

Adjuvant Lapatinib and Trastuzumab for Early Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Results From the Randomized Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial

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A B S T R A C T

Background

Lapatinib (L) plus trastuzumab (T) improves outcomes for metastatic human epidermal growth factor 2–positive breast cancer and increases the pathologic complete response in the neoadjuvant setting, but their role as adjuvant therapy remains uncertain.

Methods

In the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization trial, patients with centrally confirmed human epidermal growth factor 2–positive early breast cancer were randomly assigned to 1 year of adjuvant therapy with T, L, their sequence (T→L), or their combination (L+T). The primary end point was disease-free survival (DFS), with 850 events required for 80% power to detect a hazard ratio (HR) of 0.8 for L+T versus T.

Results

Between June 2007 and July 2011, 8,381 patients were enrolled. In 2011, due to futility to demonstrate noninferiority of L versus T, the L arm was closed, and patients free of disease were offered adjuvant T. A protocol modification required $P \leq .025$ for the two remaining pairwise comparisons. At a protocol-specified analysis with a median follow-up of 4.5 years, a 16% reduction in the DFS hazard rate was observed with L+T compared with T (555 DFS events; HR, 0.84; 97.5% CI, 0.70 to 1.02; $P = .048$), and a 4% reduction was observed with T→L compared with T (HR, 0.96; 97.5% CI, 0.80 to 1.15; $P = .61$). L-treated patients experienced more diarrhea, cutaneous rash, and hepatic toxicity compared with T-treated patients. The incidence of cardiac toxicity was low in all treatment arms.

Conclusion

Adjuvant treatment that includes L did not significantly improve DFS compared with T alone and added toxicity. One year of adjuvant T remains standard of care.

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INTRODUCTION

In 2005, trastuzumab (T), an anti-human epidermal growth factor 2 (HER2/neu) monoclonal antibody, showed a 50% reduction in the risk of disease recurrence for HER2-positive early breast cancer when combined with or after adjuvant chemotherapy compared with chemotherapy alone.^{1–4} BCIRG 006, which combined T with a

nonanthracycline-based regimen, also reported disease-free survival (DFS) benefits.⁵ Lapatinib (L), an oral anti-HER2 and anti-HER1 tyrosine kinase inhibitor, was distinguished from T preclinically after displaying an improved signaling network inhibition and a capacity to block signaling from truncated HER2 receptors.^{6,7}

When the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial was designed, the information available on L showed

potential activity against breast cancer stem cells, lack of complete cross-resistance with T, reasonable single-agent activity in T-naïve patients, modest activity against brain metastases, and an excellent cardiac safety profile in more than 3,500 patients, which made L attractive for potential adjuvant use.⁸⁻¹² The combination of T and L (L+T) demonstrated enhanced antitumor activity in a phase I trial.¹³ In a phase III trial, L plus capecitabine showed superior time to progression compared with capecitabine alone for metastatic disease that progressed on T-based therapy, although no difference in overall survival (OS) was observed.¹⁴ We report the first results of three anti-HER2 strategies that incorporated L and T and compared these with T alone as adjuvant therapy for patients with HER2-positive early breast cancer.

METHODS

Patients

Eligible patients had histologically confirmed, completely excised invasive nonmetastatic HER2-positive breast cancer defined by the 2007 American Society of Clinical Oncology/College of American Pathologists guidelines¹⁵ confirmed in one of three central laboratories before random assignment: the European Institute of Oncology (Italy), the Mayo Clinic (United States), and the Peking Union Medical College Hospital (China). Patients had either node-positive disease or node-negative disease with pathologic tumor size ≥ 1 cm. The Data Supplement provides additional eligibility criteria.

Study Design

The ALTTO trial (Breast International Group BIG 2-06/EGF106708 and North Central Cancer Treatment Group [Alliance] N063D) is an international, intergroup, open-label, phase III randomized trial in patients with HER2-positive early breast cancer. The trial compared four treatment groups, each of 1-year duration (Fig 1): intravenous T (at a loading dose of 4 mg/kg once and then 2 mg/kg weekly during chemotherapy or at a loading dose of 8 mg/kg once and then 6 mg/kg every 3 weeks when given alone); oral L (750 mg/day during chemotherapy and 1,500 mg/day when given alone); a sequence of the two agents (T→L) that started with 12 weekly doses of intravenous T followed after a 6-week washout by 34 weeks of oral L at 1,500 mg/day; and the combination of the two anti-HER2 agents (L+T) with T at the aforementioned dosages and L at 750 mg/day during chemotherapy (reduced from an initial dose of 1,000 mg/day based on safety data [primarily diarrhea] from ours and other trials¹⁶⁻¹⁹), with an escalation to 1,000 mg/day at chemotherapy completion.¹⁶⁻¹⁹ The Data Supplement shows the CONSORT diagram.

Investigators could administer anti-HER2 therapies at the completion of all chemotherapy (design 1) or with anthracycline-based chemotherapy preceding the combined administration of anti-HER2 therapies with a taxane (paclitaxel or docetaxel; design 2). Toward the end of the accrual period, investigators from North America were allowed to use an anthracycline-free regimen that comprised six cycles of docetaxel and carboplatin concomitantly with the targeted therapy (design 2B). The Data Supplement shows the allowed chemotherapy doses. Random assignment to anti-HER2 treatment occurred at various time points from initial diagnosis, depending on the design option (Fig 1).

Adjuvant endocrine therapy was given to patients with hormone receptor-positive disease unless contraindicated. Radiotherapy was mandatory in cases of breast-conserving surgery and in accordance with institutional guidelines in cases of mastectomy. Both treatments were given after completion of all chemotherapy and concomitantly with anti-HER2 treatment.

Justification for L and T→L Arms

Although testing the concept of dual inhibition was of primary interest, the efficacy and safety data on L alone (available in 2006) supported the testing of this oral regimen in the adjuvant setting.⁸⁻¹² The

inclusion of the sequential arm was motivated by the results of the Finland Herceptin trial, which showed benefit of 9 weeks of T.²⁰ This short duration was the rationale for the 12-week T administration in the T→L arm. The 6-week gap was included to avoid an overlapping action of T+L caused by the long half-life of T, and continuance with L alone would provide a possibility of an oral treatment for most of the year of therapy.²¹

Randomization, Study End Points, and Statistical Analysis

Randomization used permuted blocks stratified by timing of chemotherapy (design 1 v design 2/2B), central hormone receptor status (positive [$\geq 1\%$] v negative), and lymph node status (not applicable [neoadjuvant chemotherapy], node negative, one to three, or four or more positive nodes). The primary end point was DFS defined as time from randomization to recurrence of invasive breast cancer at local, regional, or distant sites; contralateral invasive breast cancer; second nonbreast malignancy; or death as a result of any cause, whichever occurred first. The protocol-defined end point of DFS is the same as invasive disease-free survival per subpopulation treatment effect pattern plot (STEPP).²² Secondary end points were OS, safety in general and cardiac safety, time to recurrence, time to distant recurrence, and time to first brain metastasis.

Treatment comparisons were based on Cox models stratified by the stratification factors. Moreover, a multivariable Cox model was fitted to include stratification factors, age, menopausal status, pathologic primary tumor size, and tumor histologic grade as covariates.

The study was designed to compare each of the three L-containing arms separately with the T arm. The original sample size was 8,000 patients, which was later increased to 8,400 patients to permit at least 400 enrollments to design 2B. Sample size calculations focused on the two-sided superiority comparison between the L+T arm and the T arm; 850 DFS events would provide 80% power to detect a hazard ratio (HR) of 0.80 at $\alpha = .0167$, the smallest α possible based on the Hochberg-ordered P value procedure²³ originally planned to control type I error at 0.05 across the three pairwise comparisons. The two other pairwise comparisons were to be tested for noninferiority on the basis of the null hypothesis HR of 1.11. Because recurrences were expected relatively early and to avoid extended follow-up in case of low long-term recurrence risk,² the protocol specified that the primary analysis be performed at 4.5 years median follow-up or at the occurrence of 850 DFS events in the L+T and T arms, whichever occurred first.

The L arm was closed in 2011 after the first interim analysis, and the statistical plan was amended to replace the original Hochberg approach with the more conservative Bonferroni approach, which set the α error at .025 for testing the superiority of L+T versus T in the intention-to-treat (ITT) population and at .025 for testing the noninferiority of T→L compared with T in a per protocol population (PPP; defined in the Data Supplement). The safety population included all randomly assigned patients who received at least one dose of anti-HER2 therapy. Adverse events of special interest were hepatobiliary, diarrhea, rash, febrile neutropenia, cardiac, and interstitial lung events.

Study Oversight

The Data Supplement provides details on study oversight.

RESULTS

Between June 2007 and July 2011, 8,381 patients from 945 sites in 44 countries were randomly assigned. Design 1 recruited rapidly and closed enrollment in March 2009 to permit sufficient enrollment to design 2; thus, design 1 had a longer duration of follow-up (Fig 1). Median age was 51 years (range, 18 to 82), with 10% of patients 65 years of age or older. Forty percent of patients had node-negative disease, 41% had a tumor size ≤ 2 cm, 57% had hormone receptor-positive disease, and 55% were enrolled in design 1 (Table 1). Patient characteristics according to trial design are provided in the Data Supplement. Eighty-

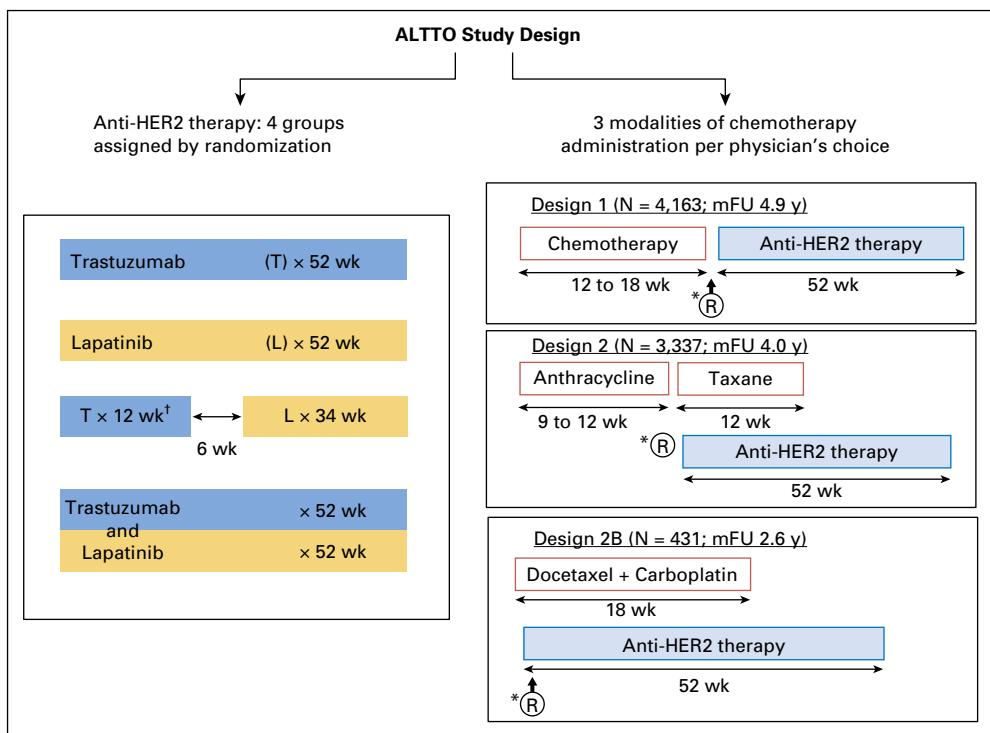


Fig 1. Study design. The numbers of patients in the intention-to-treat population for L+T, T→L, L, and T were 1,155, 1,143, 1,168, and 1,147, respectively, for design 1; 833, 837, 827, and 840 for design 2; and 105, 111, 105, and 110 for design 2B. Design 1: neoadjuvant or adjuvant chemotherapy completed before randomization; anti-HER2 agents were given alone. Design 2: anthracycline component of adjuvant chemotherapy before randomization; taxanes were given concomitantly with anti-HER2 agents. Design 2B: non-anthracycline chemotherapy was given concomitantly with anti-HER2 agents. ALTTO, Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization; HER2, human epidermal growth factor receptor 2; L, lapatinib; L+T, lapatinib plus trastuzumab; mFU, median follow-up; *R, time to randomization; T, trastuzumab; T→L, sequence of trastuzumab followed by lapatinib. ALTTO, Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization; HER2, human epidermal growth factor receptor 2; L, lapatinib; L+T, lapatinib plus trastuzumab; mFU, median follow-up; *R, time to randomization; T, trastuzumab; T→L, sequence of trastuzumab followed by lapatinib. ^tIn Design 2B T was given for 18 weeks and L for 28 weeks.

nine percent of the 4,805 patients with hormone receptor–positive tumors received endocrine therapy. Patients were treated per local practice and local hormone receptor status. If their tumors were deemed locally negative, patients did not receive endocrine therapy.

Exposure to Anti-HER2 Agents

In a post hoc analysis, at least 92% of patients across all arms were able to receive $\geq 85\%$ of the planned dose of T, whereas 66% to 76% of patients received $\geq 85\%$ of the planned L dose, depending on the arm (Data Supplement).

Safety Profile

The incidence of adverse events was higher in L-containing arms than in the T arm (Table 2). There were more discontinuations of study treatment due to toxicity in the L+T arm than in the other treatment arms, and this was more pronounced in designs 2/2B (Data Supplement). Generally, the most common adverse events leading to dose interruptions/delays or modifications for L were diarrhea, neutropenia, and rash.

The incidence of diarrhea was higher in the L-containing arms. Most events were grades 1 to 2; had a median duration of approximately 25 days; and were rarely responsible for treatment discontinuation, which occurred mostly in the L+T arm at a rate of 4% for design 1, 6% for design 2, and 9% for design 2B.

Slightly more than 50% of patients in the L-containing arms experienced skin toxicity as opposed to only 20% in the T arm. Median time to onset of these mostly grade 1 to 2 events was longer in the T→L arm (135 days) than in the other three arms (30–50 days), whereas their median duration ranged from 35 days (T) to 63 days (T→L). Nearly 99% of these events resolved, whereas only 1% to 3% led to treatment discontinuation.

The incidence of hepatobiliary events, which were mostly grade 1 to 2, was similar across all L-containing arms and higher than in the T arm. The median duration of these adverse events varied little across the four arms, ranging from 63 to 79 days. One fatal hepatobiliary toxicity event occurred in the L arm, and two occurred in the T→L arm.

Forty-seven fatal adverse events occurred as follows: 31 in 4,505 patients (0.7%) in design 1, 14 in 3,334 patients (0.4%) in design 2, and two in 431 patients (0.5%) in design 2B. A list of fatal events is provided in the Data Supplement.

The incidence of primary or secondary cardiac end points was low in all treatment arms; primary cardiac end points occurred in 0.25% to 0.97% of patients. Three fatal cardiac events occurred in the T→L arm and one in each of the other treatment arms. Other adverse events of interest, namely interstitial pneumonitis and febrile neutropenia, occurred in less than 1% of patients across all treatment arms.

The overall incidence of serious adverse events was higher in the L-containing arms and especially with concomitant chemotherapy administration (Data Supplement). Less than 1% of patients in all treatment arms experienced fatal serious adverse events related to study treatment, with no specific toxicity pattern identified (Table 2).

Efficacy (L+T v T and T→L v T)

At the median follow-up of 4.5 years (range, 1 day to 6.4 years) in the primary analysis, a 16% reduction in the DFS hazard rate was observed in L+T compared with T (555 DFS events; HR, 0.84; 95% CI, 0.70 to 1.02; $P = .048$), which was not statistically significant at the .025 significance level (Fig 2A). Results were unchanged in a multivariable model (HR, 0.85; 95% CI, 0.72 to 1.01).

No particular subgroup appeared to benefit from L+T treatment (Fig 3). Although a slightly greater effect is seen for the

Table 1. Baseline Characteristics of the Patients, Tumors, and Primary Treatments (Intention-to-Treat Groups)

Variable	L+T (n = 2,093)	T→L (n = 2,091)	L (n = 2,100)	T (n = 2,097)
Region, No. (%)				
North America (region 1)	233 (11)	244 (12)	252 (12)	230 (11)
South America (region 2)	104 (5)	113 (5)	114 (5)	113 (5)
Europe (region 3)	1,128 (54)	1,112 (53)	1,112 (53)	1,118 (53)
Asia Pacific and South Africa (region 4)	628 (30)	622 (30)	622 (30)	636 (30)
Race, No. (%)				
White	1,445 (69)	1,454 (69)	1,434 (68)	1,451 (69)
Asian	546 (26)	543 (25)	549 (26)	555 (26)
Black	38 (1)	30 (1)	43 (2)	25 (1)
Other/missing	64 (3)	64 (3)	74 (3)	66 (3)
Age, No. (%)				
Median age (range)	51 (22-80)	51 (22-80)	51 (19-82)	51 (18-80)
< 65 years	1,879 (90)	1,877 (90)	1,889 (90)	1,881 (90)
≥ 65 years	214 (10)	214 (10)	211 (10)	216 (10)
Medical history, No. (%)				
Hypertension	442 (21)	484 (23)	457 (22)	471 (22)
Hypercholesterolemia	147 (7)	172 (8)	174 (8)	157 (7)
Diabetes mellitus	93 (4)	111 (5)	100 (5)	126 (6)
Menopausal status, No. (%)				
Premenopausal	908 (43)	929 (44)	891 (42)	908 (43)
Postmenopausal [or male]	1,185 [2] (57)	1,162 [5] (56)	1,208 [2] (58)	1,189 [0] (57)
Nodal status, No. (%)				
Not applicable (neoadj CT)	168 (8)	170 (8)	167 (8)	181 (9)
Negative	845 (40)	842 (40)	841 (40)	844 (40)
One to three positive nodes	617 (29)	617 (30)	620 (30)	603 (29)
Four or more positive nodes	463 (22)	462 (22)	472 (22)	469 (22)
Pathologic tumor size, No. (%)				
Not applicable (neoadj CT)	168 (8)	170 (8)	167 (8)	181 (9)
≤ 2 cm	863 (41)	856 (41)	866 (41)	854 (41)
> 2 to ≤ 5 cm	937 (45)	928 (44)	938 (45)	933 (44)
> 5 cm	113 (5)	117 (6)	119 (6)	114 (5)
Missing	12 (1)	20 (1)	10 (< 1)	15 (1)
Hormone receptor status, No. (%)*				
Positive	1,203 (57)	1,205 (58)	1,197 (57)	1,200 (57)
Negative	890 (43)	886 (42)	903 (43)	897 (43)
Histologic grade, No. (%)				
Cannot be assessed	79 (4)	61 (3)	58 (3)	59 (3)
Well differentiated	51 (2)	59 (3)	60 (3)	48 (2)
Moderately differentiated	774 (37)	793 (38)	794 (38)	744 (36)
Poorly differentiated	1,179 (57)	1,171 (56)	1,183 (56)	1,237 (59)
Missing	10	7	5	9
Surgery for the primary tumor, No. (%)				
Breast-conserving procedure	928 (44)	975 (47)	961 (46)	931 (44)
Mastectomy	1,164 (56)	1,115 (53)	1,138 (54)	1,166 (56)
Missing	1	1	1	0
Radiotherapy, No. (%)				
Yes	1,491 (71)	1,501 (72)	1,464 (70)	1,486 (71)
No	602 (29)	590 (28)	636 (30)	611 (29)
Timing of chemotherapy, No. (%)				
Sequential (design 1)	1,155 (55)	1,143 (55)	1,168 (56)	1,147 (55)
Concurrent (design 2/2B)	938 (45)	948 (45)	932 (44)	950 (45)
Any prior anticancer treatment (neoadjuvant)				
Docetaxel	64 (3)	82 (4)	81 (4)	72 (3)
Paclitaxel	19 (< 1)	17 (< 1)	13 (< 1)	21 (1)
Any prior anticancer treatment (adjuvant)				
Docetaxel	392 (19)	388 (19)	413 (20)	389 (19)
Paclitaxel	163 (8)	184 (9)	159 (8)	162 (8)
Adjuvant endocrine therapy intended for patients with hormone receptor positivity, No. (%)†	1,203	1,205	1,197	1,200
Not given	111 (9)	118 (10)	160 (13)	117 (10)
Given	1,092 (91)	1,087 (90)	1,037 (87)	1,083 (90)
Type of endocrine therapy, No. (%)				
AI	401 (37)	371 (34)	378 (36)	381 (35)
AI and SERM	145 (13)	160 (15)	154 (15)	166 (15)
SERM	529 (48)	546 (50)	491 (47)	519 (48)
LHRH	11 (1)	6 (1)	6 (1)	7 (1)

(continued on following page)

Table 1. Baseline Characteristics of the Patients, Tumors, and Primary Treatments (Intention-to-Treat Groups) (continued)

Variable	L+T (n = 2,093)	T→L (n = 2,091)	L (n = 2,100)	T (n = 2,097)
Procedure, No. (%)				
Surgery	62 (6)	71 (7)	67 (6)	82 (8)
Radiation	0 (0)	2 (< 1)	3 (< 1)	4 (< 1)

Abbreviations: L+T, lapatinib plus trastuzumab; T→L, trastuzumab followed by lapatinib; L, lapatinib; T, trastuzumab; neoadj CT, neoadjuvant chemotherapy; AI, aromatase inhibitor; SERM, selective estrogen receptor modulator; LHRH, luteinizing hormone-releasing hormone.

*Only 10 patients had hormone receptor status derived from local laboratory results and were not enrolled within any particular treatment arm or included in any positive/negative result.

†For six patients, hormone receptor status was from a local laboratory.

hormone receptor-negative population and in patients treated with the design 1 regimen, these differences are not significant (interaction $P = .70$ and $.41$, respectively; Fig 3).

The HR for DFS for the superiority comparison of T→L versus T in the ITT population was 0.96 (97.5% CI, 0.80 to 1.15; $P = .61$; Fig 2A; Data Supplement). For the noninferiority comparison of T→L versus T in the PPP, HR was 0.93 (97.5% CI, 0.76 to 1.13; $P = .044$; Data Supplement). Again, these results were unchanged in a multivariable model (HR for superiority, 0.93; 95% CI, 0.79 to 1.10).

The 4-year OS was 95%, 95%, and 94% for L+T, T→L, and T, respectively (Fig 2B). The OS HR was 0.80 (95% CI, 0.62 to 1.03; $P = .078$) for the comparison of L+T versus T and 0.91 (95% CI, 0.71 to 1.16; $P = .433$) for the comparison of T→L versus T.

The Data Supplement shows sites of the first DFS event. Patients treated with L+T had a 22% lower hazard rate of first breast cancer recurrence (HR, 0.78; 95% CI, 0.64 to 0.94) and a 20% lower hazard rate of distant recurrences (HR, 0.80; 95% CI, 0.65 to 0.98) than those treated with T. No differences in incidence were observed for CNS as the first site of relapse (2% in all treatment arms).

Outcome of the L Arm Patients

At the first planned efficacy analysis in 2011, with a median follow-up of 1.98 years, the independent data monitoring center noted an HR of 1.52 (95% CI, 1.23 to 1.88) between DFS events for

L versus T and recommended that the L arm be closed because the likelihood of demonstrating noninferiority was small. Upon closure of this experimental arm, adjuvant commercial T was offered; of the 2,100 patients randomly assigned to L, 1,087 (52%) consented and received at least one dose of T before a DFS event, 797 (38%) after completing a full year of L. An updated ITT analysis at 4.5 years of median follow-up showed an HR of 1.34 (95% CI, 1.13 to 1.60; Fig 2A). For the 2,100 patients enrolled in the L arm, a post hoc time-dependent Cox model that included a time variable when T was initiated, showed that patients who received T had a 33% reduction in hazard of a DFS event (HR, 0.67; 95% CI, 0.49 to 0.91). An event history graph is shown in the Data Supplement.²⁴

DISCUSSION

To our knowledge, the ALTTO trial is the first to test the hypothesis that dual anti-HER2 blockade could further improve survival outcomes of patients with HER2-positive early breast cancer compared with adjuvant T. Positive results were eagerly anticipated given the almost doubling of the pathologic complete response reported in the sister neoadjuvant trial NeoALTTO, which tested the combination of L+T with paclitaxel.¹⁶

In the ITT population, a 16% reduction in the hazard of a DFS event was observed with L+T compared with T, but this effect was

Table 2. Adverse Events With Special Focus on the Most Frequent Ones (Safety Population)

Event	L+T (n = 2,061)	T→L (n = 2,076)	L (n = 2,057)	T (n = 2,076)
Adverse event, No. (%)				
Patients with at least one grade 3-4 event	944 (46)	666 (32)	840 (41)	512 (25)
Patients with at least one serious adverse event	430 (21)	352 (17)	431 (21)	292 (14)
Fatal adverse events	9 (< 1)	14 (< 1)	15 (< 1)	9 (< 1)
Treatment withdrawals for toxicity	482 (23)	262 (13)	314 (15)	169 (8)
Cardiac events, No. (%)				
Symptomatic CHF, including severe CHF (NYHA class II, III, IV)	68 (3)	37 (2)	37 (2)	53 (3)
Severe CHF (NYHA class III, IV)	22 (1)	4 (< 1)	6 (< 1)	18 (1)
LVEF ≥ 10 decrease and \geq LLN (based on worst case on therapy)	456 (23)	330 (17)	366 (19)	403 (20)
LVEF ≥ 10 decrease and $<$ LLN (based on worst case on therapy)	103 (5)	57 (3)	63 (3)	97 (5)
Primary cardiac end point	20 (< 1)	5 (< 1)	7 (< 1)	18 (< 1)
Any cardiac end point	77 (4)	50 (2)	39 (2)	94 (5)
Adverse events of special interest				
Diarrhea grade 3-4	315 (15)	100 (5)	233 (11)	27 (1)
Rash/skin toxicity grade 3-4	100 (5)	80 (4)	126 (6)	12 (1)
Hepatobiliary grade 3-4	71 (3)	54 (3)	90 (4)	16 (1)

Abbreviations: L+T, lapatinib plus trastuzumab; T→L, trastuzumab followed by lapatinib; L, lapatinib; T, trastuzumab; CHF, congestive heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LLN, lower limit of normal.

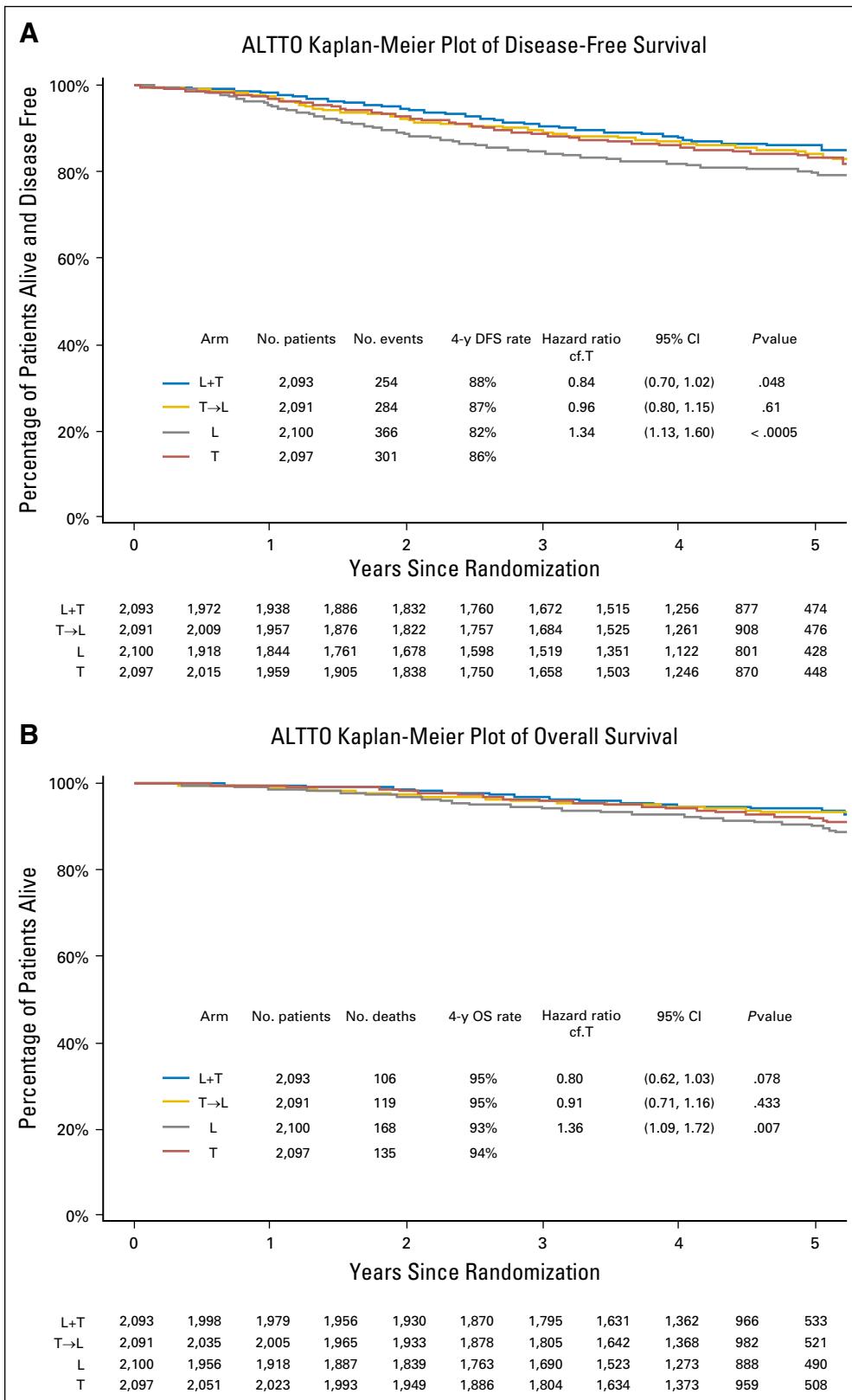


Fig 2. (A) Kaplan-Meier of DFS in the intention-to-treat population for all four study arms. (B) Kaplan-Meier of OS in the intention-to-treat population for all four study arms. ALTTO, Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization; DFS, disease-free survival; L, lapatinib; L+T, lapatinib plus trastuzumab; OS, overall survival; T, trastuzumab; T→L, trastuzumab followed by lapatinib.

modest, not statistically significant at .025, and of little clinical significance in consideration of the additional toxicity. Importantly, ALTTO was first analyzed when a clinically reasonable

median follow-up time of 4.5 years was reached, with 555 events instead of 850, potentially reducing the statistical power from the original design. The L+T combination also produced a modest

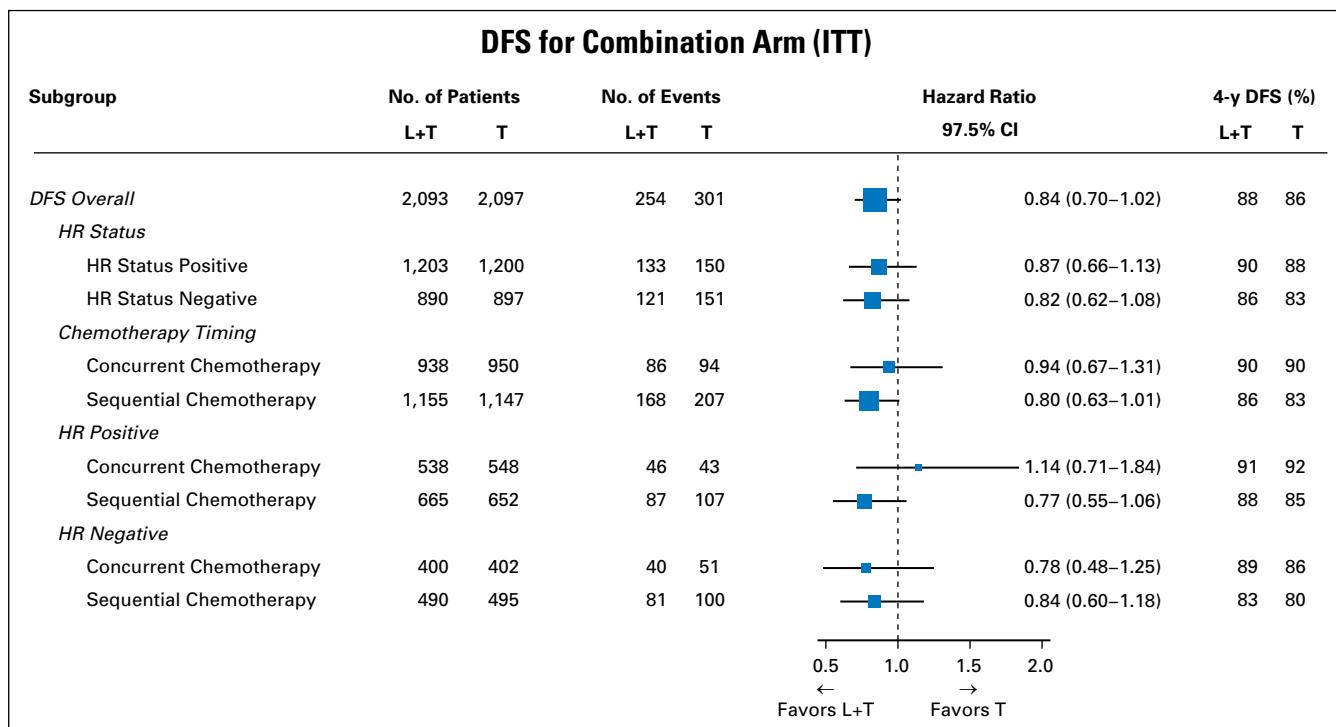


Fig 3. Whisker plot of DFS in the ITT population for L+T v T. Shorter median clinical follow-up for concurrent chemotherapy timing (3.9 years) compared with sequential chemotherapy timing (4.9 years). DFS, disease-free survival; HR, hormone receptor; ITT, intention to treat; L+T, lapatinib plus trastuzumab; T, trastuzumab.

reduction in the hazard rate of first distant recurrences but showed no detectable effect on the incidence of CNS relapse. Similarly, the noninferiority of T→L versus T could not be demonstrated in the PPP analysis, and the sequencing arm was more toxic than T (Data Supplement).

The L arm was closed early at interim analysis because a demonstration of noninferiority to T was deemed unlikely, and updated results showed that patients assigned to the L arm had a worse DFS than those treated with T alone. Post hoc analysis showed that patients assigned to L who received T before relapse had a 33% reduction in the DFS hazard rate.

ALTTO did not show any substantial incidences of life-threatening toxicities with L or L+T; in particular, the rate of cardiotoxicity in ALTTO was low, and no differences emerged across the four arms in primary cardiac end points, with New York Heart Association class 3 to 4 events or cardiac deaths occurring in less than 1% of patients. The incidence of severe hepatotoxicity from L was also low. Recently, data provided L ALT (hepatic enzymes) risk estimates for the *HLA-DRB1*07:01* allele carriage, which may discriminate causality and support safety management during the use of L combinations for the global treatment of metastatic breast cancer. No germline mutations were found in relation to diarrhea.²⁵

The ALTTO trial provides lessons about drug development. First, moving rapidly into the adjuvant setting is not without risk. When ALTTO was activated in 2007, the hypothesis that L would decrease CNS relapses, the better cardiac toxicity profile, and the reduced patient and health care system burden associated with the oral medication made each of the three experimental arms viable options to improve patient care worldwide. Since 2007, trials in advanced disease have suggested that L may have inferior

progression-free survival (PFS) to T, neoadjuvant trials with relatively small numbers of patients have shown somewhat mixed results, and the importance of the immunologic effects of T has become clearer.^{16–19,26–28} The strength of feasibility and/or efficacy preclinical and clinical data should be taken into account at the moment of a trial design. For example, we did not expect to observe the degree of toxicity (especially diarrhea), which ultimately reduced the level of enthusiasm for L in the adjuvant setting. Furthermore, after ALTTO completed accrual, phase III trials demonstrated that T was superior to L in patients with metastatic breast cancer.^{29,30} Clinical data also demonstrated that Fcγ R-mediated antibody-dependent cellular cytotoxicity plays an important role in the clinical effect of T, which may explain the superiority of T.³¹

Although ALTTO presented negative results, the benefit of dual blockade was demonstrated in advanced disease. In heavily pretreated patients with metastatic breast cancer, L+T was superior to L in terms of PFS and OS, particularly in the hormone receptor-negative population.³² In the CLEOPATRA (A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-positive Metastatic Breast Cancer) trial, the final analysis demonstrated a 6.2-month benefit in PFS and an impressive 15.7-month improvement in OS for patients treated with chemotherapy and T and pertuzumab compared with chemotherapy and T.³³

Second, ALTTO illustrates the steady improvement in clinical outcome of early breast cancer, with 4-year OS rates of approximately 95%. The control T arm had higher DFS rates than in previous large adjuvant trials,^{1,3} possibly due to more aggressive staging procedures and a large proportion of low-stage disease (T1 tumors and node-negative disease). With control arm survival rates

of this magnitude, the large trials needed to demonstrate plausible treatment effects are unlikely to be achieved.

In summary, adjuvant treatment with the combination of L+T resulted in a nonsignificant improvement in DFS, which was not clinically meaningful because of the modest treatment effect and added toxicity. Furthermore, noninferiority of the sequence of the two anti-HER2 agents compared with T was not demonstrated. One year of adjuvant T remains standard of care.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org

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GLOSSARY TERMS

anthracyclines: a class of antineoplastic agents derived from *Streptomyces* bacterium used to treat a variety of hematologic and solid malignancies. Anthracyclines have a well-established dose-related risk of cardiomyopathy and congestive heart failure. Anthracyclines include agents like daunorubicin, doxorubicin, epirubicin, and idarubicin.

disease-free survival: the survival period spanning the time from surgery to a recurrence of cancer.

HER2/neu (human epidermal growth factor receptor 2): also called ErbB2. HER2/neu belongs to the epidermal growth factor receptor (EGFR) family and is overexpressed in several solid tumors. Like EGFR, it is a tyrosine kinase receptor whose activation leads to proliferative signals within the cells. On activation, the human epidermal growth factor family of receptors are known to form homodimers and heterodimers, each with a distinct signaling activity. Because HER2 is the preferred dimerization partner when heterodimers are formed, it is important for signaling through ligands specific for any

members of the family. It is typically overexpressed in several epithelial tumors.

lapatinib: a dual tyrosine kinase inhibitor. Lapatinib has been developed as an inhibitor of the tyrosine kinase activities of ErbB1 (EGFR) and ErbB2. Like other tyrosine kinase inhibitors, it competes with ATP binding to the intracellular regions of the receptors that are activated after tyrosine phosphorylation.

overall survival: the duration between random assignment and death.

taxanes: a class of chemotherapy that leads to the disruption of microtubule function and thus stops cell division. Paclitaxel and docetaxel are examples of taxanes.

trastuzumab: a humanized anti-ErbB2 monoclonal antibody approved for treating patients whose breast cancers overexpress the ErbB2 protein or demonstrate *ErbB2* gene amplification. It is currently being tested in combination with other therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Adjuvant Lapatinib and Trastuzumab for Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Results From the Randomized Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial

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Appendix**Table A1.** ALTTO Investigators and Participating Groups

Participating Groups	Investigators
Groups and Independent Sites	
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St John of God Hospital, Bunbury, Western Australia, Australia	Buck, Martin
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Epworth Richmond, Richmond, Victoria, Australia	Jennens, Ross
Nepean Hospital, Kingswood, New South Wales, Australia	Wilcken, Nicholas
Royal Perth Hospital 2, Perth, Western Australia, Australia	Redfern, Andrew
Westmead Hospital 3, Westmead, New South Wales, Australia	Wilcken, Nicholas
Concord Repatriation General Hospital, Concord, New South Wales, Australia	Beale, Philip
Liverpool Hospital, Liverpool, New South Wales, Australia	Moylan, Eugene
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(continued on following page)

Table A1. ALTTO Investigators and Participating Groups (continued)

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Universitair Ziekenhuis Antwerpen, Edegem, Belgium	Altintas, Sevilay
Instytut im. Marii Skłodowskiej-Curie, Warsaw, Poland	Sienkiewicz-Kozlowska, Renata
Cliniques Universitaires UCL de Mont, Godinne, Yvoir, Belgium	D'Hondt, Lionel
Hôpital de Jolimont, Haine-Saint-Paul, Hainaut, Belgium	Majois, Françoise
Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)	
Institut Curie, Paris, France	Dieras, Véronique
Institut de Cancérologie Gustave Roussy, Villejuif Cedex, France	Domont, Julien
Centre François Baclesse, Caen Cedex 5, France	Levy, Christelle
Institut de Cancérologie Lucien Neuwirth, Saint-Priest en Jarez, France	Jacquin, Jean-Philippe
Clinique Pasteur, Toulouse, France	Despax, Raymond
Institut de Cancérologie de Lorraine, Vandœuvre-lès-Nancy, France	Rios, Maria
Institut Jean-Godinot, Reims, France	Eymard, Jean-Christophe
Institut de Cancérologie de l'Ouest, René Gauduchea, Saint-Herblain Cedex, France	Bourbouloux, Emmanuelle
Centre Léon Bérard, Lyon Cedex 8, France	Bachelot, Thomas
Hôpital Le Mittan, Montbeliard, France	Pivot, Xavier
Clinique Sainte Anne, Strasbourg Cedex, France	Dourthe, Louis-Marie
Hôpital Saint-Louis, Paris, France	Espie, Marc
Institut Sainte Catherine, Avignon, France	Grenier, Julien
Clinique Sainte Marguerite, Hyères, France	Berdah, Jean-François
Institut de Cancérologie Paul Papin, Angers Cedex 9, France	Abadie-Lacourtoisie, Sophie
Centre Georges François Leclerc, Dijon, France	Desmoulin, Isabelle
Centre Hospitalier Draguignan, Hôpital de la Dracénie, Draguignan Cedex, France	Caruso, Salvatore
Clinique Armoricaine de Radiologie, Saint-Brieuc, France	Hardy-Bessard, Anne-Claire
CRLCC Antoine Lacassagne, Nice, France	Ferrero, Jean-Marc
Centre d'Oncologie de Gentilly, Nancy, France	Spaeth, Dominique
Centre Hospitalier Universitaire de Lyon, Groupe Hospitalier Est, Hôpital Femme-Mère-Enfant, Bron, France	Tigaud, Jean-Dominique
Centre Jean Perrin, Clermont, Ferrand, France	Chollet, Philippe
Centre Hospitalier Layné-Mont de Marsan, Mont-de-Marsan, France	Dauba, Jérôme
Clinique de l'Orangerie, Strasbourg, France	Achille, Mihaela
Centre Hospitalier Privé Saint Grégoire, Saint-Grégoire, France	Miglianico, Laurent
Centre Régional de Lutte contre le Cancer Henri Becquerel, Rouen Cedex 1, France	Leheurteur, Marianne
Centre Régional de Lutte contre le Cancer Paoli, Calmettes, Marseille Cedex 9, France	Extra, Jean-Marc
Centre Hospitalier de Brive, Brive La Gaillarde, France	Leduc, Bernard
Centre Hospitalier Régional Universitaire de Tours, Hôpital Bretonneau, Tours Cedex 9, France	Bougnoux, Philippe
Polyclinique Francheville, Périgueux, France	Cany, Laurent
Centre Bourgogne, Lille, France	Maes, Patricia
Centre Hospitalier Universitaire de Marseille, Hôpital de la Timone, Marseille Cedex 5, France	Nicoara, Adriana
Clinique de l'Union, Saint Jean, France	Bürki, Franck
Clinique Saint Jean du Languedoc, Toulouse, France	Suc, Etienne
Hôpital Belle, Isle-Metz Cedex 01, France	Nierges, Daniela
Hôpital René Huguenin, Institut Curie, Saint Loud, France	Brain, Etienne
Centre Frédéric Joliot, Rouen, France	Randrianarivo, Harizo
Centre Hospitalier de Valenciennes, Valenciennes, France	Bonnet, Isabelle
Clinique de Flandre, Coudekerque Branche, France	Marmousez, Thierry
Clinique de la Sauvegarde, Lyon, France	Mouillet, Isabelle
Clinique Générale, Annecy, France	Catimel, Gilles
Clinique Pasteur, Toulouse, France	Chevelle, Christian
Clinique Valdegour, Nîmes, France	Legouffe, Eric
Hôpital Saint Joseph, Marseille, France	Paoli, Jean-Baptiste
Hôpital Saint Joseph, Paris, France	Deplanque, Gaël
Hôpitaux Universitaires de Strasbourg, Hôpital Central, Strasbourg, France	Kurtz, Jean-Emmanuel

(continued on following page)

Table A1. ALTTO Investigators and Participating Groups (continued)

Participating Groups	Investigators
Grupo Brasileiro de Câncer de Mama (GBECAM) Faculdade de Medicina do ABC, Santo André, Brazil Instituto Nacional do Câncer, INCA, Rio de Janeiro, Brazil Hospital São Lucas da Pontifícia Universidade do Rio Grande do Sul, Porto Alegre, Brazil Fundacao Hospital Amaral Carvalho, Jaú, Brazil CliniOnco, Porto Alegre, Brazil Hospital Moinhos de Vento, Porto Alegre, Brazil	Santi, Patricia Bines, José Barrios, Carlos Henrique Segalla, José Vinholes, Jeferson José Morelle, Alessandra
Grupo de Estudios Clínicos Oncológicos del Perú (GECO PERU) Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru Hospital Nacional Edgardo Rebagliati, Lima, Peru Hospital Nacional Guillermo Almenara, Lima, Peru Hospital Nacional Alberto Sabogal Sologuren, Callao, Peru	Gomez, Henry Hurtado de Mendoza, Fernando Salas, Fernando Philco, Manuel
German ALTTO Evangelisches Krankenhaus Bethesda Mönchengladbach, Mönchengladbach, Germany Frauenarzt-Zentrum-Zehlendorf, Berlin, Germany Praxis für Hämatologie und Onkologie, Würzburg, Germany Praxis Dr med Peter Klare, Berlin, Germany Vivantes Klinikum am Urban, Brustzentrum, Berlin, Germany Gem. Praxis Drs Nusch und Kalhor, Velbert, Germany Klinikum Chemnitz gGmbH, Frauenheilkunde, Chemnitz, Germany Praxis Dr med Jochen Wilke, Fürth, Germany Universitätsfrauenklinik Ulm, Ulm, Germany Krankenanstalt Mutterhaus der Borromäerinnen, Trier, Germany Evangelisches Waldkrankenhaus Spandau, Innere Medizin, Berlin, Germany Marien-Hospital Witten gGmbH, Brustzentrum, Witten, Germany Onkologische Schwerpunktpraxis Bielefeld, Bielefeld, Germany Universitätsklinikum Heidelberg, Frauenklinik, Heidelberg, Germany Helios Klinik Schkeuditz, Gynäkologie, Schkeuditz, Germany Universitätsklinikum Erlangen, Frauenklinik, Erlangen, Germany Schwerpunktpraxis für Gynäkologische Onkologie, Fürstenwalde, Germany Universitätsklinikum Münster, Frauenheilkunde, Muenster, Germany Studienzentrum Onkologie Ravensburg im Brustzentru, Ravensburg, Germany St Elisabeth Krankenhaus Leipzig, Brustzentrum, Leipzig, Germany Universitätsfrauenklinik Tübingen, Brustzentrum, Tübingen, Germany Universitätsklinikum Essen, Frauenheilkunde, Essen, Germany Charite-Campus Mitte, Brustzentrum, Berlin, Germany Gem. Praxis Dres Lorenz und Hecker, Braunschweig, Germany Johannes, Gutenberg, Universität Mainz, Frauenklinik, Mainz, Germany Kliniken Essen, Mitte Evangelische Huyssensstiftung, Brustz, Essen, Germany Pius Hospital, Internistische Onkologie, Oldenburg, Germany Praxis für Hämatologie und Onkologie, Bremen, Germany SRH Wald, Klinikum Gera, Brustzentrum, Gera, Germany Evangelisches Krankenhaus Ludwigsfelde, Teltow, Ludwigsfelde, Germany Hämatologische und Onkologische Schwerpunktpraxis, Stade, Germany Klinikum der Johann Wolfgang Goethe Universität, Frauenheilk, Frankfurt, Germany Klinikum der Universität zu Koeln, Frauenklinik, Cologne, Germany Klinikum Leverkusen, Onkologie und Hämatologie, Leverkusen, Germany Klinikum Oldenburg gGmbH, Onkologie, Oldenburg, Germany Klinikum Südstadt Rostock, Frauenklinik, Rostock, Germany Martin Luther Universität Halle, Frauenklinik, Halle, Germany Onkologie Gemeinschaftspraxis am Bethanien Krankenhaus, Frankfurt, Germany St Vincentius Kliniken Karlsruhe, Frauenklinik, Karlsruhe, Germany Städtisches Klinikum St Georg, Frauenklinik, Leipzig, Germany Frauenklinik Rheinfelden Betriebs GmbH, Brustzentrum, Rheinfeld, Germany Klinikum Bremerhaven Reinkenheide, Frauenklinik, Bremerhaven, Germany Oncologische Praxis Dr Strotkoetter, Wuppertal, Germany Gemeinschaftspraxis für Onkologie, Münster, Germany Georg-August Universität Göttingen, Gynäkologie, Göttingen, Germany Johanniter Krankenhaus Bonn, Innere Medizin, Bonn, Germany Kreiskrankenhaus Torgau, Frauenklinik/Brustzentrum, Torgau, Germany Onkologische Gemeinschaftspraxis Drs Goehler und Doerfl, Dresden, Germany Praxis Senologische Onkologie, Düsseldorf, Germany St Elisabeth, Krankenhaus Koeln, Gynäkologie, Cologne, Germany Städtischen Krankenhaus Frankfurt Höchst, Frauenklinik, Frankfurt, Germany Universitätsklinikum Freiburg, Frauenklinik, Freiburg, Germany Gemeinschaftspraxis Drs Vehling-Kaiser und Greif, Landshut, Germany Helios Klinikum Berlin-Buch, Brustzentrum, Berlin, Germany	Nitz, Ulrike Graffunder, Gerd Schlag, Rudolf Klare, Peter Paul, Marion Nusch, Arnd Krabisch, Petra Wilke, Jochen Janni, Wolfgang Clemens, Michael Potenberg, Jochem Hackmann, John Just, Marianne Schneweiss, Andreas Schirrmeister, Susen Loehberg, Christian Heinrich, Georg Tio, Joke Decker, Thomas Langanke, Dagmar Grischke, Eva-Maria Aktas, Bahriye Bangemann, Nikola Lorenz, Ralf Schmidt, Marcus Wilke, Hansjochen Griesinger, Frank Doering, Gabriele Zahm, Dirk Kohls, Andreas Steffens, Claus Christoph Schnappauf, Benjamin Mallmann, Peter Heider, Andrea Koehne, Claus-Henning Gerber, Bernd Thomssen, Christoph Tesch, Hans Tomé, Oliver Koehler, Uwe Sallmann, Alexandra Mouarrawy, Doraid Strotkoetter, Heribert Lerchenmueller, Christian Emons, Guenter Ko, Yon-Dschun Simon, Eike Goehler, Thomas Rezai, Mahdi Schumacher, Claudia Moebus, Volker Stickeler, Elmar Vehling-Kaiser, Ursula Mau, Christine

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Table A1. ALTTO Investigators and Participating Groups (continued)

Participating Groups	Investigators
Klinikum Bayreuth, Frauenklinik, Bayreuth, Germany	Popovic, Milos
Klinikum Fichtelgebirge Marktredwitz, Marktredwitz, Germany	Dietrich, Maria
Praxis Dres med Weniger und Bittrich, Erfurt, Germany	Weniger, Joerg
Praxis Privat-Dozentin Dr med Angela Reles, Berlin, Germany	Reles, Angela
Universitätsklinikum Bonn, Frauenheilkunde, Bonn, Germany	Wolfgarten, Matthias
Asklepios Klinik Weissenfels, Gynäkologie, Weissenfels, Germany	Lampe, Dieter
Asklepios Paulinen Klinik, Wiesbaden, Frauenklinik, Wiesbaden, Germany	Heyl, Volker
Evangelisches Krankenhaus Bergisch Gladbach, Frauenklinik, Bergisch Gladbach, Germany	Tenckhoff, David
Klinikum Offenbach GmbH, Gynäkologie, Offenbach, Germany	Jackisch, Christian
Klinikum St Georg, Franziskus Hospital, Gynäkologie, Georgsmarienhuette, Germany	von der Assen, Albert
Krankenhaus Cuxhaven, Gynäkologie, Cuxhaven, Germany	Deichert, Ulrich
Kreiskrankenhaus Rendsburg, Frauenklinik, Rendsburg, Germany	Behrens, Oliver
Praxis Dr med Johannes Selbach, Duisburg, Germany	Selbach, Johannes
St Marienhospital Vechta, Gynäkologie, Vechta, Germany	Seeger, Dietmar
Städtischen Kliniken Esslingen, Frauenklinik, Esslingen, Germany	Kuehn, Thorsten
Universitätsklinikum Eppendorf, Brustzentrum, Hamburg, Germany	Mueller, Volkmar
Universitätsklinikum Greifswald, Frauenklinik, Greifswald, Germany	Belau, Antje
Universitätsklinikum Schleswig-Holstein, Frauenklinik, Kiel, Germany	Eidtmann, Holger
Albertinen-Krankenhaus, Hamburg, Germany	Hervig, Uwe
Asklepios Klinik Bad Oldesloe, Frauenklinik, Bad Oldesloe, Germany	Fink, Heike
Elbländkliniken Meißen, Radebeul GmbH, Frauenklinik, Radebeul, Germany	Richter, Barbara
Gemeinschaftspraxis Dres Schumann, Reinhardt, und Hahn, Herne, Germany	Hahn, Lars
Gemeinschaftspraxis Drs Esser, Vaupel, und Wolter, Bonn, Germany	Esser, Martin
Hämato-Onkologie Praxis Dres Reichert und Janssen, Westerstede, Germany	Reichert, Dietmar
Hämatologisch-Onkologische Praxis, Wuppertal, Germany	Fett, Werner
Klinikum Konstanz, Frauenklinik, Konstanz, Germany	Fricke, Hans Christian
Klinikum Obergötzsch Rodewisch, Brustzentrum, Rodewisch, Germany	Schlosser, Astrid
Krankenhaus Eggenfelden, Eggenfelden, Germany	Terhaag, Juergen
Onkologische Schwerpunktpraxis Leer und Emden, Leer, Germany	Mueller, Lothar
Praxis Dr med Christiane Kreisel, Buestgens, Minden, Germany	Kreisel-Buestgens, Christiane
Praxis Dr med Helmut Forstbauer, Troisdorf, Germany	Forstbauer, Helmut
Praxis für Frauenheilkunde, München, Germany	Precht, Anita
Praxis Prof Dr sc med Horst Leitsmann, Zwickau, Germany	Lenk, Ina
Gemeinschaftspraxis Drs Hauptmann, Wagner, und Brandner, Saarbrücken, Germany	Wagner, Steffen
Gemeinschaftspraxis Drs Maintz und Groschek, Wuerselen, Germany	Maintz, Christoph
Gynäkologisch Onkologische Praxis Hannover, Hannover, Germany	Lueck, Hans-Joachim
Klinik am Eichert-Brustzentrum des Landkreises Göppingen, Göppingen, Germany	Heiss, Christoph
Klinikum Dachau, Frauenklinik/Brustzentrum, Dachau, Germany	Neteler, Jutta
Klinikum Kempten-Oberallgäu GmbH, Mehr Brustzentrum, Kempten, Germany	Felberbaum, Ricardo
Klinikum Rosenheim, Gynäkologie/Brustzentrum, Rosenheim, Germany	Beck, Thomas
Kreiskrankenhaus Böblingen, Frauenklinik, Böblingen, Germany	Weiss, Erich
Kreiskrankenhaus Hameln, Frauenklinik, Hameln, Germany	Noesselt, Thomas
Praxis Dr med Mathias Schulze, Zittau, Germany	Schulze, Mathias
Städtischen Klinikum Brandenburg, Frauenheilkunde, Brandenburg, Germany	Mueller, Cornelia
Städtisches Klinikum Magdeburg, Hämatologie/Onkologie, Magdeburg, Germany	Kahl, Christoph
Universitätsklinikum des Saarlandes, Frauenklinik, Homburg/Saar, Germany	Solomayer, Erich
Diakonissenkrankenhaus Flensburg, Frauenklinik, Flensburg, Germany	Ostertag, Horst
Gynäkologische Praxisklinik Hamburg, Hamburg, Germany	Schmidt-Rhode, Peter
Henriettenstiftung, Frauenklinik, Hannover, Germany	Schrader, Iris
Johanniter-Krankenhaus Genthin-Stendal, Brustzentrum, Stendal, Germany	Ruth, Sylvia
Krankenhaus St Elisabeth und St Barbara Brustzentrum, Halle, Germany	Lantzsch, Tilmann
Kreisklinik Aschersleben-Straßfurt, Frauenklinik, Aschersleben, Germany	Bannier, Daniela
Praxis Dr med Wolfgang Abenhardt, München, Germany	Abenhardt, Wolfgang
Schwarzwald, Baar Klinikum, Frauenklinik, Villingen, Schwenningen, Germany	Bauer, Wolfgang
Stadt klinik Baden-Baden, Frauenklinik, Baden-Baden, Germany	Hahn, Antje
Universitätsklinikum Carl Gustav Carus, Brustzentrum, Dresden, Germany	Kast, Karin
Diakonie, Klinikum Schwäbisch Hall, Frauenklinik, Schwäbisch Hall, Germany	Mayer, Christine
DRK Kliniken Berlin Köpenick, Frauenklinik, Berlin, Germany	Henke, Bettina
DRK Krankenhaus Luckenwalde, Gynäkologie, Luckenwalde, Germany	Freese, Sylvine
Evangelisches Krankenhaus Wesel, Gynäkologie, Wesel, Germany	Sawitzki, Katrin
Hämato-Onkologische Gemeinschaftspraxis, München, Germany	Salat, Christoph
Johannes Wesling Klinikum, Brustzentrum, Minden, Germany	Griesshammer, Martin
Klinikum am Steinenberg, Brustzentrum, Reutlingen, Germany	Kristen, Peter
Klinikum Itzehoe, Frauenklinik, Itzehoe, Germany	Seifert, Britta
Klinikum Landshut gGmbH, Frauenklinik/Brustzentrum, Landshut, Germany	Bauerfeind, Ingo
Klinikum rechts der Isar, Frauenklinik, München, Germany	Schmalfeldt, Barbara
Klinikum Schwäbisch Gmünd, Frauenklinik, Mutlangen, Germany	von Abel, Ekkehard

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Table A1. ALTTO Investigators and Participating Groups (continued)

Participating Groups	Investigators
Krankenhaus Bad Cannstatt, Frauenklinik, Stuttgart, Germany Kreiskrankenhaus Gummersbach, Frauenklinik, Gummersbach, Germany Oncoresearch Lerchenfeld UG, Hamburg, Germany Paracelsus-Klinik Henstedt-Ulzburg, Gynäkologie, Henstedt-Ulzburg, Germany Praxis Dr med Manfred Welslau, Aschaffenburg, Germany Praxis Dr med Stefan Fuxius, Heidelberg, Germany St Antonius Hospital, Hämatologie und Onkologie, Eschweiler, Germany St Barbara Klinik Hamm-Heessen, Gynäkologie, Hamm-Heessen, Germany Universitätsklinik Schleswig-Holstein, Campus Lübeck, Frauen, Lübeck, Germany Medical Oncology and Hematology Associates, Des Moines, IA Frauenärzte Pruner Gang, Kiel, Germany Friedrich-Ebert-Krankenhaus, Frauenheilkunde, Neumünster, Germany Gemeinschaftspraxis Drs Schilling und Till, Berlin, Germany Gynäkologisch, Onkologische Praxis, Essen, Germany Hämatologie-Onkologie Praxis Dres Reichert und Janssen, Aurich, Germany Kliniken Ludwigsburg, Bietigheim, Frauenklinik, Ludwigsburg, Germany Klinikum Coburg, Frauenklinik, Coburg, Germany Klinikum Deggendorf, Frauenklinik, Deggendorf, Germany Klinikum Garmisch, Partenkirchen, Innere Medizin, Garmisch-Partenkirchen, Germany Klinikum Ludwigshafen, Frauenklinik, Ludwigshafen, Germany Klinikum Memmingen, Memmingen, Germany Kreiskrankenhaus Sigmaringen, Gynäkologie, Sigmaringen, Germany Mammazentrum Hamburg, Hamburg, Germany Praxis Dr med Dirk Hempel, Rehling, Germany Praxis für Frauenheilkunde Dr med. Steffi Busch, Mühlhausen, Germany Robert Bosch Krankenhaus, Hämatologie/Onkologie, Stuttgart, Germany Universitätsklinikum Düsseldorf, Frauenklinik, Düsseldorf, Germany Centrum für Ganzheitliche Gynäkologie Klinik GmbH, Mannheim, Germany Dr Horst-Schmidt-Kliniken GmbH, Gynäkologie, Wiesbaden, Germany Elisabeth Krankenhaus GmbH, Brustzentrum, Kassel, Germany g.Sund, Stralsund, Germany Gemeinschaftspraxis Drs Mohm und Prange, Krex-Dresden, Germany Internistische Gemeinschaftspraxis, Friedrichshafen, Germany Krankenhaus Elim gGmbH, Hamburg, Germany Kreiskrankenhaus Bad Reichenhall, Brustzentrum, Bad Reichenhall, Germany Marienhauklinik St Josef Kohlhof, Neunkirchen, Germany Marienhospital Osnabrück, Osnabrück, Germany Praxis Dr med. Hans Werner Tessen, Goslar, Germany Praxis Dres Schmitz, Steinmetz, und Gabor, Cologne, Germany St Johannis Krankenhaus, Gynäkologie/Geburtshilfe, Landstuhl, Germany St Martinus Hospital, Frauenklinik, Olpe, Germany St Vincenz Krankenhaus Limburg, Frauenklinik, Limburg, Germany Universitätsklinikum Jena, Frauenheilkunde, Jena, Germany Westküstenklinikum Heide, Frauenklinik, Heide, Germany	Karck, Ulrich Weishap, Anja Luhn, Birgit Jahns, Barbara Klausmann, Martine Fuxius, Stefan Staib, Peter Wiebringhaus, Hermann Liedtke, Cornelia Behrens, Robert Schulz, Volker Buck, Ingrid Till, Angelika Deertz, Holger Reichert, Dietmar Ziemendorff, Gabriele Zoche, Hermann Augustin, Doris Lambertz, Helmut Dauscher-Zohlnhoefer, Martina Bechtner, Christina Stalzer, Gabriele Friedrichs, Kay Hempel, Dirk Busch, Steffi Aulitzky, Walter Neumann, Monika Diel, Ingo Neunhoeffer, Tanja Conrad, Bettina Ruhland, Frank Prange-Krex, Gabriele Euchenhofer, Birgit Lindner, Christoph Maerz, Herbert Breitbach, Georg-Peter Aleksiene, Rasa Tessen, Hans Werner Schmitz, Stephan Hansen, Claudia Schwickerath, Juergen Scheler, Peter Runnebaum, Ingo Kunz, Thomas
Chilean Cooperative Group for Oncologic Research (GOCCHI) Fundación Arturo López Pérez, Santiago, Chile Instituto Nacional del Cancer, Santiago, Chile Hospital Carlos Van Buren, Valparaíso, Chile Centro de Estudios Oncologicos Santiago, Santiago, Chile Instituto Clinico Oncologico del Sur, Temuco, Chile Hospital San Borja Arriarán, Santiago, Chile Clinica Reñaca, Viña del Mar, Chile Hospital Base Valdivia, Valdivia, Chile	Salman, Pamela Torres, Roberto Acevedo, Alejandro Majlis, Alejandro Yañez, Eduardo Del Castillo, Cesar Giannini, Osvaldo Cardemil, Juana
Italian Oncology Group of Clinical Research (GOIRC) Università degli Studi di Genova, Genova, Italy Azienda Sanitaria Unica Regionale n.3 di Fano, Fano, Pesaro-Urbino, Italy Azienda Ospedaliera "Istituti Ospitalieri" di Cremona, Cremona, Italy Ospedale Civile SS Annunziata, Sassari, Italy	Ballestrero, Alberto Mattioli, Rodolfo Passalacqua, Rodolfo Pazzola, Antonio
Israel Breast Cancer Group (IBCG) Laniado Hospital, Netanya, Israel Sheba Medical Center, Ramat Gan, Israel Soroka Medical Center, Beersheba, Israel Kaplan Medical Center, Rehovot, Israel Tel Aviv Sourasky Medical Center, Tel Aviv, Israel Wolfson Medical Center, Holon, Israel Shaare Zedek Medical Center, Jerusalem, Israel Rambam Medical Center, Haifa, Israel	Merrick, Yael Kaufman, Bella Geffen, David Efrat (Ben-Baruch), Noa Safra, Tamar Karminsky, Naly Segal, Amiel Epelbaum, Ron
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Table A1. ALTTO Investigators and Participating Groups (continued)

Participating Groups	Investigators
International Breast Cancer Study Group (IBCSG)	
Országos Onkológiai Intézet, Budapest, Hungary	Láng, István
Institutul Oncologic "Ion Chircuta" Iuj, Napoca, Romania	Eniu, Alexandru
Istituto Europeo di Oncologia (Istituto di Ricovero e Cura a Carattere Scientifico) di Milano, Milan, Italy	Colleoni, Marco
Azienda Ospedaliera Papa Giovanni XX, Bergamo, Italy	Tondini, Carlo
Fondazione Salvatore Maugeri, Istituto di Ricovero e Cura a Carattere Scientifico, Pavia, Italy	Pavesi, Lorenzo
Azienda Unità Sanitaria Locale di Rimini, Rimini, Italy	Gianni, Lorenzo
Centre Hospitalier Universitaire de Liège, Liege, Belgium	Jerusalem, Guy
Azienda Ospedaliero-Universitaria "Santa Maria della Misericordia," Udine, Italy	Puglisi, Fabio
Kantonsspital St Gallen, St Gallen, Switzerland	Hasler-Strub, Ursula
Ospedale "B. Ramazzini" di Carpi, Carpi, Modena, Italy	Artioli, Fabrizio
Centro di Riferimento Oncologico, Istituto Nazionale Tumori, Aviano, Pordenone, Italy	Spazzapan, Simon
Azienda Ospedaliera Spedali Civili di Brescia, Brescia, Italy	Simoncini, Edda
Ospedale "Misericordia e Dolce," Prato, Italy	Di Leo, Angelo
Kantonsspital Graubünden, Chur, Switzerland	von Moos, Roger
Centre Hospitalier Peltzer-La Tourelle, Verviers, Belgium	Barbeaux, Annelore
Azienda Ospedaliero di Lecco, Presidio di Lecco Alessandro Manzoni, Lecco, Italy	Visini, Marilena
Spital Thun, Simmental, Thun, Switzerland	Rauch, Daniel
Clinique St Joseph, Liège, Belgium	Graas, Marie-Pascale
Azienda Ospedaliera-Universitaria Ospedale di Circolo e Fondazione Macchi, Varese, Italy	Pinotti, Graziella
Ospedale degli Infermi, Biella, Italy	Clerico, Mario
Ospedale Beata Vergine Mendrisio, Mendrisio, Switzerland	Pagani, Olivia
Universitätsspital Basel, Basel, Switzerland	Rochlitz, Christoph
Groote Schuur Hospital, Cape Town, South Africa	van Wijk, Adriaan Leon
Centre Hospitalier Universitaire Vaudois, Centre Pluridisciplinaire d'Oncologie, Lausanne, Switzerland	Zaman, Khalil
Kantonsspital Aarau, Aarau, Switzerland	Kralidis, Elena
Centre Hospitalier Régional de Huy, Huy, Belgium	Jacquy, Caroline
Grand Hôpital de Charleroi Site-Notre Dame, Charleroi, Belgium	Canon, Jean-Luc
Hospital Fêmeina, Porto Alegre, Brazil	Oppermann, Christina
Istituto Clinico Humanitas, Rozzano, Milan, Italy	Santoro, Armando
Universitätsspital Zürich, Onkologie, Zürich, Switzerland	Pestalozzi, Bernhard
All Ireland Cooperative Research Group (ICORG)	
University College Hospital, Galway City, Ireland	Keane, Maccon
Beaumont Hospital, Dublin 9, Ireland	Breathnach, Oscar
St James Hospital, Dublin 8, Ireland	Kennedy, M John
Cork University Hospital, Cork, Ireland	O'Reilly, Seamus
Adelaide and Meath Hospital, Dublin, Ireland	Walshe, Janice
Mater Misericordiae University Hospital, Dublin, Ireland	McCaffrey, John
Institute of Cancer Research (ICR)	
Broomfield Hospital, Chelmsford, United Kingdom	Skaria, Sunil
The Royal Marsden NHS Foundation Trust, London, United Kingdom	Smith, Ian
The Royal Shrewsbury Hospital, Shrewsbury, United Kingdom	Agrawal, Rajiv
Maidstone Hospital, Maidstone, United Kingdom	Harper-Wynne, Catherine
St Bartholomew's Hospital, London, United Kingdom	Roylance, Rebecca
Huddersfield Royal Infirmary, Huddersfield, United Kingdom	Joffe, Johnathan
The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom	Smith, Ian
Churchill Hospital, Oxford, United Kingdom	Levitt, Nicola
Queens Hospital, Romford, United Kingdom	Quigley, Mary
Royal Preston Hospital, Fulwood, Preston, United Kingdom	Hogg, Martin
City General Hospital, Stoke-on-Trent, United Kingdom	Brunt, Adrian
Southend Hospital, Westcliff-on-Sea, Essex, United Kingdom	Algurafi, Hafiz
Weston Park Hospital, Sheffield, United Kingdom	Coleman, Robert
Mount Vernon Cancer Centre, Northwood, United Kingdom	Makris, Andreas
Bristol Haematology and Oncology Centre, Bristol, United Kingdom	Price, Christopher
Brighton and Sussex University Hospitals NHS Trust, Brighton, United Kingdom	Bloomfield, David
Charing Cross Hospital, London, United Kingdom	Stebbing, Justin
Royal Lancaster Infirmary, Lancaster, United Kingdom	Eaton, John
Royal Surrey County Hospital, Guildford, United Kingdom	Thandar, Hasina
St James's University Hospital, Leeds, West Yorkshire, United Kingdom	Perren, Timothy
The Royal Bournemouth Hospital, Bournemouth, United Kingdom	Hickish, Tamas
University College London Hospital, London, United Kingdom	Stein, Rob
Worthing Hospital, Worthing, United Kingdom	Mitra, Sankha Surva
Bayhealth Medical Center at Kent General, Dover, DE	Khan, Iftekhar
Derriford Hospital, Plymouth, United Kingdom	Kelly, Stephen
Dorset County Hospital, Dorchester, United Kingdom	Crellin, Robert
Nottingham University Hospitals, City Hospital Campus, Nottingham, United Kingdom	Khan, Sarah
St Helen's Hospital, St Helens, United Kingdom	Innes, Helen

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Table A1. ALTTO Investigators and Participating Groups (continued)

Participating Groups	Investigators
St Mary's Hospital, London, United Kingdom	Cleator, Susan
Velindre Cancer Centre, Cardiff, United Kingdom	Barrett-Lee, Peter
Castle Hill Hospital, Hull, United Kingdom	Lind, Michael
Cheltenham General Hospital, Cheltenham, United Kingdom	Benstead, Kim
Diana Princess of Wales Hospital, Grimsby, United Kingdom	Butt, Mohammad
Newcastle General Hospital, Newcastle upon Tyne, United Kingdom	Verrill, Mark
Poole Hospital, Poole, United Kingdom	Chakrabarti, Amitabha
St George's Hospital, London, United Kingdom	Assersohn, Laura
The Ipswich Hospital NHS Trust, Ipswich, United Kingdom	Sherwin, Karen
Blackpool Teaching Hospitals NHS Foundation Trust, Blackpool, United Kingdom	Hindley, Andrew
Queen Alexandra Hospital, Portsmouth, United Kingdom	Gulliford, Timothy
Royal Devon and Exeter Hospital, Exeter, United Kingdom	Goodman, Andrew
Royal Liverpool University Hospital, Liverpool, United Kingdom	O'Reilly, Susan
South West Wales Cancer Institute, Swansea, United Kingdom	Bertelli, Gianfilippo
Japan Breast Cancer Research Group (JBCRG)	
Aichi Cancer Center Hospital, Aichi, Japan	Iwata, Hiroji
Saitama International Medical Center, Saitama, Japan	Saeki, Toshiaki
Osaka National Hospital, Osaka, Japan	Masuda, Norikazu
St Luke's International Hospital, Tokyo, Japan	Yamauchi, Hideko
The Cancer Institute Hospital of the Japanese Foundation of Cancer Research (Ariake), Tokyo, Japan	Ito, Yoshinori
National Cancer Center Hospital East, Chiba, Japan	Mukai, Hirofumi
Tokai University Hospital, Kanagawa, Japan	Tokuda, Yutaka
Mitsui Memorial Hospital, Tokyo, Japan	Fukuuchi, Atsushi
Shikoku Cancer Center, Ehime, Japan	Aogi, Kenjirō
Tokyo Metropolitan Komagome Hospital, Tokyo, Japan	Kuroi, Katsumasa
Tsukuba University Hospital, Ibaraki, Japan	Bando, Hiroko
National Kyushu Cancer Center, Fukuoka, Japan	Ohno, Shinji
Kitano Hospital, Osaka, Japan	Yamauchi, Akira
Kyoto University Hospital, Kyoto, Japan	Ishiguro, Hiroshi
Korean Cancer Study Group (KCSG)	
National Cancer Center, Gyeonggi-do, Korea	Ro, Jung-Sil
Samsung Medical Center, Seoul, Korea	Im, Young-Hyuck
Yonsei University College of Medicine, Seoul, Korea	Sohn, Joo Hyuk
Asan Medical Center, Seoul, Korea	Kim, Sung-Bae
Seoul National University Hospital 1, Seoul, Korea	Kim, Tae-You
Ajou University Hospital, Suwon, Kyunggi-do, Korea	Ahn, Mi Sun
Inha University Hospital, Incheon, Korea	Lee, Moon-Hee
Norwegian Breast Cancer Group (NBCG)	
Rikshospitalet, Radiumhospitalet HF, Oslo, Norway	Sætersdal, Anna
Ullevål Universitetssykehus, Onkologisk avdeling, Oslo, Norway	Wist, Erik
Universitetssykehuset i Nord, Norge, Tromsø, Norway	Bremnes, Yngve
Sarah Cannon Research Institute (SCRI)	
Tennessee Oncology, Nashville, TN	Yardley, Denise
Florida Cancer Specialists, Ft Myers, FL	Hart, Lowell
Oncology Hematology Care, Cincinnati, OH	Ward, Patrick
Virginia Cancer Care, Richmond, VA	Trent, David
Tennessee Oncology, Chattanooga, TN	Daniel, Brooke
SOLTI Breast Cancer Research Group	
Hospital Universitario Valle d'Hebron, Barcelona, Spain	Bellet, Meritxell
Hospital 12 De Octubre, Madrid, Spain	Ciruelos, Eva
Clinico de Santiago, Santiago de Compostela, Spain	López, Rafael
Hospital Arnau de Vilanova, Lerida, Lerida, Spain	Morales Murillo, Serafin
Hospital Son Llatzer, Palma de Mallorca, Spain	Garau Llinás, Isabel
Hospital Virgen de la Macarena 1, Seville, Spain	Virizuela Echaburu, Juan Antonio
Institut Català d'Oncologia, Barcelona, Spain	Pernas, Sonia
Son Espases, Palma de Mallorca, Spain	Avella Mestre, Antoni
Hospital General de Valencia, Valencia, Spain	Godes, Maria Jose
Hospital Mutua De Tarrasa, Tarrasa, Barcelona, Spain	Gonzalez, Sonia
Taiwan Cooperative Oncology Group (TCOG)	
National Taiwan University Hospital, Taipei, Republic of China	Huang, Chiun-Sheng
China Medical University Hospital, Taichung, Republic of China	Wang, Hwei-Chung
Chang Gung Memorial Hospital, Taipei, Taipei, Republic of China	Chen, Shin-Cheh
Taipei Veterans General Hospital, Taipei, Republic of China	Chiou, Tzeon-Jye
Chi-Mei Hospital, Liouying, Tainan, Republic of China	Tsao, Chao-Jung
Mackay Memorial Hospital, Taipei, Republic of China	Hsieh, Ruey-Kuen
Kaohsiung Medical University Hospital, Kaohsiung, Republic of China	Hou, Ming-Feng
Tri Service General Hospital, Taipei, Republic of China	Chao, Tsu-Yi

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Table A1. ALTTO Investigators and Participating Groups (continued)

Participating Groups	Investigators
US Oncology	
Kansas City Cancer Centers, Overland Park, KS	McKittrick, Richard
Tyler Cancer Center, Tyler, TX	Richards, Donald
Ocala Oncology Center, Ocala, FL	Reynolds, Craig
Providence Alaska Medical Center, Anchorage, AK	Anderson, Jeanne
Texas Oncology, Midland, TX	Watkins, David
Alliance Hematology Oncology, Westminster, MD	Rice, Robert
Cancer Care Centers of South Texas-HOAST, San Antonio, TX	Guzley, Gregory
Oncology and Hematology Associates of Southwest Vi, Roanoke, VA	Richards, Paul
Puget Sound Cancer Centers (II), Seattle, WA	Tolman, J. Samuel
South Texas Cancer Center, McAllen, McAllen, TX	Marek, Billie
Texas Oncology, Fort Worth, Fort Worth, TX	Ruxer, Jr, Robert
Hematology and Oncology Associates, Greenville, SC	Edenfield, William
Longview Cancer Center, Texas Oncology, Longview, TX	Socoteanu, Matei
Medical Oncology Associates of Wyoming Valley, Kingston, PA	Saidman, Bruce
Texas Oncology, Bedford, Bedford, TX	Anderson, Thomas
Willamette Valley Cancer Center, Eugene, OR	Cho, Benjamin
Independent sites	
Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China	Xu, Binghe
Cancer Hospital Affiliated to Fudan University, Shanghai, People's Republic of China	Shao, Zhimin
The Hospital Affiliated to Military Medical Science, Beijing, People's Republic of China	Jiang, Zefei
Hameed Latif Hospital, Lahore, Pakistan	Aziz, Zeba
Tianjin Cancer Hospital, Tianjin, People's Republic of China	Tong, Zhongsheng
University Witwatersrand Oncology, Parktown, South Africa	Moodley, Shun
King Edward Medical College and Mayo Hospital, Lahore, Pakistan	Ahmed, Shaharyar
Central India Cancer Research Institute, Nagpur, India	Mehta, Ajay
Russian Cancer Research Centre n.a. N. N. Blokhin of RAMS, Moscow, Russian Federation	Tjulandin, Sergei
Russian Cancer Research Centre n.a. N. N. Blokhin or RAMS, Moscow, Russian Federation	Lichinitser, Michael
National Cancer Institute, Thailand, Bangkok, Thailand	Arpornwirat, Wichit
St Luke's Medical Center, Quezon City, Philippines	Li, Rubi
Institutul Oncologic "Prof. Alexandru Trestioreanu" Bucuresti, Bucharest, Romania	Dediu, Mircea
Tuen Mun Hospital, Tuen Mun, Hong Kong, Special Administrative Region, People's Republic of China	Ng, Ting Ying
Panorama Medical Centre, Cape Town, South Africa	Pienaar, Fredrieka
Nizam's Institute of Medical Sciences, Hyderabad, Andhra Pradesh, India	Digumarti, Raghunadharao
Masarykuv onkologický ústav, Brno, Czech Republic	Petrakova, Katarina
Perpetual Succour Hospital, Cebu City, Philippines	Tudtud, Dennis Ramon
Sun Yat-Sen University Cancer Center, Guangzhou, People's Republic of China	Guan, Zhongzhen
Cardinal Santos Hospital, Greenhills, West San Juan, Philippines	Chua-Tan, Marina
All India Institute of Medical Sciences, New Delhi, India	Raina, Vinod
Lviv State Regional Oncology Medicine and Diagnostics Centre, Lviv, Ukraine	Shparyk, Yaroslav
Clinical Oncology Dispensary, Kazan, Russian Federation	Khasanov, Rustem
Centrum Onkologii, Bydgoszcz, Poland	Tujakowski, Jerzy
Arkhangelsk Regional Oncology Dispensary, Arkhangelsk, Russian Federation	Burdaeva, Olga
Tata Memorial Hospital, Parel, Mumbai, India	Gupta, Sudeep
Wojewódzkie Centrum Onkologii, Gdańsk, Poland	Pikiel, Joanna
University of Santo Tomas Hospital, Manila, Philippines	Caguioa, Priscilla
Medical Sanitary Unit #97, Voronezh, Russian Federation	Ognerubov, Nikolai
Liaquat National Hospital, Karachi, Pakistan	Zahid, Naila
Pramongkutklao Hospital 2, Bangkok, Thailand	Vassanasiri, Wichai
National University Hospital (Singapore), Singapore	Lee, Soo Chin
Szegedi Tudományegyetem Onkológia, Szeged, Hungary	Kahán, Zsuzsanna
National Medical Centre, Karachi, Pakistan	Zahid, Naila
Dolnoslaskie Centrum Onkologii, Wrocław, Poland	Filipczyk-Cisarz, Emilia
Chulalongkorn Hospital, Bangkok, Thailand	Chatamra, Kris
Donetsk Regional Anticancer Center, Donetsk, Ukraine	Popovych, Oleksandr
Azienda Ospedaliera S. Gerardo di Monza, Monza, Monza and Brianza, Italy	Bidoli, Paolo
Zakład Opieki Zdrowotnej MSWiA z Warmińsko-Mazurskim Centrum Onkologii, Olsztyn, Poland	Jagiello-Grusfeld, Agnieszka
Buddhachinraj Hospital, Phitsanulok, Thailand	Pinanusorn, Sontara
Fakultní nemocnice Královské Vinohrady, Praha 10, Czech Republic	Brychta, Milan
Petz Aladár Megyei Kórház, Győr, Hungary	Pintér, Tamás
Petrov Research Institute of Oncology, St Petersburg, Russian Federation	Semiglavov, Vladimir
Euromedica General Clinic of Thessaloniki, Thessaloniki, Greece	Papazisis, Konstantinos
MrukMed Lekarz Beata Madej-Mruk i Partner, Spółka Partnerska-Poradnia, Rzeszów, Poland	Mruk, Andrzej
Národný onkologický ústav, Bratislava, Slovakia	Bohunicky, Lubomir
Sandton Oncology Medical Centre, Morningside, South Africa	Vorobiof, Daniel
Algemeen Ziekenhuis St Lucas, Gent, Belgium	Renard, Vincent

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Table A1. ALTTO Investigators and Participating Groups (continued)

Participating Groups	Investigators
Centro Oncologico de Rosario, Rosario, Argentina	Fein, Luis
Spitalul Universitar Bucuresti, Bucharest, Romania	Blidaru, Alexandru
City Clinical Oncology Dispensary, Head and Neck, St Petersburg, Russian Federation	Manikhas, Alexey
Regional Oncology Dispensary, Chelyabinsk, Russian Federation	Gladkov, Oleg
Little Company of Mary Medical Centre, Pretoria, South Africa	Slabber, Coenraad
Maharaj Nakorn Chiang Mai, Chiang Mai, Thailand	Trakultivakorn, Hongsin
Mahidol University (Siriraj Hospital 1), Bangkok, Thailand	Srimuninnimit, Vichien
Prince of Songkla Hospital, Songkla, Thailand	Dechaphunkul, Arunee
Kyiv City Oncology Hospital, Kyiv, Ukraine	Banakhevych, Natalya
Investigaciones Clinicas Ciudad Autonoma de Buenos, Buenos Aires, Argentina	Lerzo, Guillermo
AZ Nikolaas, Sint-Niklaas, Belgium	Lybaert, Willem
Azienda USL BR/1 di Brindisi, Brindisi, Italy	Cinieri, Saverio
Instituto Nacional de Cancerologia, Mexico City, Mexico	Arce-Salinas, Claudia-Haydee
SP ZOZ Opolskie Centrum Onkologii, Opole, Poland	Drosik, Kazimierz
Steve Biko Academic Hospital (Medical Oncology), Pretoria, South Africa	Dreosti, Lydia
Hospital Universitario Puerta Del Mar 2, Cadiz, Spain	Baena, Jose Maria
Jessa Ziekenhuis, Campus Virga Jesse, Hasselt, Belgium	Luyten, Daisy
Agios Savvas Hospital, Athens, Greece	Koumakis, Georgios
Queen Elizabeth Hospital, Kowloon, Hong Kong, Special Administrative Region, People's Republic of China	Ngan, Kai Cheong Roger
Szent Margit Kórház, Budapest, Hungary	Boér, Katalin
Indraprastha Apollo Hospital, New Delhi, India	Dua, Harsh
Cancer Research Center, Moscow, Russian Federation	Gorbunova, Vera
Brust Zentrum, Zürich, Switzerland	Trojan, Andreas
Netaji Subhs Chandra Bose Cancer Research Institut, Kolkata, India	Mukhopadhyay, Ashis
Central Clinical Hospital of the President of the Russian Federation, Moscow, Russian Federation	Vinogradova, Natalya
Complejo Hospitalario Nuestra Sra de Valme, Seville, Spain	Salvador Bofill, Javier
Hospital la Paz, Madrid, Spain	Zamora Aunon, Pilar
Hospital Provincial de Castellón, Castellón, Spain	Martinez de Dueñas, Eduardo
Centro Medico San Roque, San Miguel de Tucuman, Argentina	Zarba, Juan
University Hospital of Heraklion, Heraklion, Crete, Greece	Georgoulias, Vassilis
Ospedale di Treviglio, Treviglio, Bergamo, Italy	Barni, Sandro
Nuclear Medicine, Oncology and Radiotherapy Institute, Islamabad, Pakistan	Mahmood, Humera
Regional Clinical Oncology Dispensary, Kirov, Russian Federation	Sherman, Nailya
Východoslovenský onkologický ústav, Košice, Slovakia	Wagnerova, Maria
Hospital General Yague, Burgos, Spain	García Girón, Carlos
MD Anderson Cancer Center, Madrid, Spain	González Martín, Antonio
Masarykova nemocnice, Ústí nad Labem, Czech Republic	Lysy, Milan
Azienda Ospedaliera Ospedale Carlo Poma, Mantova, Italy	Cavazzini, Giovanna
Centrum Onkologii, Krakow, Poland	Ziobro, Marek
POKO POPRAD, s.r.o. - Onkologicka Ambulancia, Poprad, Slovakia	Kakalejcik, Marian
SHATOnC, Sofia, Bulgaria	Kurteva, Galina
Nemocnice Nový Jičín, Nový Jičín, Czech Republic	Donocikova, Barbara
Regional Cancer Centre, Trivandrum, India	Mathew, Beela Sarah
Azienda Ospedaliera Ospedale Niguarda Ca'Granda, Milan, Italy	Siena, Salvatore
Ospedale di Asti Struttura Operativa Complessa, Asti, Italy	Testore, Franco
Onkologický ústav svatej Alžbety, Bratislava, Slovakia	Spanik, Stanislav
Centro de Enfermedades Reumaticas, Quilmes, Buenos Aires, Argentina	Varela, Mirta
Academisch Ziekenhuis Vrije Universiteit, Brussel, Brussels, Belgium	De Grève, Jacques
Interdistrict Dispensary for Oncological Diseases "Dr Marko Markov," Varna, Bulgaria	Popov, Vassil
Nemocnice Ceske Budejovice 1, Ceske Budejovice, Czech Republic	Siffnerova, Hana
Azienda Ospedaliero di Circolo di Busto Arsizio, Presidio Ospedaliero di Saronno, Saronno, Varese, Italy	Verusio, Claudio
Regional Oncology Dispensary, Orenburg, Russian Federation	Shirinkin, Vadim
Samara Regional Oncology Center, Samara, Russian Federation	Kopp, Mikhail
Hospital Gregorio Maranon, Madrid, Spain	Martín Jiménez, Miguel
Hospital Provincial de Zamora, Zamora, Spain	Valero Alvarez Gallego, José
Hospital Reina Sofia 1, Cordoba, Spain	de la Haba, Juan
Onze Lieve Vrouw Ziekenhuis Aalst, Aalst, Belgium	Vroman, Philippe
University Hospital of Patras, Patras, Greece	Kalofonos, Haralabos
Azienda Ospedaliera San Giuseppe Moscati, Avellino, Italy	Gridelli, Cesare
Casa di Cura Poliambulanza, Brescia, Italy	Zaniboni, Alberto
Ospedale Multifunzionale Vito Fazzi, Lecce, Italy	Forcignanò, Rosachiara
Ospedale Santa Anna, Como, Italy	Giordano, Monica
Centro Oncológico Lomas, Mexico City, Mexico	Sánchez Forgach, Ernesto
Khonkaen University Hospital, Khonkaen, Thailand	Bhudhisawasdi, Vajarabhongsa
Crimean Institution Oncological Clinical Dispensary, Simferopol, Ukraine	Seferov, Bekir
Arizona Clinical Research Cancer Center, Tucson, AZ	Modiano, Manuel

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Table A1. ALTTO Investigators and Participating Groups (continued)

Participating Groups	Investigators
Centro Oncologico de Integracion Regional, Mendoza, Argentina	Hidalgo, Jorge
ISIS Clinica Especializada, Santa Fe, Argentina	Blajman, Cesar
Centre Hospitalier Régional St Joseph-Warquignies, Mons, Belgium	Casert, Vinciane
Centre Hospitalier de Wallonie Picarde Site IMC, Tournai, Belgium	Dopchie, Catherine
Ziekenhuis Oost-Limburg, Genk, Belgium	Debrock, Guy
Nemocnice Na Bulovce, Praha 8, Czech Republic	Stahalova, Vladimira
Teaching Health Centre, Prague 2, Czech Republic	Petruzelka, Lubos
Istituto per la Ricerca ed il Trattamento del Cancro, Candiolo, Turin, Italy	Montemurro, Filippo
Ospedali Riuniti di Livorno, Livorno, Italy	Cappuzzo, Federico
Irkutsk Regional Oncology Dispensary, Irkutsk, Russian Federation	Dvornichenko, Viktoria
Eastleigh Breast Care Centre, Pretoria, South Africa	Coccia-Portugal, Maria
Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain	Batista, Jose
Hospital Morales Meseguer, Murcia, Spain	García Carré, Elisa
Academisch Ziekenhuis St Jan, Brugge, Belgium	Bols, Alain
Centre Hospitalier Régional de la Citadelle, Liège, Belgium	Salmon, Jean-Paul
MHAT "Tsaritsa Yoanna," Sofia, Bulgaria	Velikova, Maya
Semmelweis Egyetem, Budapest, Hungary	Dank, Magdolna
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola (FC), Italy	Amadori, Dino
Presidio Ospedaliero di Ravenna, Ravenna, Italy	Tienghi, Amelia
Clinical del Parque, Chihuahua, Mexico	Lugo Quintana, Roberto Sergio
Sanatorio Florencia, Toluca, Estado de México, Mexico	Gomez-Villanueva, Angel
Onko-Med, Sp. z o.o., Olsztyn, Poland	Jagiello-Grusfeld, Agnieszka
Oncology Dispensary, Omsk, Russian Federation	Merkulov, Vladimir
Fakultná Nemocnica s poliklinikou Žilina, Žilina, Slovakia	Hubry, Richard
Hospital Clínico Universitario, Salamanca, Spain	Rodríguez Sánchez, César
Hospital Nuestra Señora De Los Lirios, Alcoy, Alicante, Spain	Oltra, Amparo
Institute of Medical Radiology, Kharkiv, Ukraine	Tarasova, Oksana
Irmandade da Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil	Zereu, Manuela
Interdistrict Dispensary for Oncological Diseases Shumen, Shumen, Bulgaria	Markova, Hristina
Fakultní nemocnice u svaté Anny v Brně, Brno, Czech Republic	Bednarik, Otakar
Nemocnice Jihlava, Jihlava, Czech Republic	Slavicek, Lubomir
Nemocnice Pardubice, Pardubice, Czech Republic	Vanasek, Jaroslav
Ospedale Belcolle, Viterbo, Italy	Moscetti, Luca
Ospedale dell'Alta Val d'Elsa, Azienda USL 7 Siena, Poggibonsi, Siena, Italy	Crispino, Sergio
Centrul de Oncologie Medicala, Iasi, Romania	Volovat, Constantin
Hospital de Elda 1, Elda, Spain	Llorca, Cristina
Hospital General de Segovia, Segovia, Spain	Esteban Herrera, Beatriz
Hospital Lucus Augusti, Lugo, Spain	Alvarez Gómez, Elena
Hospital Marques de Valdecilla, Santander, Spain	López Vega, Jose Manuel
Instituto de Oncología Ángel H. Roffo, Ciudad Autónoma de Buenos Aires, Buenos Aires, Argentina	Alvarez, Ana
Sint Elisabeth Ziekenhuis, Turnhout, Belgium	Pelgrims, Gino
Biocâncer, Belo Horizonte, Brazil	Portella, Marcos
Hospital Santa Izabel, Salvador, Brazil	Andrade, Lívia
Fakultní nemocnice v Motol, Praha 5, Czech Republic	Prausova, Jana
Tartu University Clinics, Tartu, Estonia	Padrik, Peeter
Hygeia Diagnostic & Therapeutic Center of Athens, Athens, Greece	Kosmidis, Paris
Fővárosi Onkormányzat Uzsoki Utcai Kórháza, Budapest, Hungary	Landherr, László
Azienda Ospedaliera Universitaria San Martino, Genoa, Italy	Sobrero, Alberto
Institut Oncologic "Prof Dr Alexandru Trestioreanu" Bucuresti, Bucharest, Romania	Stanculeanu, Dana Lucia
City Clinical Hospital #1, Novosibirsk, Russian Federation	Sidorov, Sergey
Regional Clinical Oncology Dispensary, Ryazan, Russian Federation	Shomova, Marina
Hospital de Navarra, Pamplona, Spain	Illarramendi, Jose Juan
Hospital Carlos, Haya, Malaga, Spain	Carabantes, Francisco
Hospital de Donostia, San Sebastián, Spain	Alvarez Lopez, Isabel
Hospital De Mataro, Barcelona, Spain	Lianes, Pilar
Virgen de la Salud, Toledo, Spain	Chacón López-Muñiz, José Ignacio
Imelda Ziekenhuis, Bonheiden, Belgium	Wynendaele, Wim
Nemocnice Chomutov, Chomutov, Czech Republic	Pribylova, Jana
Thomayerova nemocnice, Praha 4, Czech Republic	Abrahamova, Jitka
Hygeia Diagnostic & Therapeutic Centre of Athens, Athens, Greece	Karydas, Irini
Ospedale Versilia, Lido Di Camaiore (Lucca), Italy	Amoroso, Domenico
Presidio Ospedaliero Annunziata, Cosenza, Italy	Palazzo, Salvatore
Hospital Cruces, Baracaldo/Vizcaya, Spain	Lopez Vivanco, Guillermo
Hospital de la Princesa 2, Madrid, Spain	Donnay Candil, Olga
Hospital de Móstoles 1, Móstoles/Madrid, Spain	Méndez Ureña, Miguel
Hospital Virgen de las Nieves, Granada, Spain	Gonzalez, Encarna

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Table A1. ALTTO Investigators and Participating Groups (continued)

Participating Groups	Investigators
North American Breast Cancer Group, US Sites	
American College of Surgeons Oncology Group (ACOSOG)	
Princeton Community Hospital, Princeton, NJ	Gonzales-Chambers, Rowena
Cancer and Leukemia Group B (CALGB)	
North Shore University Hospital, Manhasset, NY	Budman, Daniel
Washington University School of Medicine, St Louis, MO	Naughton, Michael
Rex Cancer Center, Raleigh, NC	Moore, Susan
Fort Wayne Medical Oncology Hematology, Fort Wayne, IN	Nattam, Sreenivasa
Saint Barnabas Cancer Center, Livingston, NJ	Michaelson, Richard
Lake Region General Hospital, Laconia, NH	Weckstein, Douglas
Moores Cancer Center, UCSD, La Jolla, United States	Parker, Barbara
Roswell Park Cancer Institute, Buffalo, NY	Levine, Ellis
Virginia Oncology Associates, Hampton, VA	Conkling, Paul
Wake Forest University Health Sciences, Winston-Salem, NC	Melin, Susan
Moores University of California, La Jolla, CA	Parker, Barbara
Ohio State University Medical Center, Columbus, OH	Mrozek, Ewa
University of Nebraska Medical Center, Omaha, NE	Reed, Elizabeth
New Hampshire Oncology-Hematology, Concord, NH	Weckstein, Douglas
New Hampshire Oncology-Hematology, Hooksett, NH	Weckstein, Douglas
Florida Hospital, Orlando, FL	Zehngebott, Lee
Georgetown University Hospital, Washington, DC	Isaacs, Claudine
Oncology Care Associates, St Joseph, MI	Lester, Eric
Palo Alto Medical Foundation, Camino Division, Mountain View, CA	Yu, Peter
Saint Francis Medical Center, Grand Island, NE	Reed, Elizabeth
University of Maryland at Baltimore, Baltimore, MD	Tkaczuk, Katherine
Cape Cod Hospital, Hyannis, MA	Basile, Frank
Ingalls Memorial Hospital, Harvey, IL	Kozloff, Mark
University of North Carolina, Chapel Hill, NC	Carey, Lisa
Chemistry in Cancer Research (CICR)	
Edwards Comprehensive Cancer Center, Huntington, WV	Tria Tirona, Maria
Jackson-Madison County General Hospital, Jackson, TN	Asmar, Salomon
Marion L. Shepard Cancer Center, Washington, NC	Inzerillo, John
Saint Francis Hospital and Medical Center, Topeka, KS	Hurwitz, Michael
Eastern Cooperative Oncology Group Study (ECOG)	
Vanderbilt University 1, Nashville, TN	Mayer, Ingrid
West Virginia University Charleston, Charleston, WV	Jubelirer, Steven
Northwestern University, Chicago, IL	Gradishar, William
Johns Hopkins University, Baltimore, MD	Wolff, Antonio
Saint Joseph Mercy Hospital, Ann Arbor, MI	Stella, Philip
Indiana University Medical Center 1, Indianapolis, IN	Storniolo, Anna
St Vincent's Hospital & Medical Center, New York, NY	Klein, Paula
Hackensack University Medical Center, Hackensack, NJ	Waintraub, Stanley
Advocate Christ Medical Center, Oak Lawn, IL	Weese, James
Dean Clinic, Madison, WI	Sanyal, Amit
Evanston Northwestern Healthcare, Evanston, IL	Merkel, Douglas
Fox Chase Cancer Center, Philadelphia, PA	Goldstein, Lori
Mary Imogene Bassett Hospital, Cooperstown, NY	Bravin, Eric
New York University Medical Center, Division of Vascular Surgery, New York, NY	Novik, Yelena
Pottstown Memorial Medical Center, Pottstown, PA	Song, Wei
Fox Valley Hematology and Oncology, Appleton, WI	Bar-Lev, Avi
Aultman Hospital, Canton, OH	Weeman, Kisa
Medical Consultants, Muncie, IN	Spahr, Joseph
Reading Hospital and Medical Center, West Reading, PA	Cescon, Terrence
St Lukes Health Network, Bethlehem, PA	Nakajima, Hikaru
Somerset Medical Center, Somerville, NJ	Rosenbluth, Jonathan
Swedish American Hospital, Rockford, IL	Einhorn, Harvey
Boca Raton Community Hospital, Boca Raton, FL	Koletsky, Alan
Montefiore Medical, Bronx, NY	Sparano, Joseph
Oakwood Hospital, Dearborn, MI	Stella, Philip
NCCTG Alliance	
Illinois Cancer Care, Peoria, IL	Le-Lindqwister, Nguyet
Rapid City Regional Hospital, Rapid City, SD	Schroeder, Mark
Memorial Healthcare System, Joe DiMaggio Children's Hospital, Hollywood, FL	Perez, Alejandra
Mayo Clinic Cancer Center, Rochester, MN	Perez, Edith
McFarland Clinic, Ames, IA	Merchant, Joseph
Edna Williams Cancer Center at the Baptist Cancer, Jacksonville, FL	Guthrie, Troy
Fairview Southdale Medical Oncology, Edina, MN	Flynn, Patrick
Mayo Clinic Jacksonville, Jacksonville, FL	Perez, Edith

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Table A1. ALTTO Investigators and Participating Groups (continued)

Participating Groups	Investigators
Medcenter One Health Systems, Bismarck, ND	Wos, Edward
Mayo Clinic, Scottsdale, AZ	Perez, Edith
Rice Memorial Hospital, Willmar, MN	Flynn, Patrick
Front Range Cancer Specialists, Ft Collins, CO	Medgyesy, Diana
Memorial Medical Center, Las Cruces, NM	Royce, Melanie
Green Bay Oncology at Saint Vincent, Green Bay, WI	Jaslawski, Anthony
Saint John's Hospital, Healtheast, Maplewood, MN	Flynn, Patrick
Duluth Clinic Community Clinical Oncology Program, Duluth, MN	Nikcevich, Daniel
Cancer Center of Kansas-Pratt, Pratt, KS	Dakhil, Shaker
Cox Medical Center, Springfield, MO	Carolla, Robert
Exempla Lutheran Medical Center, Wheat Ridge, CO	Sturtz, Keren
Franciscan Skemp Healthcare, La Crosse, WI	Gill, Paula
Kettering Medical Center, Kettering, OH	Gross, Howard
Oklahoma Community Clinical Oncology Program, Tulsa, OK	Keller, Alan
University of New Mexico, Albuquerque, NM	Royce, Melanie
Mercy Cancer Center, Mason City, IA	Vemula, Arvind
Midelfort Clinic-Clairemont Campus, Eau Claire, WI	Chakrabarti, Sakti
University of Hawaii, Honolulu, HI	Cho, Jonathan
Big Sky Oncology, Great Falls, MT	Harrer, Grant
Green Bay Oncology-Sturgeon Bay, Sturgeon Bay, WI	Jaslawski, Anthony
Guthrie Clinical Research, Sayre, PA	O'Brien, Edward
Hematology Oncology Associates, Albuquerque, NM	Royce, Melanie
Lawrence Memorial Hospital, Lawrence, KS	Dakhil, Shaker
Minnesota Oncology Hematology at Maplewood, Maplewood, MN	Flynn, Patrick
Regions Hospital, St Paul, MN	Flynn, Patrick
Tripler Army Medical Center, Honolulu, HI	Berenberg, Jeffrey
United Hospital, St Paul, MN	Flynn, Patrick
Illinois CancerCare, Peru, IL	Le-Lindqvister, Nguyet
Kauai Medical Clinic, Lihue, HI	Cho, Jonathan
Queens Medical Center, Honolulu, HI	Cho, Jonathan
National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)	
British Columbia Cancer Agency, Cancer Centre, Southern Interior, Kelowna, British Columbia, Canada	Ellard, Susan
Allan Blair Cancer Centre, Regina, Saskatchewan, Canada	Salim, Muhammad
Centre hospitalier universitaire de Sherbrooke, Hospital Fleurimont, Sherbrooke, Quebec, Canada	Dufresne, Jean
British Columbia Cancer Agency, Vancouver Cancer Centre, Vancouver, British Columbia, Canada	Chia, Stephen
Algoma District Cancer Program, Sault Ste Marie, Ontario, Canada	Spadafora, Silvana
Dr Léon-Richard Oncology Centre, Moncton, New Brunswick, Canada	Ghedira, Skander
Prince Edward Island Cancer Treatment Centre, Charlottetown, Prince Edward Island, Canada	Dryer, Dagny
National Surgical Adjuvant Breast and Bowel Project (NSABP)	
Frederick Memorial Hospital, Frederick, MD	O'Connor, Brian
Methodist Eastbrook Cancer Center, Omaha, NE	Block, Margaret
Baylor College of Medicine, Houston, TX	Rimawi, Mothaffar
Saint Joseph Medical Center, Towson, MD	Couzi, Rima
Holy Cross Hospital, Silver Spring, MD	Aylesworth, Cheryl
Radiation Therapy Oncology Group (RTOG)	
Trinity Cancer Care Center, Minot, ND	Watanabooniyakhet, Patanit
North Shore Medical Center, Peabody, MA	Come, Steven
Southwest Oncology Group (SWOG)	
Wayne State University, Detroit, MI	Flaherty, Lawrence
MD Anderson Cancer Center, Orlando, FL	Shah, Nikita
Stormont-Vail Regional HealthCare, Topeka, KS	Einspahr, David
Loyola University Medical Center, Maywood, IL	Lo, Shelly
University of Utah, Salt Lake City, UT	Werner, Theresa
Caritas St Elizabeth Medical Center, Boston, MA	Martin, Leslie
Dekalb Medical Center, Decatur, GA	Seay, Thomas
Oncare Hawaii, Honolulu, HI	Cho, Jonathan
Columbia University Medical Center, New York, NY	Hershman, Dawn
Medical University of South Carolina, Charleston, SC	Kramer, Rita
Poudre Valley Hospital, Fort Collins, CO	Romero, Paolo
Singing River Hospital System, Pascagoula, MS	Clarkson, James
Tulane University Health Science Center, New Orleans, MO	Safah, Hana
University of California at Davis, Davis, CA	Chew, Helen
University of Tennessee-Knoxville, Knoxville, TN	Panella, Timothy
City of Hope National Medical Center, Duarte, CA	Luu, Thehang
John B. Amos Cancer Center, Columbus, GA	Pippas, Andrew
Providence Hospital, Southfield, MI	Bloom, Robert
St Joseph Hospital, Bellingham, WA	Rivkin, Saul

(continued on following page)

Table A1. ALTTO Investigators and Participating Groups (continued)

Participating Groups	Investigators
St Luke's Mountain State Tumor Institute, Boise, ID University of Louisville, Louisville, KY	Walters, Ted Jain, Dharamvir
Undefined	
Memorial Medical Center, Springfield, IL	Wade, James
Meritcare Medical Group, Fargo, ND	Steen, Preston
Alegent Health Bergan Mercy Medical Center, Omaha, NE	Soori, Gaminí
Billings Clinic, Billings, MT	Marchello, Benjamin
Mount Carmel Health Center West, Columbus, OH	Kuebler, J. Philip
Northwest Community Clinical Oncology Program, Tacoma, WA	Colman, Lauren
West Michigan Cancer Center, Kalamazoo, MI	Lord, Ray
CentraCare Clinic, Saint Cloud, MN	Jurgens, Donald
Dartmouth-Hitchcock Medical Center, Lebanon, NY	Schwartz, Gary
Siouxland Hematology-Oncology Associates, Sioux City, IA	Wender, Donald
Hematology-Oncology Associates of Central New York, East Syracuse, NY	Kirshner, Jeffrey
Lincoln Medical Education Foundation Cancer Resources, Lincoln, NE	Soori, Gaminí
Cancer Therapy & Research Center, San Antonio, TX	Karnad, Anand
Grant Medical Center, Columbus, OH	Kuebler, J. Philip
Grant/Riverside Methodist Hospital, Columbus, OH	Kuebler, J. Philip
Iowa Blood and Cancer Care, Cedar Rapids, IA	Zenk, David
Maine Centre for Cancer Medicine, Scarborough, ME	Weisberg, Tracey
Alegent Health Immanuel Medical Center, Omaha, NE	Soori, Gaminí
Cancer Care Associates, Oklahoma City, OK	Pant, Shubham
Legacy Good Samaritan Hospital and Medical Center, Portland, OR	Vuky, Jacqueline
Mercy Physicians of Oklahoma, Oklahoma City, OK	Canfield, Vikki
Penn State Hershey Medical Center, Hershey, PA	Cream, Leah
Wilford Hall Medical Center, Lakeland Air Force Base, TX	Renshaw, John

The above centers had an accrual of more than one patient.