

ID	study	author	year
----	-------	--------	------

1 TARGET J. Bonneterre 2000

2 the North American trial J. M. Nabholz 2000

the International  
3 Letrozole Breast Cancer Group Henning Mouridsen 2001

4 Alfredo Milla-Santos, M.D. 2003

5 Anthony Howell 2004

6 EORTC

Robert J.  
Paridaens

2008

7/10/12

FIRST

John F. R.  
Robertson/[John](#)  
[F. R.](#) 2009/[2012/2015](#)  
[Robertson](#)/Matthew  
J. Ellis

8

[GEICAM] 2001/2003

Antonio Llombart-  
Cussac, MD, PhD

2012

9

SWOG

Rita S. Mehta, M.D

2012

11

PALOMA-1/TRIO-18

Richard S Finn

2014

13            PALOMA-2            Richard S. Finn            2016

14            MONALEESA-2            G. N. Hortobagyi            2016

15            FALCON            John F R Robertson\*            2016

16            FACT            Jonas Bergh            2012

journal

clinicaltria.gov

foundation

Journal of Clinical Oncology

Supported by a grant  
from AstraZeneca,  
Macclesfield, United  
Kingdom.

Journal of Clinical Oncology

Supported by a grant  
from AstraZeneca,  
Wilmington, DE, and  
Macclesfield, United  
Kingdom.

Journal of Clinical Oncology

Supported by Novartis  
Pharma AG, Basel,  
Switzerland.

Am J Clin Oncol

Journal of Clinical Oncology

Supported by AstraZeneca  
Pharmaceuticals,  
Wilmington, DE.

Journal of Clinical Oncology

Supported in part by a  
grant from Pfizer  
Inc and Grant No. 2U10  
CA11488-25  
5U10 CA11488-34 from the  
National  
Cancer Institute  
(Bethesda, MD).

Journal of Clinical  
Oncology/[Breast cancer  
research and  
treatment](#)/Journal of Clinical  
Oncology

NCT00274469

AstraZeneca

Cancer

a research grant from  
Pfizer S.A.

The new england journal of  
medicine

NCT00075764

the National Cancer  
Institute and  
AstraZeneca

The Lancet. Oncology

NCT00721409

by Pfizer

The New England journal of  
medicine

NCT01740427

by Pfizer

The new england journal of  
medicine

NCT01958021

Novartis Pharmaceuticals

The Lancet

NCT01602380

AstraZeneca

Journal of Clinical Oncology

—

AstraZeneca

study design	randomization	N(total sample size)
randomized, double-blind, multicenter		668
randomized, double-blind, multicenter study	The randomization scheme was stratified by center.	353
phase III, randomized, double-blind, double- dummy, parallel group study	Treatment was allocated according to computer-generated randomization lists that used permuted blocks of a fixed size and no stratification.	907
phase III, prospective, randomized, single-center trial	Patients were randomly allocated between the two treatment groups following Meinert's methodology.	238
double-blind, randomized, parallel-group, double-dummy trial	The random assignment schedule was produced by the Biostatistics Group at AstraZeneca, using computer software that incorporates a standard procedure for generating random numbers. A separate random assignment schedule was produced for each center.	587 (6 patients did not receive any trial treatment)

multicenter, randomized open-label phase II/III study	Central randomization was performed at the EORTC Data Center in a 1:1 ratio, using the minimization method <sup>12</sup> based on stratification for institution	371
phase II, open-label, randomized, multicenter, parallel-group trial	Patients were randomized sequentially using randomization cards. To prevent biasing the results of the tumor assessments, a blinded independent review was performed by a radiologist at BioImaging Technologies (Leiden, The Netherlands). Other post hoc analyses were performed by the Biostatistics department at AstraZeneca.	205
randomized, open-label cross-over, phase 2 study	Randomization was performed and stratified using the Pocock and Simon algorithm	103
phase 3, randomized trial	Randomization was performed at a central location, with stratification according to prior receipt or no prior receipt of adjuvant tamoxifen therapy.	707 (694, ITT数据)
international, phase 2, multicentre, open-label, randomised study	used an interactive web-based randomisation system to register and randomly assign patients with two stratifications factors	165

double-blind, phase 3 study, randomised	Randomization was stratified according to site of disease	666
randomized, double-blind, placebo-controlled, phase 3 trial	Randomization was stratified according to the presence or absence of liver or lung metastases.	668
phase 3, randomised, double-blind, doubledummy international trial	a computer-generated randomisation scheme and an integrated voice or web response system	462
open-label, prospective, randomized, phase III study	Randomization was computerized, with stratification according to prior adjuvant therapy (yes/no) and study center according to the minimization method.	514

region	disease stage	treatment group (name / dose)
83 sites in Europe, Australia, New Zealand, South America, and South Africa.	locally advanced or metastatic breast cancer	anastrozole 1mg once daily + placebo(tamoxifen)
97 sites in the United States and Canada	locally advanced or metastatic breast cancer	anastrozole 1mg once daily + placebo(tamoxifen)
201 centers in 29 countries	locally advanced (stage IIIB by American Joint Committee on Cancer criteria, 1992) or locoregionally recurrent disease not amenable to treatment by surgery or radiotherapy or with metastatic breast cancer	letrozole 2.5mg once daily + placebo(tamoxifen)
	ABC	anastrozole 1mg daily po
171 centers in 26 countries	metastatic or locally advanced breast cancer	fulvestrant 250mg im(5ml)once monthly+placebo(tamo xifen)20mg orally once daily

81 centers, 79sites	metastatic or locally recurrent inoperable breast cancer with at least one bidimensionally measurable lesion	exemestane 25mg orally once daily
62 centers in nine countries (Brazil, Bulgaria, Czech Republic, France, Italy, Poland, Spain, United Kingdom, and the United States)	locally advanced or metastatic breast cancer who were not amenable to therapy of curative intent	fulvestrant 500mg/month plus 500mg on day 14 of month 1
13 Spanish centers	locally advanced or metastatic breast cancer	exemestane 25mg orally once daily
—	metastatic breast cancer	anastrozole 1mg once daily orally+fulvestrant (1 loading dose 500mg) im day 1, followed by 250mg im day 14/28 of the first cycle, and thereafter every 28 days
50 sites in 12 countries (Canada, France, Germany, Hungary, Ireland, Italy Russia, South Africa, South Korea, Spain, Ukraine, USA; appendix)	locally recurrent disease not amenable to surgery or evidence of metastatic disease	oral palbociclib 125 mg once daily for 3 weeks followed by 1 week off treatment in a 28-day cycle+letrozole 2.5mg qd

186 sites in 17 countries	advanced breast cancer	palbociclib 125mg qd 3/4w +letrozole 2.5mg qd
29 countries, patients at 223 trial centers	locally recurrent or metastatic breast cancer	ribociclib (600 mg per day on a 3-weeks-on, 1-week-off schedule in 28-day treatment cycles) plus letrozole (2.5 mg per day on a continuous schedule)
113 academic hospitals and community centres in 20 countries in Asia, Europe, North America, South America, and South Africa	locally advanced or metastatic breast cancer	Fulvestrant 500 mg days 0, 14 (+3 days), 28 (+3 days), and every 28 (+3 days) thereafter as two 5 mL im (plus daily anastrozole placebo)
11 countries at 77 centers	relapse after or during primary treatment (with/without adjuvant endocrine therapy, with/without adjuvant chemotherapy, with/without adjuvant radiotherapy) were included in the study	fulvestrant 500 mg intramuscular on day 1 and 250mg on days 15 and 29 and thereafter every fourth week 3 days+anastrozole orally 1mg

vs control group / frequency)	n (sample size)	age (years, range)	Weight, * kg (n)
tamoxifen 20mg once daily + placebo (anastrozole)	340	328 67 (34-91) 66 (41-92)	68 (40-121)
tamoxifen 20mg once daily + placebo (anastrozole)	171	182 68 (30-88) 67 (40-92)	72 (43-121)
tamoxifen 20mg once daily + placebo (letrozole)	453	454 65 (31-96) 64 (31-93)	—
tamoxifen 40mg daily po	121	117 60.2 (56-77) 60.6 (55-77)	—
tamoxifen 20mg orally once daily+placebo (fulves- trant 250mg im (5ml) once monthly)	313	274 67 (43-93) 66 (43-92)	65.1 (31.4-117.3)

tamoxifen 20mg  
orally once daily      182      189 63 (37–86)      62 (37–87)      ——

anastrozole 1mg  
orally once daily      102      103 66 (40–89)      68 (48–87)      ——

anastrozole 1mg  
orally once daily      51 (47, 在OR及CB的时候用的该数据)  
                            52 (50, 在OR及CB的时候用的该数据)      67.9 (45–94)      72.6 (46–85)      ——

anastrozole 1mg once  
daily orally      350      345      65 (27–92)      65 (36–91)      ——

letrozole 2.5mg qd      84      81      63 (54–71)      64 (56–70)      ——

letrozole 2.5mg qd	444	222	62 (30 - 89)	61 (28 - 88)	---
placebo plus letrozole	334	334	62 (23-91)	63 (29-88)	---
Anastrozole 1mg orally once daily (plus fulvestrant placebo on days 0, 14, 28, and every 28 days thereafter)	230	232	64.0 (38-87)	62.0 (36-90)	---
anastrozole orally at 1mg per day	258	256	65.2 (33-86)	63.4 (36-90)	---

Median, range)	Race or ethnicity (n, %)	ECOG performance status
68 (42–111)	—	—
69 (36–140)	—	—
—	—	WHO: 0–2, 100%
—	0:98 1:14 2:9	—
65.0 (31.0–138.8)	White: 245, 78.3% Black: 5, 1.6% South Asian: 2, 0.6% Hispanic: 6, 1.9% Asian: 39, 12.5% Other: 16, 5.1%	White: 223, 81.4% Black: 3, 1.1% South Asian: 2, 0.7% Hispanic: 6, 2.2% Asian: 28, 10.2% Other: 12, 4.4%

WHO PS  
0:84, 46. 2%  
1:79, 43. 4%  
2:19, 10. 4%

WHO:0-2, 100%

0:24 (47. 1%)  
1:15 (29. 4%)  
2:9 (17. 6%)  
U:3 (5. 9%)

ECOG: 0-2 100%

0: 46 (55%)  
1: 38 (45%)

—	White:344 (77.5%) Asian:65 (14.6%) Black:8 (1.8%) Other:27 (6.1%)	White:172 (77.5%) Asian:30 (13.5%) Black:3 (1.4%) Other:17 (7.7%)	0:257 (57.9%) 1:178 (40.1%) 2:9 (2.0%)
—	White:269 (80.5%) Asian:28 (8.4%) Black:10 (3.0%) Other or unknown:27 (8.1%)	White:280 (83.8%) Asian:23 (6.9%) Black:7 (2.1%) Other or unknown:24 (7.2%)	0:205 (61.4%) 1:129 (38.6%)
—	White:175 (76%) Asian:36 (16%) Black or other:19 (8%)	White:174 (75%) Asian:34 (15%) Black or other:24 (10%)	WHO: 0:117 (51%) 1:106 (46%) 2:7 (3%)
—	White:242 (93.8%) Black:1 (0.4%) Asian:4 (1.6%) Other:11 (4.3%)	White:237 (92.6%) Black:2 (0.8%) Asian:2 (0.8%) Other:15 (5.9%)	—

ce status(n, %)	HR status	Her2-status
—	ER+ and/or PgR+154 (45. 3%)	ER+ and/or PgR+144 (43. 9%)
—	ER+ and/or PgR+151 (88. 3%)	ER+ and/or PgR+161 (88. 95%)
WHO: 0— 2, 99. 78% (434/454)	ER+ and/or PgR+294 (65%)	ER+ and/or PgR+305 (67%)
0:91 1:16 2:10	ER+:100%	ER+:100%
WHO:0—2, 100%	ER+ and/or PgR+247 (78. 9%)	ER+ and/or PgR+212 (77. 4%)

WHO PS

0:80, 42. 3%  
1:84, 44. 4%  
2:25, 13. 2%

ER+ and/or  
PgR+168 (92. 3%)

ER+ and/or  
PgR+178 (94. 2%)

—

WHO:0-2, 100%

ER+ and/or  
PgR+102 (100%)

ER+ and/or  
PgR+103 (100%)

2+/3+:19, 18. 6%  
Negative:48, 47. 1%  
Unknown:35, 34. 3%

0:21 (40. 4%)  
1:12 (23. 1%)  
2:11 (21. 2%)  
U:8 (15. 3%)

ER or PR(either  
>10 fmol/mg  
by biochemical  
assay or 10%  
positive cells by  
immunohistochemis-  
try) 100%

ER or PR(either  
>10 fmol/mg  
by biochemical  
assay or 10%  
positive cells  
by  
immunohistochem-  
istry) 100%

—

ECOG: 0-2 100%

ER+ and/or PR+ :  
100%

ER+ and/or PR+  
: 100%

positive:31/297 (10. 4%)  
negative:266/297 (89. 6%)

0: 45 (56%)  
1: 36 (44%)

ER+:100%

ER+:100%

negative:100%

0:102 (45.9%)  
1:117 (52.7%) ER+:100% ER+:100% negative:100%  
2:3 (1.4%)

0:202 (60.5%) ER+:332 (99.4%) ER+:333 (99.7%) negative:100%  
1:132 (39.5%) PR+:271 (81.1%) PR+:278 (83.2%)

WHO:  
0:115 (50%) ER+ and/or PgR+230 (100%) ER+ and/or PgR+232 (100%) negative:100%  
1:105 (45%)  
2:12 (5%)

— ER+ and/or PgR+ (100%) ER+ and/or PgR+ (100%) —

atus (n, %)	Breast cancer disease status at first diagnosis
—	Advanced:163 (47. 9%) Early:176(51. 8%) Unknown:1 (0. 3%)
—	Advanced:169 (51. 5%) Early:158 (48. 2%) Unknown:1 (0. 3%)
—	Advanced:52 (30. 4%) Early:118(69. 0%) Unknown:1 (0. 6%)
—	Advanced:60 (33. 0%) Early:122 (67. 0%) Unknown:0 (0%)
—	Stage of disease at study entry [Stage IV or earlier disease:145, 32%; Metastatic, relapsed:308, 68%]
—	Stage of disease at study entry [Stage IV or earlier disease:146, 32%; Metastatic, relapsed:308, 68%]
—	—
—	—
—	—

2+/3+: 19, 18. 4%  
Negative: 49, 47. 6%  
Unknown: 35, 34. 0%

Disease stage:  
LABC only: 19, 18.6%  
MBC: 83, 81.4%

Disease stage:  
LABC only: 18, 17.5%  
MBC: 85, 82.5%

Tumor stage:  
IIIB:9 (17.6%)  
IV:42 (82.4%)

Tumor stage:  
IIIB:6 (11.5%)  
IV:46 (88.5%)

positive:25/295(8.5%)  
negative:270/295(91.5%)

—

— — —

negative:100%

III: 2 (2%)  
IV: 82 (98%)

	I 51 (11.5%)	I 30 (13.5%)
	II 137 (30.9%)	II 68 (30.6%)
	III 72 (16.2%)	III 39 (17.6%)
negative:100%	IV 138 (31.1%)	IV 72 (32.4%)
	Unknown 36 (8.1%)	Unknown 12 (5.4%)
	Other or data missing 10 (2.3%)	Other or data missing 1 (0.5%)

negative:100% ——

negative:231 (100%) locally advanced:28 (12%) locally advanced:32 (14%)  
positive:1 (<1%) Metastatic:202 (88%) Metastatic:200 (86%)

—

—

—

## Prior treatments

Hormonal only:31 (9.1%)	Hormonal only:20 (6.1%)
Cytotoxic only:64 (18.8%)	Cytotoxic only:62 (18.9%)
Both:10 (2.9%)	Both:15 (4.6%)
None:234 (68.8%)	None:231 (70.4%)
Unknown:1 (0.3%)	Unknown:0 (0%)

Hormonal only:21 (12.3%)	Hormonal only:20 (11.0%)
Cytotoxic only:32 (18.7%)	Cytotoxic only:37 (20.3%)
Both:15 (8.8%)	Both:13 (7.1%)
None:102 (59.6%)	None:111 (61.0%)
Unknown:1 (0.6%)	Unknown:1 (0.5%)

Prior chemotherapy [None:320, 71%; Adjuvant only:93, 21%; Treatment for advanced disease:40, 9%] adjuvant antiestrogen therapy [yes:84, 19%; no:369, 81%]	Prior chemotherapy [None:301, 66%; Adjuvant only:105, 23%; Treatment for advanced disease:48, 11%] Prior adjuvant antiestrogen therapy [yes:83, 18%; no:371, 82%]
---	---

CMF:32	CMF:34
Doxorubicin:19	Doxorubicin:17

Surgery for primary breast cancer:186 (59.4%) Adjuvant cytotoxic chemotherapy:71 (22.7%) Radiotherapy for primary breast cancer:81 (25.9%) Radiotherapy for metastatic disease:16 (5.1%) Adjuvant tamoxifen treatment:69 (22.0%)	Surgery for primary breast cancer:159 (58.0%) Adjuvant cytotoxic chemotherapy:66 (24.1%) Radiotherapy for primary breast cancer:80 (29.2%) Radiotherapy for metastatic disease:16 (5.8%) Adjuvant tamoxifen treatment:68 (24.8%)
---	---

Prior radiotherapy:75 (41. 2%)  
Previous systemic therapy:76 (41. 7%)  
Previous chemotherapy:55 (30. 2%)  
Previous adjuvant amoxifen:38 (20. 9%)  
Prior radiotherapy:79 (41. 8%)  
Previous systemic therapy:79 (41. 8%)  
Previous chemotherapy:63 (33. 3%)  
Previous adjuvant amoxifen:39 (20. 6%)

Prior endocrine treatment:  
No(73, 71. 6%)  
>12months (28, 27. 5%)  
Prior chemotherapy:for ABC(0, 0%)  
Adjuvant chemotherapy for  
eBC:29, 28. 4%

Prior endocrine treatment:  
No(80, 77. 7%)  
>12months (23, 22. 3%)  
Prior chemotherapy:for ABC(0, 0%)  
Adjuvant chemotherapy for  
eBC:25, 24. 3%

Prior systemic therapy:  
Adjuvant tamoxifen:26 (51%)  
Chemotherapy: (Neo) adjuvant  
only:17 (33. 3%)  
Metastatic only:2 (3. 9%)  
Both:5 (9. 8%)

Prior systemic therapy:  
Adjuvant tamoxifen:26 (50%)  
Chemotherapy: (Neo) adjuvant  
only:17 (32. 7%)  
Metastatic only:2 (3. 8%)  
Both:7 (13. 5%)

Prior adjuvant tamoxifen:  
yes(141, 40. 4%) no(208, 59. 6%)  
Prior adjuvant chemotherapy:  
yes(129, 37. 0%) no(220, 63. 0%)

Prior adjuvant tamoxifen:  
yes(139, 40. 3%) no(206, 59. 7%)  
Prior adjuvant chemotherapy:  
yes(103, 29. 9%) no(242, 70. 1%)

None:44 (52%)  
Chemotherapy:34 (40%)  
Hormonal:27 (32%)  
[Tamoxifen:24 (29%)  
Anastrozole:8 (10%)  
Letrozole:2 (2%)  
Exemestane:4 (5%) ]

None:37 (46%)  
Chemotherapy:37 (46%)  
Hormonal:28 (35%)  
[Tamoxifen:24 (30%)  
Anastrozole:11 (14%)  
Letrozole:1 (1%)  
Exemestane:2 (2%) ]

Chemotherapy 213 (48.0%)	Chemotherapy 109 (49.1%)
Neoadjuvant 54 (12.2%)	Neoadjuvant 32 (14.4%)
Adjuvant 180 (40.5%)	Adjuvant 89 (40.1%)
Adjuvant hormonal therapy 249 (56.1%)	Adjuvant hormonal therapy    126 (56.8%)
Tamoxifen 209 (47.1%)	Tamoxifen 98 (44.1%)
Anastrozole 56 (12.6%)	Anastrozole 29 (13.1%)
Letrozole 36 (8.1%)	Letrozole 16 (7.2%)
Exemestane 30 (6.8%)	Exemestane 13 (5.9%)
Goserelin 5 (1.1%)	Goserelin 6 (2.7%)
Toremifene 7 (1.6%)	Toremifene 1 (0.5%)
Other 3 (0.7%)	Other 4 (1.8%)
Neoadjuvant or adjuvant chemotherapy: 146 (43.7%)	Neoadjuvant or adjuvant chemotherapy: 145 (43.4%)
Neoadjuvant or adjuvant endocrine therapy: 175 (52.4%)	Neoadjuvant or adjuvant endocrine therapy: 171 (51.2%)
[ana:47, 14.1%;	[ana:42, 12.6%;
exe:19, 5.7%;	exe:25, 7.5%;
Goserelin:6, 1.8%;	Goserelin:3, 0.9%;
let:34, 10.2%;	let:25, 7.5%;
tam:140, 41.9%;	tam:145, 43.4%;
other:2, 0.6%]	other:4, 1.2%]
Chemotherapy:	Chemotherapy:
Locally advanced or metastatic breast cancer: 36 (16%)	Locally advanced or metastatic breast cancer: 43 (19%)
Adjuvant: 35 (15%)	Adjuvant: 27 (12%)
Neoadjuvant: 11 (5%)	Neoadjuvant: 16 (7%)
Radiotherapy: 53 (23%)	Radiotherapy: 50 (22%)
Immunotherapy: 0	Immunotherapy: 0
Hormonal therapy: 2 (1%)	Hormonal therapy: 1 (<1%)
Adjuvant endocrine therapy: 180 (69.8%)	Adjuvant endocrine therapy: 168 (65.6%)
Adjuvant radiotherapy: 159 (61.6%)	Adjuvant radiotherapy: 171 (66.8%)
Adjuvant chemotherapy: 108 (41.9%)	Adjuvant chemotherapy: 127 (49.6%)
Other previous cancer therapy: 3 (1.2%)	Other previous cancer therapy: 1 (0.4%)

Sites of disease	
Soft tissue:230 (67. 6%) [skin:183 (53. 8%) Lymph:145 (42. 6%) ] Bone:156 (45. 9%) <b>Visceral:103 (30. 3%)</b> [lung:74 (21. 8%) liver:32 (9. 4%) intra-abdominal:10 (2. 9%) ] Other:1 (0. 3%) No assessable disease:2 (0. 6%) Soft tissue:86 (50. 3%) [skin:52 (30. 4%) Lymph:63 (36. 8%) ] Bone:112 (65. 5%) <b>Visceral:83 (48. 5%)</b> [lung:76 (44. 4%) liver:13 (7. 6%) intra-abdominal:7 (4. 1%) ] Other:0 (0%) No assessable disease:2 (1. 2%) Soft tissue only: 113 (25%) Bone: 146 (32%) Bone only†: 69 (15%) Bone and soft tissue:77 (17%) <b>Viscera: 194 (43%)</b> Viscera only: 52 (12%) Viscera and bone: 44 (10%) Viscera and soft tissue: 41 (9%) Viscera, bone, and soft tissue:57 (13%)	Soft tissue:225 (68. 6%) [skin:183 (55. 8%) Lymph:148 (45. 1%) ] Bone:158 (48. 2%) Visceral:124 (37. 8%) [lung:100 (30. 5%) liver:31 (9. 5%) intra-abdominal:5 (1. 5%) ] Other:2 (0. 6%) No assessable disease:0 (0%) Soft tissue:91 (50. 0%) [skin:50 (27. 5%) Lymph:64 (35. 2%) ] Bone:98 (53. 8%) Visceral:87 (47. 8%) [lung:68 (37. 4%) liver:30 (16. 5%) intra-abdominal:8 (4. 4%) ] Other:1 (0. 5%) No assessable disease:2 (1. 1%) Soft tissue only: 116 (25%) Bone: 130 (29%) Bone only†: 72 (16%) Bone and soft tissue: 58 (13%) Viscera: 208 (46%) Viscera only: 61 (13%) Viscera and bone: 44 (10%) Viscera and soft tissue: 51 (11%) Viscera, bone, and soft tissue:52 (11%)
Lung:57 Bone:46 Soft tissue:18	Lung:53 Bone:49 Soft tissue:15
Lymph node:140 (44. 7%) Breast:130 (41. 5%) Bone:86 (27. 5%) Lung:79 (25. 2%) Skin/soft tissue:69 (22. 0%) Liver:30 (9. 6%) Other:7 (2. 2%)	Lymph node:122 (44. 5%) Breast:113 (41. 2%) Bone:89 (32. 5%) Lung:67 (24. 5%) Skin/soft tissue:53 (19. 3%) Liver:27 (9. 9%) Other:10 (3. 6%)

**Visceral:87 (47. 8%)**  
Bone only:21 (11. 5%)  
Bone+soft tissueL:43 (23. 6%)  
Soft tissue:31 (17. 0%)

Visceral:88 (46. 6%)  
Bone only:22 (11. 6%)  
Bone+soft tissueL:45 (23. 8%)  
Soft tissue:34 (18. 0%)

Bone only:10, 9. 8%  
Soft tissue only:2, 2. 0%  
**Any visceral disease:48, 47. 1%**  
Any liver metastases:15, 14. 7%  
Any lung metastases:30, 29. 4%

Bone only:8, 7. 8%  
Soft tissue only:0, 0%  
Any visceral disease:58, 56. 3%  
Any liver metastases:14, 13. 6%  
Any lung metastases:42, 40. 8%

**Visceral:yes (25, 49%) no (27, 54%)**

NO of disease sites:  
1 (13, 25. 5%)  
2 (20, 39. 2%)  
>=3 (18, 35. 3%)

Visceral:yes (29, 55. 8%) no (23, 44. 2%)

NO of disease sites:  
1 (12, 23. 1%)  
2 (16, 30. 8%)  
>=3 (24, 46. 2%)

Bone only:75 (21. 5%)  
**Visceral:181 (51. 9%)**  
Nonvisceral:93 (26. 6%)

Bone only:76 (22. 0%)  
Visceral:167 (48. 4%)  
Nonvisceral:102 (29. 6%)

**Visceral:37 (44%)**  
Bone only:17 (20%)  
Other (non-visceral):30 (36%)

Visceral:43 (53%)  
Bone only:12 (15%)  
Other (non-visceral):26 (32%)

<b>Visceral</b> 214 (48.2%)	Visceral 110 (49.5%)
Nonvisceral 230 (51.8%)	Nonvisceral 112 (50.5%)
Bone only 103 (23.2%)	Bone only 48 (21.6%)
breast:8 (2.4%)	breast:11 (3.3%)
Bone any:246 (73.7%)	Bone any:244 (73.1%)
Bone Only:69 (20.7%)	Bone Only:78 (23.4%)
<b>Visceral (liver, lung, other</b>	<b>Visceral (liver, lung, other</b>
<b>visceral metastases):197, 59.0%</b>	<b>visceral metastases):196, 58.7%</b>
Lymph nodes:133 (39.8%)	Lymph nodes:123 (36.8%)
Other:35 (10.5%)	Other:22 (6.6%)
<b>Visceral disease:135 (59%)</b>	<b>Visceral disease:119 (51%)</b>
Bone or musculoskeletal only:24 (10%)	Bone or musculoskeletal only:24 (10%)
Breast only:3 (1%)	Breast only:2 (1%)
Skin or soft tissue only:8 (3%)	Skin or soft tissue only:6 (3%)
Other non-visceral:60 (26%)	Other non-visceral:81 (35%)
Breast:1 (0.4%)	Breast:1 (0.4%)
Bone only:63 (24.4%)	Bone only:71 (27.7%)
<b>Any visceral disease:134 (51.9%)</b>	<b>Any visceral disease:124 (48.4%)</b>
Liver:57 (22.1%)	Liver:40 (15.6%)
Lung:66 (25.6%)	Lung:68 (26.6%)
Recurrence:locally (53, 20.5%)	Recurrence:locally (39, 15.2%)
metastatic (245, 95.0%)	metastatic (242, 94.5%)

Measurable disease	primary objectives
--------------------	--------------------

301 (88.5%)	286 (87.2%)	TTP/ORR/tolerability
-------------	-------------	----------------------

117 (68.4%)	140 (76.9%)	ORR/TTP/tolerability
-------------	-------------	----------------------

---	---	TTP
-----	-----	-----

---	---	ORR/clinical benefit rate[CBR]/TTP in patients achieving a CB/ OS/toxicity analysis.
-----	-----	--

235 (75.1%)	208 (75.9%)	TTP
-------------	-------------	-----

—

—

PFS

89, 87. 3%

93, 90. 3%

clinical benefit rate  
(CBR)

—

—

ORR

yes:188 (53. 9%)  
no:161 (46. 1%)

yes:188 (54. 5%)  
no:157 (45. 5%)

PFS

—

—

PFS

— — PFS

— — locally assessed PFS

193 (84%) 196 (84%) PFS

yes:129 (50. 0%) yes:113 (44. 1%) TTP  
no:129 (50. 0%) no:143 (55. 9%)

TTP/PFS (median, months)	OR rate (T vs C) (CR+PR)	secondary objectives
8.2 vs 8.3 HR(tam:ana):0.99 (95%CI:0.86- ) P=0.941	32.9% VS 32.6% P=0.787	TTF/DOR/duration of clinical benefit/survival
11.1 vs 5.6 HR (tam:ana): 1.44 (95%CI:1.16- ) P=0.005	21.1% vs 17.0%	TTF/DOR/duration of clinical benefit
9.4 vs 6.0 HR:0.70 (95%CI:0.60-0.82) P=0.0001	137, 30% vs 92, 20% OR:1.71 95%CI:1.26-2.31 P=0.0006	ORR/ duration of overall response/rate of clinical benefit/duration of clinical benefit/ time to treatment failure (TTF), time to response(TTR)/ number of deaths/overall survival
18.0 vs 7.0 HR:0.13 95%CI:0.08, 0.20 P<0.01	43 (36%) vs 31 (26%) P=0.172	
6.8 vs 8.3 95%CI:0.98, 1.44 P=0.088	31.6% (99) vs 33.9% (93) OR:0.87 95%CI:0.61-1.24 P=0.45	objective response rate/ clinical benefit rate/ duration of response/ time to treatment failure/ time to death

158 (87%) vs 161(85%) median PFS:9. 9(8. 7–11. 8) vs 5. 8(5. 3–8. 1) HR:0. 84 95%CI:0. 67–1. 05	45. 6%(83) vs 31. 2%(59) OR:1. 85 95%CI:1. 21–2. 82 P=0. 005	Overall survival/ORR
medianTTP:not been reached at the time of analysis vs 12. 5 HR:0. 63 95%CI:(0. 39, 1. 00) P=0. 0496 <b>medianTTP:23. 4 vs 13. 1</b> HR:0. 66 95%CI:(0. 47, 0. 92) P=0. 01	93, 35. 5% vs 89, 36. 0% OR:1. 02 95%CI:(0. 56, 1. 87) P=0. 947	objective response rate (ORR) / TTP/duration of clinical benefit (DoCB) / duration of response (DoR) / TTF/OS
progressed events:63(61. 8%) VS 79(76. 7%)		
49 vs 51(用的这个总人 数)median TTP:6. 1(95%CI:2. 5–9. 6) vs 12. 1(95%CI:7. 3–16. 8) HR:1. 13 (95%CI:0. 75– 1. 72) P=0. 558	17(36. 2%, 95%CI:18. 5– 45. 9) vs 23(46%, 95%CI:32. 2– 59. 8) (总人数: 47 vs 50)	clinical benefit rate (CBR) / TTP/ overall survival/toxicity
median PFS: 15. 0(95%CI:13. 2, 18. 4) vs 13. 5(95%CI:12. 1, 15. 1) 268 vs 297 HR:0. 80 (95%CI:0. 68, 0. 94) P=0. 007	(measurable disease) 27% vs 22% P=0. 26	OS/CBR/ORR(measurable disease patients)/clinical benefit(all patients)
20. 2 (95%CI:13. 8, 27. 5) vs 10. 2(95%CI:5. 7, 12. 6) HR 0. 488 95%CI:(0. 319, 0. 748) p=0. 0004	36, 43%(95%CI:32, 54) vs 27, 33%(95%CI:23, 45) p=0. 13	ORR/clinical benefit/duration of response/OS

24.8 (22.1– not estimable) vs 14.5 (12.9–17.1) events: 194 (43.7%) vs 137 (61.7%) HR: 0.58; 95%CI: (0.46, 0.72) P<0.001	42.1% (95%CI: 37.5–46.9) vs 34.7% (95%CI: 28.4–41.3) p=0.06	OS/ORR/duration of response/clinical benefit/patient-reported outcomes/ pharmacokinetic effects, safety, and tissue biomarker assessments
not reached (95%CI: 19.3, not reached) vs 14.7 (95%CI: 13.0, 16.5) HR: 0.56 (95%CI: 0.43, 0.72) P=3.29*10^-6	136 vs 92 40.7% (95%CI: 35.4, 46.0) vs 27.5% (95%CI: 22.8, 32.3)	OS/ORR/ the clinical benefit rate (overall response plus stable disease lasting 24 weeks or more)/ safety/ quality-of-life assessments
median PFS: 16.6 (95%CI: 13.83, 20.99) vs 13.8 (95%CI: 11.99, 16.59) progression events: 143 (62%) vs 166 (72%) HR: 0.797 (95%CI: 0.637, 0.999) P=0.0486	measurable disease: ORR: 46% (89/193) vs 45% (88/196) OR: 1.07 95%CI: 0.72, 1.61 P=0.7290	ORR (with measurable disease at baseline)/duration of response/expected duration of response/clinical benefit rate / duration of clinical benefit/ expected duration of clinical benefit/OS
200, 77.5% vs 200, 78.1% median TTP: 10.8 vs 10.2 HR: 0.99 95%CI: 0.81, 1.20 P=0.91	129, 31.8% vs 113, 33.6% OR: 0.92 95%CI: 0.54, 1.58 P=0.76	objective response / TTF/ duration of response (DoR)/ clinical benefit rate / overall survival (OS)/

TTF	duration of response (median, months) (T vs C)	clinical benefit (T vs C) (CR+PR+SD>=24weeks, n, %)
6.2 vs 6.0months HR(tam:ana):1.03 (95%CI:0.89- )	16.4(3.6-39.2) , 112 vs 17.0(2.7-36.9) , 107	56.2% VS 55.5%
7.6 vs 5.4 135(79%) vs 152(84%) HR(tam:ana):1.35 (95%CI:1.11- )	16.1(2.1-30.1) vs 17.9(2.8-30.4)	59.1% vs 45.6% p=0.0098
40weeks vs 25weeks HR:0.71 (95%CI:0.61-0.82) P=0.0001	102weeks vs 100weeks HR:0.84 (95%CI:0.56-1.26) P=0.4	221, 49%(95%CI:44-54) vs 173, 38%(95%CI:34-43) OR:1.55 95%CI:1.19-2.01 P=0.001
248(79.2%) vs 205(74.8%) HR:1.24 95%CI:1.03-1.50 P=0.026	17.3 vs 19.8	100(83%) vs 65(56%) P<0.001
		170, 54.3% vs 170, 62.0% 95%CI:(-17.96,-1.11) P=0.026

17.6 vs 12.7  
HR:0.73  
95%CI: (0.54, 1.00)  
P=0.05

fulvHD had not been  
reached at the time of  
analysis vs 14.2

74, 72.5% vs 69, 67.0%  
OR:1.30  
95%CI: (0.72, 2.38)  
P=0.386

28 (59.6%) vs 34 (68%)

73% vs 70% P=0.39

20.3 (95%CI:13.4, 25.8  
) vs 11.1  
(95%CI:9.3, 31.6)      68, 81% (95%CI:71 – 89)  
                                vs 47, 58% (95CI:47, 69) ;  
                                p=0.0009

22.5 (95%CI:19.8 - 28.0)      84.9% (95%CI:81.2, 88.1)  
vs  
16.8 (95%CI:14.2 - 28.5)      vs 70.3% (63.8, 76.2)  
P<0.001

266 vs 243  
79.6% (95%CI:75.3, 84.0)  
vs  
72.8% (95%CI:68.0, 77.5)

20.0 (95%CI:15.90, 27.63)  
vs  
13.2 (95%CI:10.64, 16.72)  
Expected duration of  
response:11.4 vs 7.5  
OR:1.52  
95%CI:1.03, 2.26  
P=0.0367

78% (180/230) vs  
74% (172/232)  
OR:1.25  
95%CI:0.82, 1.93  
P=0.3045

12.4 vs 11.4  
HR:1.00  
95%CI:0.83, 1.21  
P=0.99

55.0% vs 55.1%  
OR:1.0  
95%CI:0.71, 1.41  
P=0.99

survival	duration of clinical benefit(median, months) (T vs C)	median duration of follow-up(months)
>=24weeks: 15. 2(3. 6, 39. 2), 191 vs 14. 7(2. 7, 41. 4), 182		19
>=24weeks: 16. 5(2. 1, 30. 1) vs 14. 5(2. 5, 30. 4)		17. 7
81weeks vs 84weeks HR:0. 81 95%CI:0. 62–1. 07 P=0. 1		
TTD:17. 4 vs 16. 0 73/121(60%) vs 104/117(89%) HR:0. 64 95%CI:0. 47–0. 86 P=0. 003		13. 3
36. 9 vs 38. 7 HR:1. 29 95%CI:1. 01, 1. 64 P=0. 04	14. 5 (median extended follow- up:31. 3)	

OS events: 82 (45%) vs  
81 (43%)  
median OS: 37.2 (29.2–  
45.5) vs 43.3 (32.8–  
51.6)  
HR: 1.13  
95%CI: 0.85–1.50

49 (总)

median OS: 54.1 vs 48.4

died: 63, 61.8% vs

74, 71.8%

HR: 0.70

95%CI: 0.50–0.98

P=0.04

both treatments had not  
been reached at the time of  
analysis

8 (242.5 days) vs  
5.9 (179 days)  
**18.8 VS 12.9**

48.3  
(95%CI: 18.3, 78.3) vs  
19.9  
(95%CI: 15.32, 24.46)  
HR: 1.33  
(95%CI: 0.78, 2.25)  
P=0.296

9.1 (0.07, 79.96)

deaths: 154 vs 176  
47.7 (95%CI: 43.4, 55.7)  
vs  
41.3 (95%CI: 37.2, 45.0)  
HR: 0.81  
(95%CI: 0.65, 1.00)  
P=0.049

35 (3, 78)

37.5 (95% CI 28.4 – NE  
, 30 events) vs 33.3 (95%  
CI 26.4–NE 31 events)  
(HR 0.813, 95% CI  
0.492, 1.345; p=0.42

29.6 (27.9, 36.0)

immature 23

immature 15. 3

67 (29%) /230 vs  
75 (32%) /232  
HR:0. 88  
95%CI:0. 63, 1. 22  
P=0. 4277

22. 1 (95%CI:18. 46, 24. 87) vs  
19. 1 (95%CI:16. 53, 20. 47)

102 (39. 5%) vs  
102 (39. 8%)  
median OS:37. 8 vs 38. 2  
HR:1. 00  
95%CI:0. 76, 1. 32  
P=1. 00

8. 9 (0-54)

safety(n)	Hot flashes (n, %)	Nausea (n, %)	Asthenia (n, %)
336+329	66 (19. 6%) 62 (18. 8%) 42 (12. 5%) 44 (13. 4%)	29 (8. 6%) 16 (4. 9%)	
	62 (36. 5%) 44 (24. 2%) 52 (30. 6%) 62 (34. 1%)	54 (31. 8%) 65 (35. 7%)	
910	81 (18%) 70 (15%) 66 (15%) 72 (16%)		
	4 (3%) 16 (14%)		
581	15 (4. 8%) 23 (8. 5%)	13 (4. 2%) 11 (4. 1%)	

— G1/2:34.6% G1/2:38.1% G1/2:17.0% G1/2:19.0%  
G3/4:0.5% G3/4:0% G3/4:0% G3/4:0.5%

101+103 14(13.6%) 0.109

51+52 2(3.9%) 2(3.8%)

678(346+332)

17(21%) 9(12%) 21(25%) 10(13%) 11(13%) 3(4%)

334+330      70 (21. 0%)    78 (23. 6%)    172 (51. 5%)    94 (28. 5%)

228+232      26 (11%)      24 (10%)      24 (11%)      24 (10%)

63 (24. 6%)    35 (13. 8%)

pain(n, %)	Bone pain(n, %)	Peripheral edema(n, %)	Constipation(n, %)
------------	-----------------	------------------------	--------------------

27 (8. 0%) 25 (7. 6%) 21 (6. 3%) 20 (6. 1%) 21 (6. 3%) 18 (5. 5%) 21 (6. 3%) 28 (8. 5%)

43 (25. 3%) 48 (26. 4)

89 (20%) 83 (18%)

G1/2:31.9% G1/2:27.5% G1/2:29.1% G1/2:29.1%  
G3/4:2.7% G3/4:3.2% G3/4:3.8% G3/4:5.8%

0.139 0.097 0.099

2(3.9%) 4(7.7%) 3(5.9%) 1(1.9%)

12(14%) 12(15%)

13 (6%) 11 (5%)

Pharyngitis (n, %)	Hypertension (n, %)	Back pain (n, %)	Arthralgia (n, %)	Dyspne
--------------------	---------------------	------------------	-------------------	--------

15 (4.5%) 30 (9.1%) 18 (5.4%) 27 (8.2%)

41 (24.1%) 43 (23.6%)

77 (17%) 79 (17%) 63 (14%) 58 (13%) 62 (14%)

3 (1.0%) 10 (3.7%)

0.099      0.087      0.089

4(7.8%)      —      4(7.8%)

66 (19.8%) 58 (17.6%) 91 (27.2%) 95 (28.8%)

15 (7%) 21 (9%) 21 (9%) 14 (6%) 38 (17%) 24 (10%) 9 (4%)

a (n, %)	Cough (n, %)	Fatigue (n, %)	Vasodilatation (n, %)
----------	--------------	----------------	-----------------------

66 (15%) 49 (11%) 47 (10%) 48 (11%) 51 (11%)

39 (12.6%) 50 (18.5%)

G1/2:35.7%      G1/2:35.4%  
G3/4:1.1%      G3/4:1.1%

4 (7.7%)

65 (19. 5%)	59 (17. 9%)	122 (36. 5%)	99 (30. 0%)
13 (6%)	12 (5%)	8 (3%)	26 (11%)
			16 (7%)

Neutropenia (n, %)	grade 3/4	n (%)



276 (62. 2%) / 49 (22. 1%) / 5  
60 (13. 5%) (2. 3%)

221 105  
248 (74. 3%) 17 (5. 2%) (66. 2%) (31. 8%)  
/50 (15. 0%) /3 (0. 9%)

1. 红色的表示不确定，需要核对
2. 第7篇与第10篇是同一个试验FIRST，  
数据相互补充，纳为同一个试验，用蓝色标注第10篇的数据，用紫色标注第12篇  
数据  
第11篇和16篇为同一个试验，用棕色表  
示第16篇的OS数据  
第17篇文献为第14篇更新数据，用橄榄  
绿表示

n (样本量)		(总样本量	)
340	328	668	668
171	182	353	353
453	454	907	907
121	117	238	238
313	274	587	587
182	189	371	371
102	103	205	205
51	52	103	103
350	345	695	707
84	81	165	165
444	222	666	666
334	334	668	668
230	232	462	462
258	256	514	514
3433	3169	6602	6614