs. 164 events (12.6%), HR = 0.84 (95% CI = 0.67 - 1.05), p = 0.12	5-year DFS: not found experimental arm vs.75.2%, HR = 0.78
Joensuu H, et al. [73]	RFS	docetaxel + capecitabine + cyclophosphamide + epirubicin + capecitabine vs. docetaxel + cyclophosphamide + epirubicin + fluorouracil	753 vs. 747	5-year RFS: 86.6% vs. 84.1%, HR = 0.79 (95% CI = 0.60 - 1.04), p = 0.087	5-year RFS: 88.5% vs. 83.0%, HR = 0.65
Janni W, et al. [74]	DFS	epirubicin /cyclophosphamide + docetaxel vs. fluorouracil / epirubicin / cyclophosphamide	689 vs. 675	221 events (32.1%) vs. 190 events (28.1%), HR = 1.087 (95% CI = 0.878 – 1.346), p = 0.444	non-inferiority margin: HR = 1.15

pCR: pathological complete response, OS: overall survival, PFS: progression-free survival, TTP: time-to-progression, BCFL: breast cancer-free interval, BCRFS: breast cancer recurrence-free survival, DFS: disease-free survival, IDFS: invasive disease-free survival, RFS: recurrence-free survival, EFS: event-free survival, OR: odds ratio, CI: confidence interval, M: months, HR: hazard ratio

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