Systematic Review

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Adjuvant and Neoadjuvant Therapy for Breast Cancer: A Systematic Review

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ABSTRACT

Breast cancer (BC) is the most frequent type of cancer among women. The neoadjuvant therapy was administered before surgery, and the adjuvant therapy was administered post-surgery. The goal of this systematic review is to study the effects of adjuvant and neoadjuvant BC therapy on patient outcomes and mortality. In July 2023, systematic searches were conducted through the Cochrane Library, Web of Sciences, Google Scholar, EMBASE, and PubMed databases. The search method focused on studies that included all patients with BC stages 1, 2, and 3 and excluded studies that included patients with metastatic and recurrent BC. The risk of bias in the included studies was evaluated using the Cochrane risk of bias technique. Throughout our search, 27 relevant studies with 161,552 patients were discovered. Anti-human epidermal growth factor 2 therapy (trastuzumab, pertuzumab), chemotherapy (anthracycline), endocrine therapy (tamoxifen, aromatase inhibitor), and bisphosphonates were recommended treatments for BC patients. Choices for radiotherapy included whole breast, partial breast, tumor bed boost, regional nodes, and chest wall choices after breast-conserving surgery. We discover that while the majority of treatments reduced the mortality or recurrence rates of BC, anthracycline, chemotherapy, and radiation led to an overall rise in non-BC deaths. The systemic assessment discovered several variables that impact a patient's quality of life. Based on these advantages and disadvantages, various treatment options for patients and recommendations for groups of women are made.

Keywords: Breast cancer, adjuvant, neoadjuvant, oncology

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Key Points

- The systemic assessment discovered several variables that impact a patient's quality of life.
- The majority of treatments reduced the mortality or recurrence rates of breast cancer, anthracycline chemotherapy, and radiation led to an overall rise in non-breast cancer death.

Introduction

Breast cancer (BC) is the most prevalent malignancy in the world and the main reason women die from tumor-related causes. It causes 15% of all cancer deaths and roughly 30% of cancer cases in women (1-3). A multidisciplinary team is necessary to treat a patient with BC, whether by surgery or radiation therapy, as well as systemic therapies using a variety of medications (4).

Neoadjuvant chemotherapy (NACT) was introduced in the 1970s, aiming to downstage locally advanced inoperable cancer to operable cases. NACT was subsequently extended to operable early BC, mainly to allow breast-conserving surgery (BCS), and is now widely used, particularly for large tumors (5-8). Furthermore, NACT might be more likely to eradicate micro metastatic disease than chemotherapy delayed until after surgery. Despite their adverse events, these therapies decrease BC mortality and recurrence, so highly trained clinical decision-makers are needed (9, 10). In 2016, a systemic review and meta-analysis done in Boston found that neoadjuvant endocrine therapy (NET), mainly when administered alone, has significantly decreased toxicity and is linked to response rates that are comparable to those of neoadjuvant combination chemotherapy, suggesting that NET should be given another look as a potential therapeutic option under the proper conditions. To develop logical NET combinations and prognostic biomarkers, further research is necessary to determine the optimum neoadjuvant therapy for estrogen receptor-positive BC (11).

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In another study done in 2021 in China, a systemic review and meta-analysis found 3842 triple-negative breast cancer (TNBC) patients, and a total of nine randomized clinical trials (RCTs) were included. Overall, disease-free survival (DFS) and overall survival (OS) were markedly improved with combined capecitabine regimens in neoadjuvant and adjuvant chemotherapy (12).

In a Switzerland study in 2022, a systemic review and meta-analysis found that the 21 RCTs with 11 regimens of neoadjuvant anti-human epidermal growth factor receptor 2 (HER2) therapy (T-DM1PC, T-DM1, and PTC_T-DM1P) had a good combination of effectiveness and safety. In contrast, the pertuzumab, trastuzumab, and chemotherapy (PTC) regimen had the greatest DFS (13).

We present a systematic review of the data required to estimate the proportional benefits and risks of modern adjuvant and neoadjuvant treatment options recommended in current clinical guidelines for and their effects on mortality and patient outcomes.

Materials and Methods

Literature Search Strategy

This systematic review was prospectively registered in PROSPERO (CRD42023446212) and adhered to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines. A comprehensive electronic search was conducted by the Web of Sciences, Google Scholar, PubMed, Cochrane Library, and EMBASE databases for studies published between 2013 and 2023. The search strategy was designed independently by two authors and was approved by the rest of the team. An amalgamation of medical subject headings, such as "breast cancer", "adjuvant", and "neoadjuvant" was used to identify all studies inclusively. References to the selected studies were further reviewed to identify missing articles.

Inclusion/Exclusion Criteria

Two team members independently assessed each study using pre-defined inclusion and exclusion criteria-the inclusion criteria: All patients diagnosed with BC stage 1,2, and 3. Where the exclusion criteria are metastatic BC and recurrent BC, disagreements between reviewers regarding including a particular study were discussed and resolved through consensus. The studies included are RCTs, non-randomized studies, and observational studies with a control group. This process ensures that only relevant studies meeting the criteria are included in the review. The databases used to collect the included papers are Web of Sciences, Google Scholar, PubMed, Cochrane Library, and EMBASE.

Risk of Bias (Quality) Assessment

A risk-of-bias assessment was conducted to evaluate the internal validity of the included studies. More specifically, the Critical Appraisal Skills Programme (CASP) tool was used to minimize the risk of bias. Two independent reviewers conducted the assessment; they evaluated the studies for methods of randomization, treatment allocation, blinding, selection bias, performance bias, detection bias, attrition bias, and reporting bias. The risk of bias assessment was conducted at the study level.

Synthesis Methods

The criteria for data synthesis will be based on the minimum number of studies and the level of consistency. The data that will be synthesized will include outcomes related to adjuvant and neoadjuvant treatments of BC and their effects on mortality and patient outcomes.

All records resulting from the primary search were imported to Mendeley for deduplication. Then, the result was subsequently imported into Rayyan and screened by three authors for relevance based on the title and abstract. The full texts of all retained studies were then screened by all authors for final inclusion or exclusion. Disagreements at any stage of the screening process were resolved through discussion and consensus among all authors.

Data extracted for the retained studies included year, country, study sample, and study design. A meta-analysis was not possible due to the heterogeneity across the studies regarding interventions and outcomes.

Results

Study Characteristics

The 27 included studies consisting of 12 systematic reviews and meta-analyses, eight systematic reviews, three systematic reviews and network meta-analyses, two review articles, one meta-analysis, and one network of meta-analyses. All the included studies were published between 2013 and 2023. The sample size varied between studies, with a peak of 49,133. With a total of more than 215,853 participants, this systematic review covers a wide range of BC patients undergoing several BC interventions.

The stages of cancer were established to be early or late, with 11 studies emphasizing the early-stage intervention and five studies focusing only on the late-stage intervention. The remaining studies involved interventions with either mixed stages or irrespective of the cancer stage. The treatment was administered as neoadjuvant in 11 studies, nine as neoadjuvant plus adjuvant, and five as adjuvant.

Early-Stage Intervention

Different interventions have shown favorable outcomes in early-stage cancer treatment, including hormonal therapy, radiotherapy, targeted therapy, antimicrotubule agents, and chemotherapy. The findings suggest that a combination of these interventions can be beneficial in managing early-stage cancer, providing better survival rates, and reducing the risk of recurrence.

Neoadjuvant and adjuvant chemotherapy combined with capecitabine significantly improved both DFS and OS in the early stages, with a response rate of hazard ratio (HR) 0.75; 95% confidence interval (CI), 0.65–0.86 (Table 1) (12). Some interventions, such as NACT, were found to reduce mortality rates in early-stage cancer patients. Results suggest that trastuzumab plus chemotherapy may be more effective than chemotherapy alone in achieving pathological complete response (pCR) in HER2-positive BC patients undergoing neoadjuvant treatment with HER2-targeted therapies. The pooled results showed significantly higher pCR rates than chemotherapy, with a pooled relative risk (RR) of 1.81 (95% CI 1.36, 2.42) (Table 1) (13).

Targeted therapy has demonstrated promising results in improving OS and reducing the risk of recurrence (HR = 0.59, 95% CI: 0.51, 0.69), most effectively decreasing the risk of disease progression or recurrence among the comparisons (Table 2) (14).

Chemotherapy, both neoadjuvant and adjuvant, has effectively reduced mortality rates and improved survival outcomes. Significant improvement in OS was observed (HR = 0.85; 95% CI, 0.75–0.96; $p = 0.008$) (15).

Table 1. Summary of the 27 studies used for the adjuvant and neoadjuvant therapy for breast cancer systematic review

Author, year	Country	Study design	Number of participants	Stage of cancer	Type of intervention
Pinto et al. (22) 2013	Belgium	R	8,300	Early, late	Neoadjuvant + Adjuvant
Charehbili et al. (19) 2014	Netherlands	S	26 studies	Early, late	Neoadjuvant
Leal et al. (25) 2015	Brazil	SM	9 studies	Early, late	Neoadjuvant
Zhang et al. (28) 2015	China	SM	5,415	Early	Neoadjuvant
Zhang et al. (15) 2016	China	SM	9,097	Early	Neoadjuvant + Adjuvant
Spring et al. (11) 2016	USA, Boston	SM	3,490	Early, late	Neoadjuvant
Li and Shao (24) 2016	China	S	22,391	Early, late	Neoadjuvant + Adjuvant
Recht et al. (27) 2016	USA	S		Early	Adjuvant
De Felice et al. (18) 2017	Italy	SM	2,447	Late	Neoadjuvant
Pistelli et al. (33) 2018	Italy	S	6,812	Early, late	Neoadjuvant + Adjuvant
Zaheed et al. (31) 2019	Australia	R	1,695	Early	Neoadjuvant + Adjuvant
Shen et al. (14) 2019	USA, Texas	NM	13,621	Early	Adjuvant
Genuino et al. (30) 2019	Thailand	SM	10,635	Early	Adjuvant
Wang et al. (17) 2020	China	M	971	Late	Neoadjuvant
Surov et al. (35) 2020	Germany	SM	1,827	Early, late	Neoadjuvant
Huo et al. (12) 2021	China	SM	3,842	Early	Neoadjuvant + Adjuvant
Hong et al. (20) 2021	China	SM	1,028	Early, late	Neoadjuvant
Salvo et al. (34) 2021	Canada	SM	21 studies	Early	Adjuvant
Ahmed et al. (23) 2021	UK	S	3,766	Early, late	Neoadjuvant
Hickey et al. (36) 2021	USA	S	15,187	Early	
Kerr et al. (9) 2022	UK	S	13,864	Early	Neoadjuvant + Adjuvant
Nikyar et al. (26) 2022	Sweden	SM	17,224	Late	Adjuvant
Giordano et al. (16) 2022	United States	S	12,454	Late	Neoadjuvant + Adjuvant
Schettini et al. (29) 2022	Switzerland	SNM	49,133	Late	
Gunasekara et al. (13) 2022	Switzerland	SNM		Early	Neoadjuvant
Yuan et al. (21) 2022	China	SNM	12,024	Early, late	Neoadjuvant + Adjuvant
Ergun et al. (32) 2023	Turkey	SM	630	Early, late	Neoadjuvant

S: Systematic review; M: Meta-analysis; SM: Systematic review and meta-analysis; SNM: Systematic review and network meta-analysis; NM: Network of meta-analysis; R: Review articles, these 27 studies included 12 systematic reviews and meta-analyses, 8 systematic reviews, 3 systematic reviews and network meta-analyses, 2 review articles, 1 meta-analysis, and 1 network meta-analysis, with a total of more than 215,853 participants. In 11 studies, the patients were diagnosed with early-stage BC, and 5 studies focused on late-stage BC. The remaining studies involved interventions with either mixed stages or irrespective of the cancer stage. The treatment was administered as neoadjuvant in 11 studies, nine as neoadjuvant plus adjuvant, and five as adjuvant

Late-Stage Intervention

The findings contribute to understanding different interventions and their impact on outcomes in late-stage cancer, providing valuable information for clinical decision-making and treatment strategies. With emphasis on the importance of targeted therapies and antimicrotubule agents in achieving favorable outcomes for late-stage cancer patients. Trastuzumab as an adjuvant along with chemotherapy resulted in significant outcomes in terms of DFS [0.95 (95% CI, 0.71 to 1.25)] (Table 3) (16).

Additionally, the findings suggest that hormonal therapies cannot significantly improve OS or pCR. In a neo-adjuvant-based intervention study by Wang et al. (17), the rate of patients undergoing neoadjuvant hormonal therapy (NHT) was significantly lower than that of those undergoing NACT [odds ratio (OR), 0.48; 95% CI, 0.26–0.90]. Furthermore, NET and NACT had no statistically significant difference in the overall objective response rate (ORR) (pooled OR, 1.05; 95% CI, 0.73–1.52) (Table 3) (17).

Radiotherapy in late-stage cancer patients showed reduced locoregional recurrence (LRR). A study done by De Felice et al. in 2017 (18) shows that regional nodal irradiation was mainly associated with a reduction in the rate of LRR (4.3% *vs.* 6.8%) and a statistically significant improvement in 10-year DFS (82% *vs.* 77%, $p = 0.01$) and distant free survival (86.3% *vs.* 82.4%, $p = 0.03$) rates. In contrast, there was no significant difference in OS at ten years between groups (82.8% *vs.* 81.8%, $p = 0.38$) (Table 3) (18).

Aromatase inhibitors (AI) as a hormonal neoadjuvant were found to have higher response rates and better outcomes compared to tamoxifen in terms of clinical response, radiological response, and BCS. In a study

Table 2. Summary of early-stage breast cancer interventions

Author, year	Intervention	Class	Response rate	Survival rate	Recurrence rate
Zhang et al. (15) 2016	B	C	HR 0.85; (95% CI, 0.75–0.96)	DFS (HR 0.93; 95% CI, 0.85–1.02)	
Zaheed et al. (31) 2019	B	C	RR 1.15 (0.96 to 1.38)	HR 0.80, (95% CI, 0.60 to 1.08)	
Huo et al. (12) 2021	B	C	HR 0.75; (95% CI, 0.65–0.86)	HR 0.63; (95% CI, 0.53–0.77)	
Shen et al. (14) 2019	A	T	HR 0.59, (95% CI, 0.51, 0.69)		HR 0.59, (95% CI, 0.51, 0.69)
Genuino et al. (30) 2019	A	C/T		Reduce mortality by 33%	RR (95% CI, 21.6% for C/T *vs.* 29.4% for C
Kerr et al. (9) 2022	B	C/H		Reduce mortality 10–25%	RR 1.37, (95% CI, 1.17–1.61)
Salvo et al. (34) 2021	A	H			17.2% (95% CI, 14.6%–20.3%)
Recht et al. (27) 2016	A	R		DFS 21.0%, *vs.* 4.3%	45.5% without *vs.* 33.8%
Hickey et al. (36) 2021		R		Similar	RR 2.83 (95% CI, 1.23–6.51)
Zhang et al. (28) 2015	N	R		RR 0.88, (95% CI, 0.66–1.17)	RR 2.83, (95% CI, 1.23–6.51)
Gunasekara et al. (13) 2022	N	C/T	RRs (95% CI) of 1.81 (1.36, 2.42)		HR (95% CI) of 0.54 (0.32–0.91).

OS: Overall survival; HR: Hazard ratio; RR: Risk ratio; LRR: Locoregional recurrance; OR: Overall response; DFS: Disease free survival; H: Hormonal; R: Radiotherapy; T: Targeted; AM: Antimicrotubule agent; C: Chemotherapy; N: Neoadjuvant; A: Adjuvant; B: Neoadjuvant + adjuvant; CI: Confidence interval, the table summarizes various interventions and their outcomes in early-stage cancer patients. It includes information on response rates, survival rates, and recurrence rates from different stud-ies and authors. Interventions range from chemotherapy to targeted therapy, with some studies showing reductions in mortality rates and recurrence rates, while others indicate no significant difference or even increased risk

Table 3. Summary of late-stage breast cancer interventions

Author, year	Intervention	Class	Response rate	Survival rate	Recurrence rate
Wang et al. (17) 2020	N	H	OR 1.05; (95% CI, 0.73–1.52)	HR 0.92; (95% CI, 0.55–0.94)	
Nikyar et al. (26) 2022	A	R	HR 0.24; (95% CI 0.11–0.49)		LRR HR 0.59; (95% CI 0.42–0.81)
De Felice et al. (18) 2017	N	R		OS 82.8% *vs.* 81.8% (without)	LRR: 4.3% vs. 6.8% (without)
Giordano et al. (16) 2022	A	T	1.09 (90% CI, 0.97 to 1.21)	DFS [0.95 (95% CI, 0.71 to 1.25)]	
Schettini et al. (29) 2022	B	AM	OR 6.57, (95% Crl: 2.05–21.63)		

OS: Overall survival; HR: Hazard ratio; LRR: Locoregional recurrence; OR: Overall response; DFS: Disease free survival; H: Hormonal; R: Radiotherapy; T: Targeted; AM: Antimicrotubule agent; N: Neoadjuvant; A: Adjuvant; B: Neoadjuvant + adjuvant; CI: Confidence interval, the table presents interventions and their outcomes in late-stage cancer patients. It includes response rates, survival rates, and recurrence rates from various authors and studies. Interventions span from ne-oadjuvant to adjuvant therapies, with results showing varied impacts on overall survival, disease-free survival, and locoregional recurrence. Some interventions demonstrate significant improvements in sur-vival rates and recurrence rates, while others show no significant difference or even increased risk

by Spring et al. (11), there was a significantly higher clinical response rate (OR, 1.69; 95% CI, 1.36–2.10; $p<0.001$; n = 1352), radiological response rate (OR, 1.49; 95% CI, 1.18–1.89; $p<0.001$; n = 1418), and BCS rate (OR, 1.62; 95% CI, 1.24–2.12; $p<0.001$; n = 918) compared with tamoxifen (11). Furthermore, a study by Charehbili et al. (19) shows similar findings when it comes to the comparison of AI and tamoxifen in terms of a response rate of 70% for AI *vs.* 51% for Tyro3, Axl and MerTK (TAM) in a third study by Hong et al. (20). The pCR is: OR = 0.34, 95% CI = 0.04–2.85, $p = 0.318$. Leal et al. (25), 2015, reported a significant overall response and found the response rate to be OR 1.9; 95% CI 1.17–3.08 (Table 4).

Table. 4 Summary of early and late breast cancer interventions

Author, year	Intervention	Class	Response rate	Survival rate	Recurrence rate
Spring et al. (11) 2016	N	H	OR, 1.69; 95% CI, 1.36–2.10; p<0.001		3.3 for hormonal and 3.4% for chemotherapy
Ergun et al. (32) 2023	N	C/H	82% *vs.* 72.7%; OR:1.77, 95% CI, 1.20–2.62		
Charehbili et al. (19) 2014	N	H	70% for AI *vs.* 51% for TAM		
Li and Shao (24) 2016	B	C/H/T	RR 1.29; 95% CI, 1.14–1.47;	HR 0.79 (0.69–0.90)	15 years 33% for TAM *vs.* 46.2% without
Surov et al. (35) 2020	N	C	35.6% responders		
Hong et al. (20) 2021	N	H	OR 0.34, 95% CI, 0.04–2.85		
Pistelli et al. (33) 2018	B	H	HR 0.72; 95% CI, 0.60 to 0.85	DFS 92.8% with TAM	>25 BMI 50% recurrence with anastrozole
Leal et al. (25) 2015	N	H	OR 1.9; 95% CI, 1.17–3.08		
Ahmed et al. (23) 2021	N	R		61.4% to 81% at 5 years	0.8%–10% for local recurrence
Yuan et al. (21) 2022		C	RR: 0.98, 95% CI, 0.93–1.03	HR: 0.84, 95% CI, 0.73–0.97	
Pinto et al. (22) 2013	B	C/T		OS 0.66 [95% (95% CI) 0.57e0.77]	0.65 (95% CI, 0.55, 0.75)

OS: Overall survival; HR: Hazard Ratio; LRR: Locoregional recurrence; OR: Overall response; DFS: Disease free survival; H: Hormonal; R: Radiotherapy; T: Targeted; AM: Antimicrotubule agent; N: Neoadjuvant; B: Neoadjuvant + Adjuvant; AI: Aromatase inhibitor; TAM: tamoxifen BMI: Body mass index CI: Confidence interval, the table provides data on interventions and their outcomes in both early and late-stage cancer therapy. Authors and studies examine various intervention classes, including neoadjuvant, chemotherapy, hormonal therapy, and targeted therapy. Results show response rates, survival rates, and recurrence rates, with some interventions indicating significant improvements in survival and response rates while others show mixed or inconclusive results. Notably, hormonal therapies like aromatase inhibitors and tamoxifen demonstrate varied impacts on recurrence rates, with some studies suggesting significant re-ductions in recurrence

Chemotherapy in a study by Yuan et al. (21) found that trastuzumab combined with lapatinib therapy was found to be superior to standard trastuzumab therapy alone in terms of OS, DFS/event-free survival, and pathologic complete response. Illustrating the response rate to be RR: 0.98, 95% CI: 0.93–1.03, and the survival rate to be HR: 0.84, 95% CI: 0.73–0.97, Another study by Pinto et al. (22) found that trastuzumab has improved both DFS and OS in patients with early HER-2-positive BC with moderate-to-high risk of recurrence when given in combination with or in sequence with adjuvant chemotherapy. The study reports the survival rate to be OS = 0.66 [95% (CI 95%) 0.57e0.77] and the recurrence rate to be 0.66 (95% CI: 0.57–0.77) and the recurrence rate to be 0.65 (95% CI: 0.55–0.75) (Table 4).

For radiotherapy, a study by Ahmed et al. (23) shows the five-year survival to be 61.4% to 81% and the local recurrence to be 0.8–10% (Table 4).

Intervention Efficacy

AI as a neoadjuvant had higher response rates and better outcomes than tamoxifen in clinical response, radiological response, and BCS. A study done by Spring et al. (11) shows a significantly higher clinical response rate (OR, 1.69; 95% CI, 1.36–2.10; p<0.001; n = 1352), radiological response rate (OR, 1.49; 95% CI, 1.18–1.89; p<0.001; n = 1418), and BCS rate (OR, 1.62; 95% CI, 1.24–2.12; p<0.001; n = 918) compared with tamoxifen. Moreover, a study by Li and Shao (24) reports that AIs have shown superiority over tamoxifen in terms of clinical response rate and breast conservation rate in neoadjuvant therapy where OS (relative HR = 0.82; 95% CI, 0.69–0.99). A third study that compares AI to tamoxifen illustrates a reduction in BC mortality or recurrence by 10–25%. Kerr et al. (9). Lastly, a study by Leal et al. (25) reports an ORR (OR 1.9; 95% CI 1.17–3.08) (Table 5).

A study by Charehbili et al. (19) illustrates that the favorable toxicity profile of NHT makes it a very suitable treatment option for patients unfit for chemotherapy. Studies have shown that AIs, rather than tamoxifen, are the preferred agents for NHT in postmenopausal patients. Longer treatment durations demonstrated more significant clinical responses and BCS rates with acceptable tolerability (70.4% vs. 50.5%, p = 0.004).

A subgroup analysis done Hong et al. (20) showed that all three types of cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors improved the complete clinical and pathological response rate in BC patients, with similar efficacy to NACT and a decreased risk of adverse events. Patients who received ribociclib were over ten times more likely to

Table 5. Summary of included studies

Study	Main drug	Type of intervention	Control	Response			
				Disease free survival	Recurrence	Pathological complete response	Overall response clinical/radiological
Zhang et al. (15) 2016	Cape	NACT	NA	HR: 0.93; (95% CI, 0.85–1.02; $p = 0.12$)			HR 0.85; (95% CI, 0.75–0.96; $p = 0.008$)
Spring et al. (11) 2016	AI	NHT	TAM				OR: 1.69; (95% CI, 1.36–2.10; $p<0.001$)
Wang et al. (17) 2020	Mulitple	NHT	NACT			OR: 0.48; (95% CI, 0.26-0.90)	OR: 1.05; (95% CI, 0.73–1.52)
Zaheed et al. (31) 2019	Taxanes	NHT	AC	HR: 0.84, (95% CI 0.65 to 1.09)		RR 1.15, (95% CI 0.96 to 1.38; 1280)	HR 0.80, (95% CI 0.60 to 1.08)
Huo et al. (12) 2021	Cape	NACT	Without	HR: 0.75; (95% CI, 0.65–0.86; $p<0.001$)			HR: 0.63; (95% CI, 0.53–0.77; $p<0.001$)
Shen et al. (14) 2019	Tras	AT	AC+ CP+ TAX				HR: 0.59, (95% CI, 0.51, 0.69)
Ergun et al. (32) 2023	CT+ H	NHT	NACT			(6.5% vs. 3.8%; OR:1.72, 95% CI 0.82–3.62).	ORR (82% *vs.* 72.7%; OR: 1.77, 95% CI 1.20–2.62)
Charehbili et al. (19) 2014	AN	NHT	TAM				70.4% *vs.* 50.5%, $p = 0.004$
Li and Shao (24) 2016	TAM	NHT	AI				RH 0.82; (95% CI, 0.69–0.99)
Genuino et al. (30) 2019	Tras	AT	AC		HRs: 0.65 (95% CI: 0.55, 0.75, $p<0.001$)		
Kerr et al. (9) 2022	TAM+AI	NHT	TAM		0.67 (95% CI 0.61–0.73)		
	Ribo	KI	TAM			OR 10.31, (95% CI = 3.59–29.61, $p<0.001$)	
Hong et al. (20) 2021	Palbo	KI	TAM			OR 7.39, (95% CI = 1.26–43.40, $p = 0.027$)	
	Abema	KI	TAM			OR 8.28, (95% CI = 3.41–20.11, $p<0.001$)	
Pistelli et al. (33) 2018	TAM	NHT	AN	92.8% with TAM, 92.0% with AN			
Nikyar et al. (26) 2022	NACT then ART	R	NACT		HR 0.59; (95% CI 0.42–0.81; $p<0.001$)	HR 0.24; (95% CI 0.11–0.49; $p<0.0001$)	
Leal et al. (25) 2015	AI	NHT	TAM				OR 1.9; 95% CI 1.17–3.08
Salvo et al. (34) 2021	TAM	NHT	Letrozole		17.2% (95% credible interval: 14.6–20.3%)		
Ahmed et al. (23) 2021	NRT	NRT	Multiple	61.4% to 81% at 5 years	0.8–10% for local recurrence	14% to 42%	OS 71.6% to 84.2%

Table 5. Continued

Study	Main drug	Type of intervention	Control	Response			
				Disease free survival	Recurrence	Pathological complete response	Overall response clinical/radiological
Recht et al. (27) 2016	R	ART	Without	21.0%, compared to 4.3%	45.5% without vs. to 33.8% with		
Zhang et al. (28) 2015	IORT	R	EBRT	0.88 (95% CI: 0.66–1.17)	RR for IBTR was 2.83 (95% CI 1.23–6.51)		
Giordano et al. (16) 2022	Tras+ CT	AT	Biosimilar + CT	0.95 (95% CI: 0.71 to 1.25)		1.09 (90% CI, 0.97 to 1.21)	
	PTX± Bev	AMA	CP + MTX + 5-FU			OR 6.57, (95 % CrI: 2.05–21.63)	
Schettini et al. (29) 2022	PTX± Bev	AMA	AC+-CP+ TAX			OR 3.45, 95 %CrI	
	PTX± Bev	AMA	Cape + Bev			OR 2.47, (95 %CrI:1.08–5.73)	
	Tras + CT	NAT	CT		HR (95% CI) of 0.54 (0.32–0.91).	RRs (95% CI) of 1.81 (1.36, 2.42; I2 = 0%)	
Gunasekara et al. (13) 2022	TYK + CT	NAT	Tras + CT			RR of 0.74 (95% CI 0.63, 0.87).	
	TYK+ Tras+ CT	NAT	Tras + CT			RRs of 1.26 (95% CI 1.11, 1.42)	
	TYK+ Tras+ CT	NAT	TYK+ CT			RRs 1.66 (95% CI 1.33, 2.06)	
Yuan et al. (21) 2022	Tras + TYK	AT	Tras	HR 1.22, (95% CI: 1.05–1.41, $p = 0.008$)			
	TYK	NAT	Tras				
Pinto et al. (22) 2013	Tras	AT		0.60 (95% CI 0.50–0.71, $p<0.00001$)	reduced by 40%		

OS: Overall survival; HR: Hazard ratio; LRR: Locoregional recurrence; RH: Relative hazard; OR: Overall response; DFS: Disease free survival; H: Hormonal; R: Radiotherapy; T: Targeted; AM: Antimicrotubule agent; N: Neoadjuvant; B: Neoadjuvant + Adjuvant; AI: Aromatase inhibitor; NACT: Neoadjuvant chemotherapy; NHT: Neoadjuvant hormonal therapy; AT: Adjuvant targeted therapy; KI: Kinase inhibitor; NRT: Neoadjuvant radiotherapy; ART: Adjuvant radiotherapy; AMA: Antimicrotubule agent; NAT: Neoadjuvant targeted therapy; CT: Chemotherapy; NA: Neo-adjuvant; TAM: tamoxifin; Tras: Trastuzumab; TYK: Lapatinib; PBI: Partial breast irradiation; IORT: Intraoperative radiotherapy; Bev: Bevacizumab; PTX: Paclitaxel; Ribo: Ribociclib; Palbo: Palbociclib; Abema: Abemaciclib; Cape: Capecitabine; AN: Anastrozole; WBRT: Whole breast radiotherapy; EBRT: Whole-breast external beam radiotherapy; AC: Anthracyclines; CP: Cyclophosphamide; MTX: Methotrexate; 5-FU: 5-fluorouracil; TAX: Taxane, the table provides a summary of the included studies in this systematic review, including the type of intervention, disease-free survival, recurrence, pathological complete response, and radiological response

achieve complete cell cycle arrest (CCCA) than those who did not. The 95% CI for this OR was 3.59–29.61, which means there is a high degree of certainty that the actual OR falls within this range. Similarly, the OR for palbociclib was 7.39, with a 95% CI of 1.26–43.40, and the OR for abemaciclib was 8.28, with a 95% CI of 3.41–20.11. These results suggest that all three CDK 4/6 inhibitors effectively improve CCCA, although the degree of improvement may vary (Table 5).

In a study by Nikyar et al. (26) adjuvant locoregional radiation therapy (LRRT) significantly reduced the risk of LRR in patients with N+ at diagnosis and ypN0 (HR 0.59; 95% CI 0.42–0.81). However, no statistically significant difference was found in DFS or OS. Moreover, a subgroup analysis including three studies with data on the impact of LRRT on LRR in patients with pCR (both ypT0 and ypN0) showed a statistically significant lower risk of LRR in patients who received LRRT (HR 0.24; 95% CI 0.11–0.49; $p<0.0001$) (Table 5).

Another study by Ahmed et al. (23) for patients who received neo-adjuvant radiotherapy (NRT) found that pCR values ranged from 14% to 42% in the patients who received NRT, and the 5-year DFS rates ranged from 61.4% to 81% in the patients who received NRT. Moreover, the 5-year OS rates ranged from 71.6% to 84.2% in the patients who received NRT (Table 5).

A study by Recht et al. (27) illustrates that postmastectomy radiotherapy (PMRT) reduces the risks of locoregional failure (LRF), recurrence, and BC mortality. Reporting the DFS to be 21.0% with PMRT, compared to 4.3% without the intervention. Along with a recurrence rate of 33.8% with PMRT *vs.* 45.5% without (Table 5).

Ipsilateral breast tumor recurrence (IBTR) was significantly higher in patients with intraoperative radiotherapy (IORT) compared to those with whole-breast external beam radiotherapy, with a risk ratio (RR) of 2.83 (95% CI 1.23–6.51). However, the two treatment modalities had no significant difference in overall mortality, with a pooled RR of 0.88 (95% CI: 0.66–1.17). Zhang et al. (Table 5) (28).

For antimicrotubule agents, a study done Schettini et al. (29) shows that paclitaxel + bevacizumab was likely to be significantly associated with superior ORR than several poly- chemotherapy regimens like cyclophosphamide + methotrexate + 5-fluorouracil [OR: 6.57, 95% credible intervals (CrI): 2.05–21.63], FEC (OR: 4.44, 95% CrI: 1.33–15.23), ixabepilone + capecitabine (OR: 3.45, 95% CrI: 1.02–12.03), or capecitabine + bevacizumab (OR: 2.47, 95% CrI: 1.08–5.73) (Table 5).

Results suggest that trastuzumab chemotherapy (TC) and lapatinib trastuzumab chemotherapy (LTC) may be more effective than chemotherapy (C) or lapatinib chemotherapy (LC) in achieving pCR in HER2-positive BC patients undergoing neoadjuvant treatment with HER2-targeted therapies. The pCR rates for four different treatment comparisons were TC vs. C, LC vs. TC, LTC vs. TC, and LTC vs. LC. The pooled results of a study by Gunasekara et al. (13) showed that TC had significantly higher pCR rates than C, with a pooled RR of 1.81 (95% CI 1.36, 2.42). Similarly, LTC had significantly higher pCR rates than TC and LC, with pooled RRs of 1.26 (95% CI 1.11, 1.42) and 1.66 (95% CI 1.33, 2.06), respectively. Conversely, LC had significantly lower pCR rates than TC, with a pooled RR of 0.74 (95% CI 0.63, 0.87) (Table 5).

Efficacy of different adjuvant trastuzumab-containing chemotherapy combinations for patients with early HER2-positive primary BC. For severe cardiac adverse events. A study by Shen et al. (14) based on their analysis, found that anthracycline-cyclophosphamide with concurrent trastuzumab (ACT+H) showed the best OS compared to other combinations. Compared to ACT, ACT+H (HR = 0.59, 95% CI: 0.51, 0.69) most effectively decreased the risk of disease progression or recurrence among the comparisons. In another study by Genuino et al. (30), The analysis found that combining trastuzumab with chemotherapy lowered the risks of death and relapse by one-third, with recurrence rates (95% CI) of 21.6% (16.6%, 26.5%) for the trastuzumab-chemotherapy group and 29.4% (24.6%, 34.2%) for the chemotherapy alone group. In a third study, Giordano et al. (16) found that in 2022, trastuzumab has shown efficacy in improving progression-free survival (PFS) by 1.09 (90% CI, 0.97 to 1.21), and DFS 0.95 (95% CI, 0.71 to 1.25), and OS in patients with advanced HER2-positive BC. Lastly, a study by Pinto et al. (22) in 2013 found that trastuzumab, when given in combination with or in sequence with adjuvant chemotherapy, has shown a significant improvement in disease-free and OS in women with HER2-positive BC, reducing mortality by one-third and the risk of relapse by 40% (Table 5).

In a study by Zhang et al. (15), Adding capecitabine to standard neoadjuvant regimens in early BC. Adding capecitabine did not improve DFS for all patients. DFS (HR = 0.93; 95% CI, 0.85–1.02; p = 0.12) However, a sub-analysis revealed that capecitabine provided a benefit in DFS for patients with the triple-negative subtype and extensive axillary involvement. The addition of capecitabine demonstrated a significantly superior OS in the meta-analysis (HR = 0.85; 95% CI, 0.75–0.96; p = 0.008). In another study by Huo et al. (12) in 2021, it was found that capecitabine-based regimens in neoadjuvant and adjuvant chemotherapy showed significantly improved DFS (HR = 0.75; 95% CI, 0.65-0.86; p<0.001) and OS (HR = 0.63; 95% CI, 0.53–0.77; p<0.001) in early-stage TNBC patients (Table 5).

The study by Wang et al. (17) suggests that postmenopausal HR-positive BC patients may have a better tumor response after NACT compared to NET, while the addition of endocrine therapy to chemotherapy may not provide significant clinical benefits compared to monotherapy. The pCR rate of patients undergoing NET was significantly lower than that of those undergoing NACT. (pooled OR, 0.48; 95% CI, 0.26–0.90) There was no statistically significant difference in the ORR between NET and NACT. (pooled OR, 1.05; 95% CI, 0.73–1.52) (Table 5).

The neoadjuvant studies done by Zaheed et al. (31) in 2019 suggested that the administration of taxanes first probably resulted in little to no difference in OS (HR 0.80, 95% CI 0.60 to 1.08) and DFS (HR 0.84, 95% CI 0.65 to 1.09). The administration of taxanes first also resulted in little to no difference in pathological complete response (RR 1.15, 95% CI 0.96 to 1.38) (Table 5).

In the HR-positive/HER2-negative BC study by Ergun et al. (32) in 2023, NACT significantly increased ORR without an increase in serious adverse events. Although the pCR rate increased numerically, it was not statistically significant. (6.5% *vs.* 3.8%; OR: 1.72, 95% CI 0.82–3.62). The study also reports that the NaCET arm exhibited a significantly higher ORR (82% *vs.* 72.7%; OR: 1.77, 95% CI: 1.20–2.62) (Table 5).

Discussion and Conclusion

Neoadjuvant and adjuvant treatments are recommended for BC. These therapies reduce cancer mortality and recurrence but have adverse effects. Therefore, this systematic review aims to study BC's adjuvant and neoadjuvant treatments and their effects on mortality and patient outcomes.

Anti-Human Epidermal Growth Factor 2 Therapy with Chemotherapy

Neoadjuvant and adjuvant therapies combining trastuzumab with chemotherapy have shown significant efficacy in improving DFS and OS in patients with early-stage and locally advanced HER2-positive BC. Gunasekara et al. (13) concluded that the T-DM1PC (trastuzumab emtansine + pertuzumab + chemotherapy), T-DM1 (trastuzumab emtansine), and PTC_T-DM1P (pertuzumab + trastuzumab + chemotherapy followed by T-DM1P) regimens are the most effective and safe neoadjuvant anti-HER2 therapies for early-stage and locally advanced HER2-positive BC. These regimens have the optimal balance between efficacy (pCR) and serious adverse events (SAE). The PTC regimen has the highest DFS rate among these regimens.

Additionally, Pinto et al. (22) reported that using trastuzumab in combination with or in sequence with adjuvant chemotherapy has significantly improved the DFS and OS of patients with early HER-2-positive BC with a moderate-to-high risk of recurrence. The patient outcomes were also concluded by Giordano et al. (16) that adding trastuzumab to chemotherapy as adjuvant therapy significantly improves DFS outcomes.

Moreover, Shen et al. (14) concluded that the concurrent use of anthracycline-cyclophosphamide and taxane or taxane plus carboplatin with trastuzumab resulted in the most clinical benefits for early-stage HER2-positive primary BC. Additionally, taxane and carboplatin with trastuzumab had the lowest cardiotoxicity. This is proved by Genuino et al. (30) that administering adjuvant trastuzumab in a weekly cycle concurrently with an anthracycline-taxane chemotherapy regimen appears to be a preferred option to optimize its favorable effect on improving DFS and preventing significantly higher risk for cardiotoxic effects.

Endocrine/Hormone Therapy Comparable to Chemotherapy

NHT is comparable in efficacy to NACT in hormone receptor-positive (HR+) BC patients with lower toxicity, but there is a higher risk of recurrence in node-positive patients. Spring et al. (11) concluded that NET, even as monotherapy, is associated with similar response rates as neoadjuvant combination chemotherapy but with significantly lower toxicity. It was also proved by Hong et al. (20) that the combination therapy comprising neoadjuvant CDK 4/6 inhibitors and NET demonstrated increased efficacy and toxicity compared to endocrine monotherapy. It also showed comparable efficacy and better safety than NACT. Evidence has been accrued by Li and Shao (24) of the benefits of ovarian ablation or suppression in premenopausal patients and AIs in postmenopausal patients for longer durations of adjuvant NET as well as for the clinical utility of NET.

Moreover, Leal et al. (25) reported the safety of neoadjuvant hormone therapy and reported that it could not be considered equivalent to chemotherapy. Additionally, it was reported that AIs are preferable to tamoxifen when using neoadjuvant hormone therapy due to their higher response rates. It could be proved by Pistelli et al. (33) that in premenopausal patients with HR+BC, the combination of AIs and a gonadotropin hormone-releasing hormone analog is a safe and effective treatment option. Charehbili et al. (19) reported that NHT has shown comparable efficacy to NACT in patients with HR+ BC. However, Wang et al. (17) reported that postmenopausal women with HR+ BC can respond better to tumor treatment with NACT than NET. Although neoadjuvant chemoendocrine therapy has improved prognostic outcomes compared to NET or NACT alone, such benefits may not be observed in this specific group of patients. Similar to other findings by Ergun et al. (32), the combination of NACT and NET leads to an increased ORR in patients with BC without a significant increase in SAE.

Additionally, Yuan et al. (21) reported that the effectiveness of combining pyrotinib with chemotherapy is superior to combining lapatinib with chemotherapy in the treatment of BC but has more safety risks. However, Salvo et al. (34) concluded that there is a high risk of BC recurrence, particularly among node-positive patients. Approximately 1 in 6 women with node-positive HR+/HER2-early-stage BC who undergo NET experience recurrence or death within five years of starting the treatment.

Chemotherapy

Anthracyclines and taxanes are commonly used chemotherapeutic agents for early-stage BC, but recent studies have identified risks associated with these drugs. Additionally, the benefits of combining neoadjuvant and adjuvant chemotherapy with capecitabine are mentioned for improved outcomes. Zaheed et al. (31) reported that anthracyclines and taxanes are effective chemotherapeutic agents commonly used in treating early-stage BC, either before or after surgery. Schettini et al. (29) reported that nab-paclitaxel had the highest overall response rates, while capecitabine and eribulin had the highest PFS and OS rates, respectively. It was also proved by Huo et al. (12) that combining neoadjuvant and adjuvant chemotherapy with capecitabine significantly improved DFS and OS in early-stage triple-negative BC patients with tolerable adverse events.

Moreover, Zhang et al. (15) concluded that adding capecitabine to neoadjuvant therapy did not improve DFS but OS. Furthermore, the toxicity profile of capecitabine remained favorable, and no capecitabine-related deaths were reported in the included trials. Additionally, Kerr et al. (9) reported an increased risk of leukemia associated with taxanes, while the risk of heart disease and leukemia is associated with anthracyclines. Surov et al. (35) concluded that the pretreatment apparent diffusion coefficient alone cannot predict the response to NACT in BC.

Radiotherapy

Neoadjuvant and adjuvant radiotherapy options can reduce LRR in BC, but their impact on OS varies, while IORT carries a higher risk of tumor recurrence. Ahmed et al. (23) reported that BC treatment could involve neoadjuvant radiotherapy, which can streamline oncological treatment, provide chemosensitization to enhance pCR before definitive surgery and provide treatment alternatives to ER-positive patients who are less likely to respond to chemotherapy. Moreover, De Felice et al. (18) concluded that regional nodal irradiation could reduce the LRR rate and improve disease-free and distant-free survival rates but did not significantly differ in OS at ten years. It was also proved by Nikyar et al. (26) that adjuvant LRRT after NACT can significantly reduce the risk of LRR but does not provide any survival benefit regarding DFS or OS. According to the Kerr et al. (9) study, radiotherapy options for BC include whole breast, partial breast, tumor bed boost, regional nodes after BCS, and chest wall and regional nodes after mastectomy. The study also found that anthracycline chemotherapy and radiotherapy may increase overall non-breast-cancer mortality.

Additionally, the authors identified heart disease, lung cancer, and esophageal cancer as the main radiation risks, with the risk increasing with higher doses of radiation to the heart, lungs, and esophagus, respectively. Moreover, the authors recommended bisphosphonate therapy for BC treatment. Recht et al. (27) also concluded that PMRT reduces the risks of LRF, LRR, and BC mortality for tumor BC patients with one to three positive axillary nodes. Hickey et al. (36) reported that altered fraction size regimens of radiation therapy do not have a clinically meaningful effect on local recurrence, are associated with decreased acute toxicity, and do not seem to affect breast appearance, late toxicity, or patient-reported quality-of-life measures for selected women treated with BCS. Moreover, Zhang et al. (28) concluded that IORT has a significantly higher risk of IBTR than whole-breast external beam radiotherapy. Overall mortality does not differ significantly.

Patient's Outcome Regarding Adjuvant and Neoadjuvant Therapy

AIs as neoadjuvant have higher response rates, improved outcomes, and better BCS results compared to tamoxifen. Similarly, Spring et al. (11) and Li and Shao (24) studies reported higher efficacy of AIs than tamoxifen. It could be explained by the Kerr et al. (9) study, which proved using AIs led to a reduction in BC mortality or recurrence by 10–25% as compared to tamoxifen. Leal et al. (25) also reported a higher ORR of AIs than tamoxifen in postmenopausal patients.

Moreover, Charehbili et al. (19) reported that NHT's favorable toxicity profile makes it an optimal treatment for patients unfit for chemotherapy.

In HER2-positive BC patients undergoing neoadjuvant HER2-targeted therapy, trastuzumab, and LTC may be more effective than chemotherapy or LC in achieving pCR. Gunasekara et al. (13) reported that TC had significantly higher pCR rates than chemotherapy, and LTC had significantly higher pCR rates than TC and/or LC. According to adjuvant therapy, trastuzumab-containing chemotherapy combinations showed the best OS compared to other combinations. Shen et al. (14) reported that anthracycline-cyclophosphamide with concurrent trastuzumab resulted in better OS compared to anthracycline-cyclophosphamide, reducing the risk of disease progression or recurrence. The reason could be that Genuino et al. (30) and Pinto et al. (22) studies proved that combining trastuzumab with chemotherapy showed a significant reduction of one-third in the risks of death and relapse, leading to decreased recurrence rates. Moreover, Giordano et al. (16) reported the high efficacy of trastuzumab in improving PFS, DFS, and OS in patients with advanced HER2-positive BC. In HR-positive/HER2-negative BC patients, NACT significantly increases ORR without an increase in serious adverse events, as stated by Ergun et al. (32). Moreover, Wang et al. (17) reported that NACT had a better tumor response NET in postmenopausal HR-positive BC patients.

In early-stage BC, capecitabine-based treatments in neoadjuvant and adjuvant chemotherapy showed significantly improved DFS and OS. This could be explained by the Huo et al. (12) meta-analysis study that proved these findings. However, Zhang et al. (15) reported that adding capecitabine to standard neoadjuvant regimens in early BC did not improve DFS.

Additionally, Schettini et al. (29) reported that paclitaxel + bevacizumab had superior ORR than several poly-chemotherapy regimens like ixabepilone + capecitabine or capecitabine + bevacizumab.

The adjuvant LRRT can reduce the risk of LRR. Nikyar et al. (26) stated the same finding; however, no statistically significant difference was found in DFS and OS. Neo-adjuvant radiotherapy can result in variable pCR values and 5-year survival rates, as stated by Ahmed et al. (23). Additionally, it was proved by Recht et al. (27) and Zhang et al. (28) studies that PMRT reduces the risks of LRF and LRR, and IORT is associated with a higher risk of IBTR compared to whole-breast external beam radiotherapy.

The study conducted a comprehensive search across multiple databases, including Web of Sciences, Google Scholar, PubMed, Cochrane Library, and EMBASE, which captured relevant studies and minimized selection bias. It also conducted a risk of bias assessment using the CASP tool, which helped to assess the internal validity of the included studies and provided insights into the quality of the evidence. The studies included were for the early and late stages of BC using neoadjuvant and adjuvant treatments. The studies included meta-analysis studies, which provided more precise estimates of treatment effects. The study's limitation was that metastatic and recurrent BC were excluded. Future studies should consider including metastatic and recurrent BC patients. This would help evaluate the efficacy of radiotherapy in these specific populations. Additionally, future studies should aim for more extended follow-up periods to assess the long-term effects of radiotherapy on survival, recurrence rates, and treatment-related complications.

Based on a comprehensive systematic review, AIs, as neoadjuvant therapy, were the most effective ET with a high ORR and reduced BC mortality or recurrence. Regarding anti-human epidermal growth factor 2 therapy, combining Trastuzumab with chemotherapy was the optimal treatment in HER2-positive BC patients as neoadjuvant and adjuvant therapy, with a significant reduction of one-third in the risks of death and relapse, leading to decreased recurrence rates. Additionally, capecitabine-based treatments in neoadjuvant and adjuvant chemotherapy for early-stage cancer improved the DFS and OS in BC patients. Radiotherapy had a significant role in BC treatment by reducing LRR risk (adjuvant therapy), producing variable pCR rates and 5-year survival rates (neo-adjuvant therapy), and reducing LRF and recurrence (postmastectomy therapy). However, most treatments reduced BC mortality or recurrence rates; anthracycline, chemotherapy, and radiation led to a rise in non-BC deaths overall.

Authorship Contributions

Surgical and Medical Practices: A.S.Q., S.M.A., R.M.A., A.A.A.A., F.A.T., M.J.A., A.A.A., S.A.A., A.H.M.; Concept: A.S.Q., S.M.A., A.A.A.A., A.H.M.; Design: A.S.Q., S.M.A., R.M.A., A.H.M.; Data Collection or Processing: A.S.Q., A.A.A.A., F.A.T., M.J.A., A.A.A., S.A.A.; Analysis or Interpretation: A.S.Q., M.J.A., A.A.A., S.A.A.; Literature Search: A.S.Q., S.M.A., R.M.A., A.A.A.A., F.A.T.; Writing: A.S.Q., S.M.A., A.A.A.A., F.A.T., M.J.A., A.A.A., S.A.A., A.H.M.

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