

con il Patrocinio dell'Associazione Italiana di Oncologia Medica



SAPIENZA
UNIVERSITÀ DI ROMA

AZIENDA OSPEDALIERA
SANT'ANDREA
FACOLTÀ DI MEDICINA E
PSICOLOGIA



Progetto **CANOA**
CARCINOMA
MAMMARIO:
QUALI **NOVITÀ** PER IL 2013?

“Saper leggere” uno studio clinico per migliorare la pratica clinica

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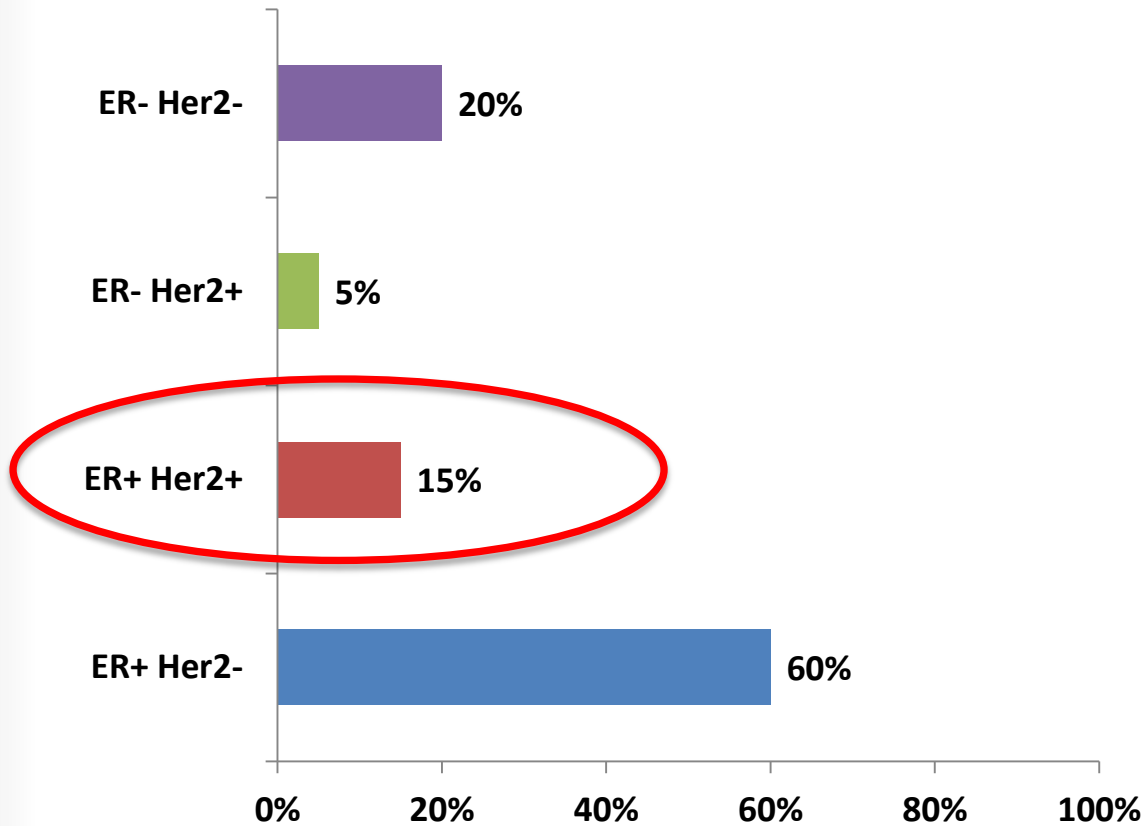


Negrar - Verona 22-23 marzo 2013
Ospedale Sacro Cuore - Don Calabria

*Metastasi viscerali:
altre opzioni oltre
la chemioterapia.
Ormonoterapia
e Agenti anti-Her2*

- Valentina Sini -

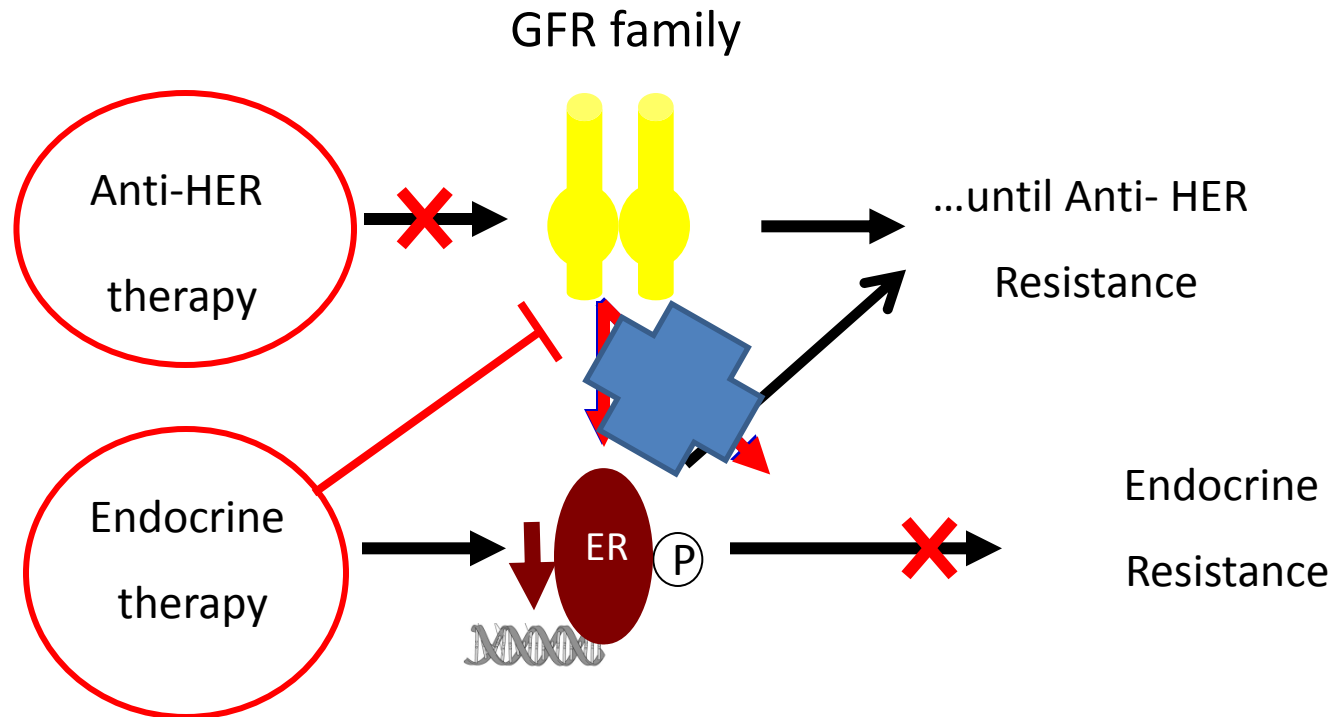
Metastatic Breast Cancer



- ER+ Her2-
- ER+ Her2+
- ER- Her2+
- ER- Her2-



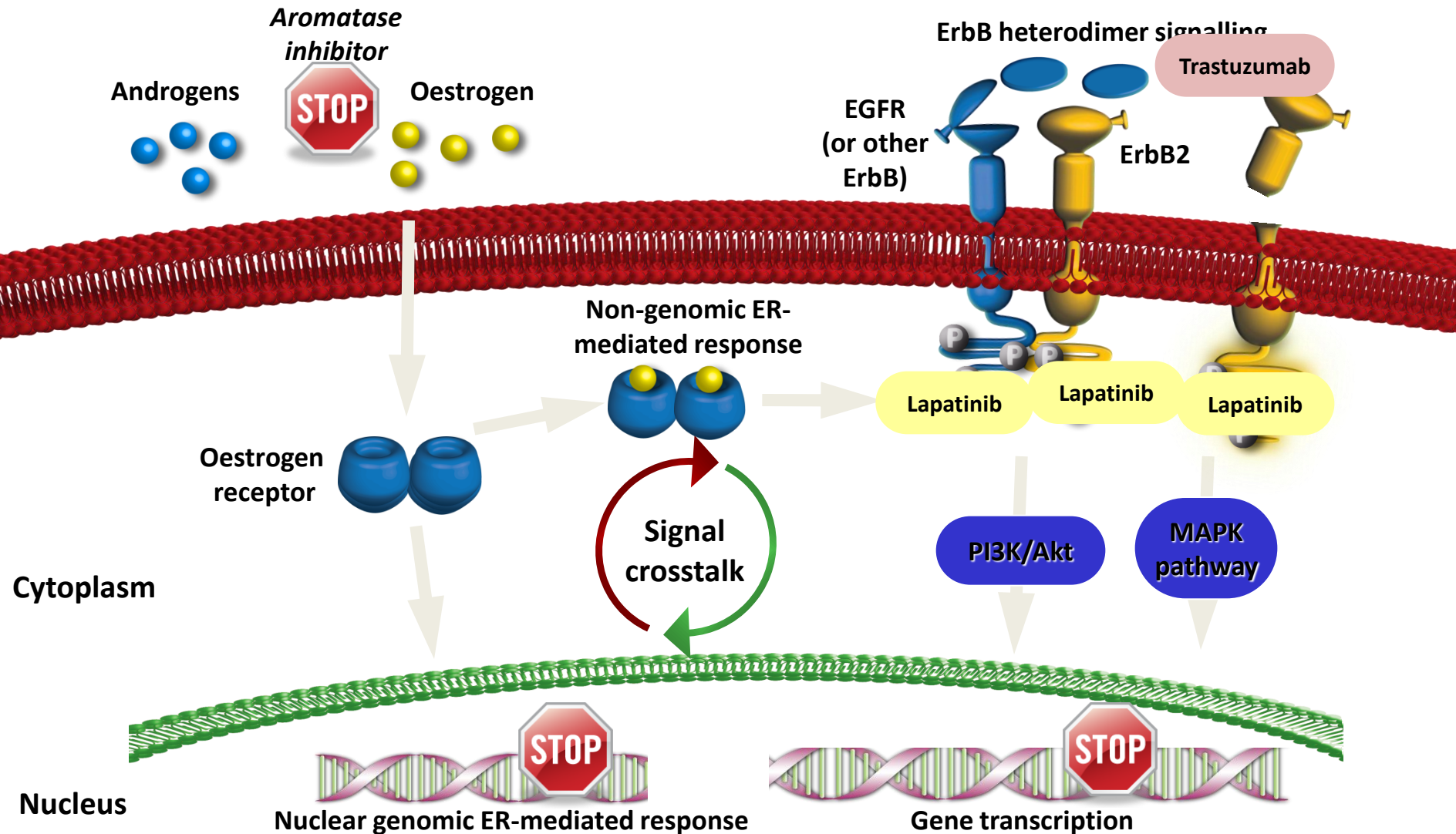
Her2+/ER+ mBC



Rationale for combined targeted therapy

- Dual targeting of oestrogen and growth factor signalling (EGFR/ErbB2) is one rational approach to overcome endocrine resistance¹⁻⁴
- Agents that target both EGFR and ErbB2 may be more efficacious at overcoming endocrine resistance than those that target ErbB2 alone^{1,5}

Overcoming endocrine resistance: mode of action in ErbB2+/HR+ breast cancer



Therapeutic strategies in Her2+/ER+ mBC

- Block ER activity
- Block HER2 in the most efficient way
- In patients with NO lifethreatening or extensive visceral disease (no Bulky disease)



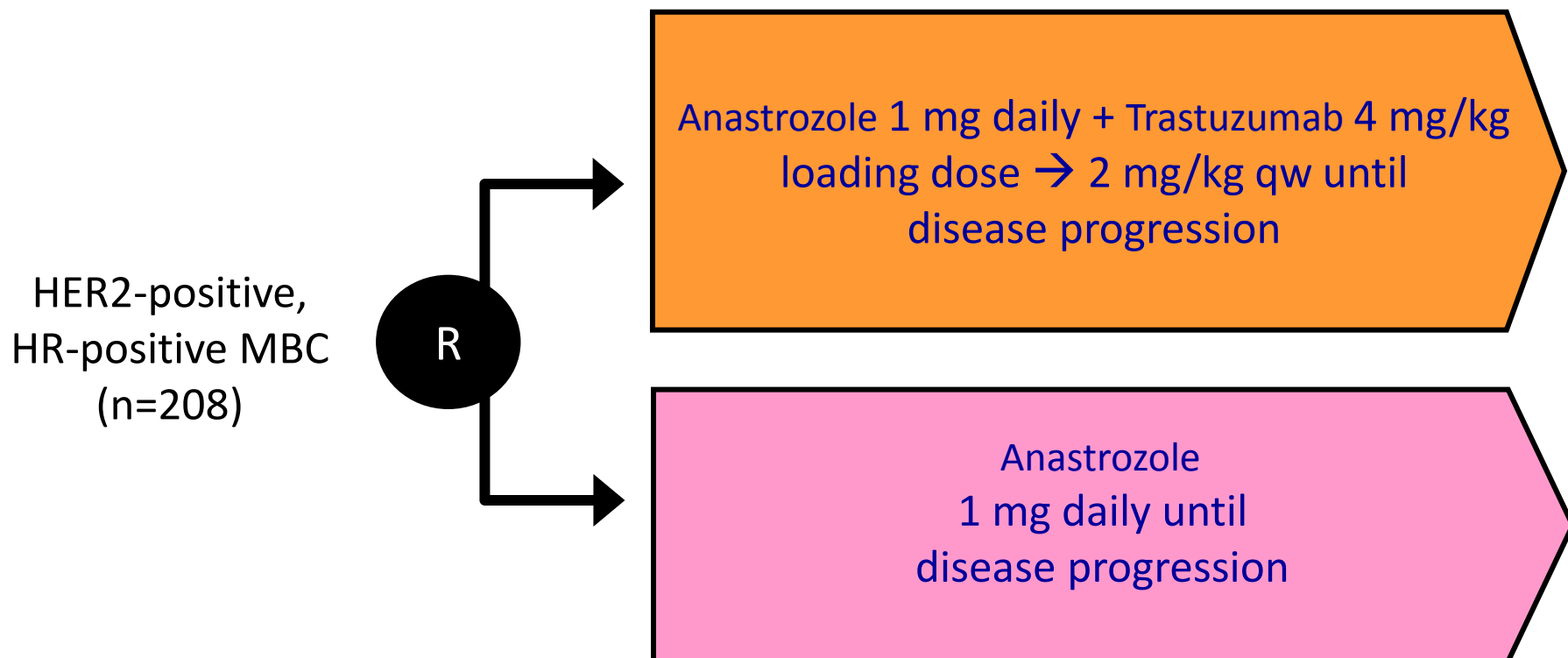
OUTLINE

- TAnDEM Trial [*Kaufman et al, J Clin Oncol 2009*]
- EGF30008 Trial [*Johnston S, et al J Clin Oncol 2009*]
- Guidelines
- Treatment algorithms



Trastuzumab Plus Anastrozole Versus Anastrozole Alone for the Treatment of Postmenopausal Women With Human Epidermal Growth Factor Receptor 2–Positive, Hormone Receptor–Positive Metastatic Breast Cancer: Results From the Randomized Phase III TAnDEM Study

Bella Kaufman, John R. Mackey, Michael R. Clemens, Poonamalle P. Bapsy, Ashok Vaid, Andrew Wardley,

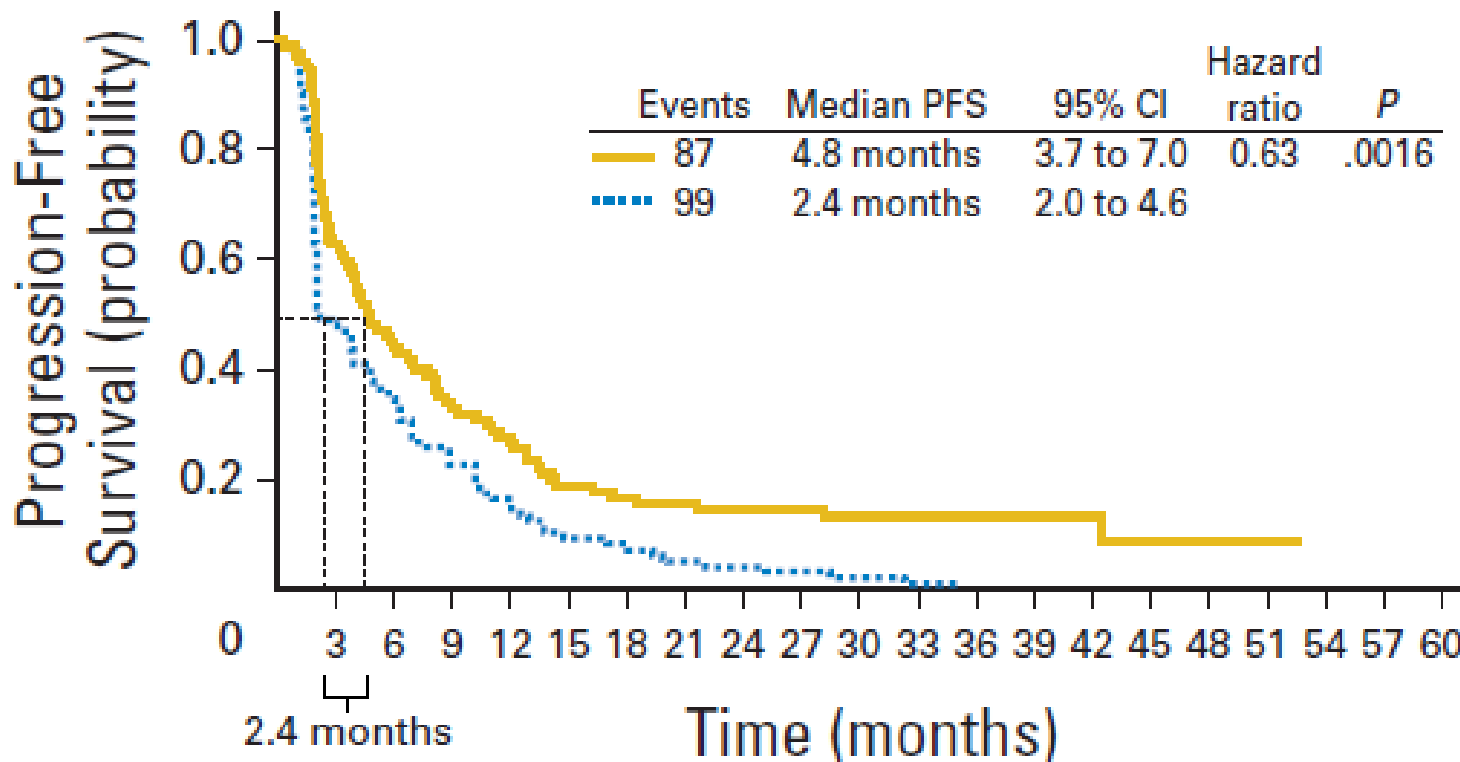


[Crossover to receive trastuzumab was actively offered to all patients who progressed on anastrozole alone]

Baseline Patient characteristics

| Characteristic | Trastuzumab + Anastrozole (n = 103) | | Anastrozole Alone (n = 104) | |
|---|--|-------|-----------------------------|-------|
| | No. of Patients | % | No. of Patients | % |
| Age, years | | | | |
| Median | 56 | | 54 | |
| Range | 31-85 | | 27-77 | |
| Hormone receptor status* | | | | |
| Primary and/or metastatic lesion ER and/or PgR positive (local) | 103 | 100.0 | 104 | 100.0 |
| Primary and/or metastatic lesion ER and/or PgR positive (central) | 77 | 74.8 | 73 | 70.2 |
| Time from diagnosis of primary disease, months | | | | |
| Median | 25.6 | | 27.3 | |
| Range | 0.6-419 | | 0.6-154.3 | |
| Time from diagnosis of metastatic disease, months | | | | |
| Median | 1.6† | | 1.2 | |
| Range | 0.3-67.1 | | 0.3-19.3 | |
| No. of metastatic sites per patient | | | | |
| Median | 2 | | 2 | |
| Range | 1-5 | | 1-5 | |
| No. of lesions per patient | | | | |
| Median | 4 | | 4 | |
| Range | 1-14 | | 1-13 | |
| Site of metastases | | | | |
| Lung | 43 | 41.7 | 48 | 46.2 |
| Liver | 33 | 32.0 | 29 | 27.9 |
| Bone | 64 | 62.1 | 53 | 51.0 |
| Soft tissue | 46 | 44.7 | 44 | 42.3 |
| Other | 72 | 69.9 | 65 | 62.5 |
| Previous therapy | | | | |
| Hormonal | 62 | 60.2 | 69 | 66.3 |
| Tamoxifen for metastatic disease | 5 | 4.9 | 3 | 2.9 |
| Chemotherapy | 55 | 53.4 | 62 | 59.6 |
| Anthracycline | 46 | 44.7 | 53 | 51.0 |
| Bisphosphonate | 28 | 27.2 | 27 | 26.0 |
| LVEF, % | | | | |
| Median | 62 | | 63 | |
| Range | 50-82 | | 51-89 | |

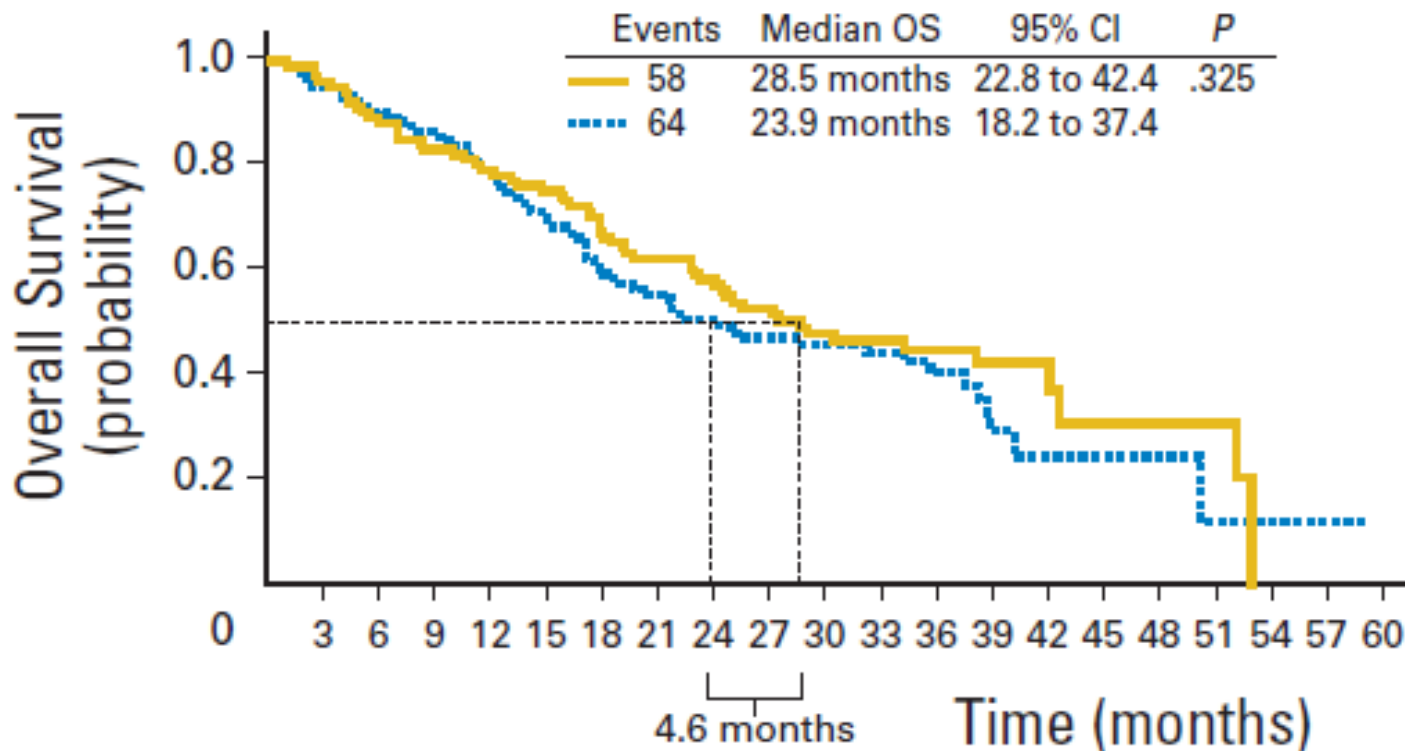
Progression-Free Survival



No. at risk

| | | | | | | | | | | | | | |
|-----------------------------|-----|----|----|----|----|----|----|---|---|---|---|---|---|
| — Trastuzumab + anastrozole | 103 | 48 | 31 | 17 | 14 | 13 | 11 | 9 | 4 | 1 | 1 | 0 | 0 |
| ⋯ Anastrozole alone | 104 | 36 | 22 | 9 | 5 | 4 | 2 | 1 | 0 | 0 | 0 | 0 | 0 |

Overall Survival



No. at risk

| | | | | | | | | | | | | | |
|-----------------------------|-----|----|----|----|----|----|----|----|----|---|---|---|---|
| — Trastuzumab + anastrozole | 103 | 91 | 83 | 76 | 63 | 49 | 36 | 24 | 12 | 4 | 3 | 0 | 0 |
| ···· Anastrozole alone | 104 | 96 | 87 | 73 | 58 | 42 | 34 | 22 | 5 | 2 | 1 | 1 | 0 |

Overall Response Rates

| Response | Best Overall Response | | | |
|---------------------|---------------------------------------|-------|-------------------------------|------|
| | Trastuzumab + Anastrozole (n = 74) | | Anastrozole Alone (n = 73) | |
| | No. of Patients | % | No. of Patients | % |
| Complete response* | 0 | 0 | 0 | 0 |
| Partial response | 15 | 20.3† | 5 | 6.8 |
| Stable disease | 28 | 37.8 | 28 | 38.4 |
| Progressive disease | 30 | 40.5 | 36 | 49.3 |
| Not evaluable | 1 | 1.4 | 4 | 5.5 |

ORR: 20.3% vs 6.8%

CBR: 58.1% vs 45.2%

SAEs

| Adverse Event | Common Adverse Events, All Grades | | | | Grade 3 Adverse Events | | | | Grade 4 Adverse Events | | | |
|-----------------|-------------------------------------|------|------------------------------|------|-------------------------------------|------|------------------------------|------|-------------------------------------|-----|------------------------------|-----|
| | Trastuzumab + Anastrozole (n = 103) | | Anastrozole Alone* (n = 104) | | Trastuzumab + Anastrozole (n = 103) | | Anastrozole Alone* (n = 104) | | Trastuzumab + Anastrozole (n = 103) | | Anastrozole Alone* (n = 104) | |
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Total | 90 | 87.4 | 68 | 65.4 | 24 | 23.3 | 16 | 15.4 | 5 | 4.9 | 1 | 1.0 |
| Fatigue | 22 | 21.3 | 10 | 9.6 | 1 | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Diarrhea | 21 | 20.4 | 8 | 7.7 | 1 | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vomiting | 22 | 21.3 | 5 | 4.8 | 3 | 2.9 | 1 | 1.0 | 0 | 0 | 0 | 0 |
| Arthralgia | 15 | 14.6 | 10 | 9.6 | 0 | 0 | 1 | 1.0 | 0 | 0 | 0 | 0 |
| Pyrexia | 18 | 17.5 | 7 | 6.7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Back pain | 15 | 14.6 | 7 | 6.7 | 2 | 1.9 | 2 | 1.9 | 0 | 0 | 0 | 0 |
| Dyspnea | 13 | 12.6 | 9 | 8.7 | 1 | 1.0 | 0 | 0 | 1 | 1.0 | 0 | 0 |
| Nausea | 17 | 16.5 | 5 | 4.8 | 1 | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cough | 14 | 13.6 | 6 | 5.8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Headache | 14 | 13.6 | 6 | 5.8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nasopharyngitis | 17 | 16.5 | 2 | 1.9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Bone pain | 11 | 10.7 | 6 | 5.8 | 2 | 1.9 | 0 | 0 | 0 | 0 | 0 | 0 |
| Constipation | 12 | 11.7 | 5 | 4.8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Chills | 15 | 14.6 | 0 | 0 | 1 | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypertension | 7 | 6.8 | 4 | 3.8 | 2 | 1.9 | 4 | 3.8 | 0 | 0 | 0 | 0 |

Lapatinib Combined With Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer

Stephen Johnston, John Pippin Jr, Xavier Pivot, Mikhail Lichinitser, Saeed Sadeghi, Veronique Dieras,

Patient Population

- ER+/PgR+ (HR+)
- Postmenopausal
- HER2+, HER2- or unknown
- Stage IIIb/IIIc, IV
- No prior treatment for MBC

Stratification

- Disease sites
 - Bone only/other sites
- Interval since prior adjuvant anti-estrogen therapy
 - < 6 mo / ≥ 6 mo or None

R
A
N
D
O
M
I
Z
E



Letrozole 2.5 mg daily
+
Placebo



Letrozole 2.5 mg daily
+
Lapatinib 1500 mg daily

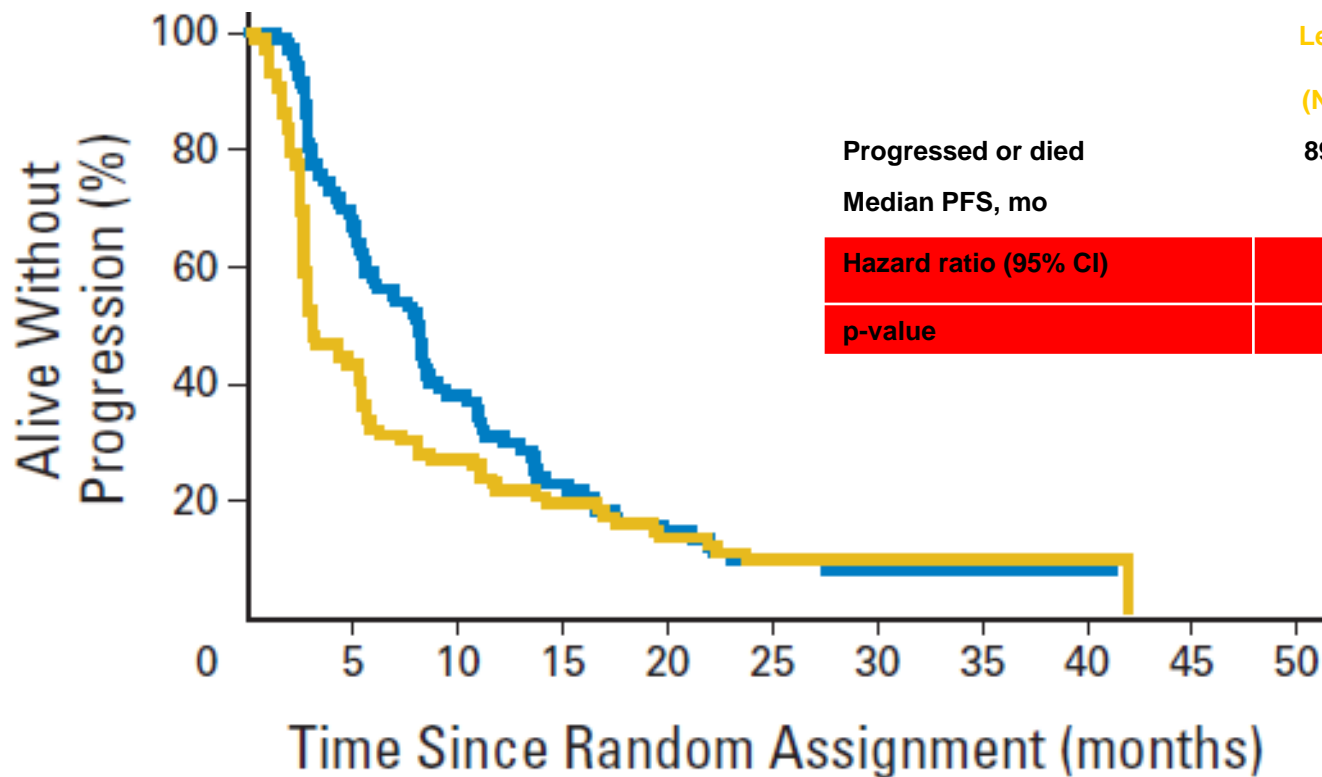
n = 1286 pts (including n=219 HER2+)

Baseline Patient characteristics

| Demographic or Clinical Characteristic | HER2 Positive | | | | ITT | | | |
|---|----------------------------------|-----|------------------------------------|-----|----------------------------------|-----|------------------------------------|-----|
| | Letrozole + Placebo (n = 108) | | Letrozole + Lapatinib (n = 111) | | Letrozole + Placebo (n = 644) | | Letrozole + Lapatinib (n = 642) | |
| | No. of Patients | % | No. of Patients | % | No. of Patients | % | No. of Patients | % |
| Age, years* | | | | | | | | |
| Median | 59 | | 60 | | 63 | | 62 | |
| Range | 45-87 | | 44-85 | | 35-95 | | 31-94 | |
| ECOG performance status* | | | | | | | | |
| 0 | 51 | 47 | 59 | 53 | 349 | 54 | 370 | 58 |
| ≥ 1 | 57 | 53 | 51 | 46 | 286 | 44 | 268 | 42 |
| Hormone receptor status* | | | | | | | | |
| ER/PgR positive | 69 | 64 | 74 | 67 | 414 | 64 | 420 | 65 |
| ER positive/PgR negative | 20 | 19 | 19 | 17 | 90 | 14 | 91 | 14 |
| Disease stage | | | | | | | | |
| IIIB or IIIC | 7 | 6 | 5 | 5 | 30 | 5 | 25 | 4 |
| IV | 101 | 94 | 106 | 95 | 613 | 95 | 616 | 96 |
| No. of metastatic sites* | | | | | | | | |
| Median | 2 | | 2 | | 2 | | 2 | |
| Range | 1-7 | | 1-7 | | 0-7 | | 0-7 | |
| Disease stage | | | | | | | | |
| Bone only | 18 | 17 | 16 | 14 | 85 | 13 | 94 | 15 |
| Visceral or soft tissue | 90 | 83 | 95 | 86 | 559 | 87 | 548 | 85 |
| Liver | 37 | 34 | 33 | 30 | 171 | 27 | 146 | 23 |
| Lung | 40 | 37 | 43 | 39 | 242 | 38 | 248 | 39 |
| Lymph node | 43 | 40 | 57 | 51 | 304 | 47 | 312 | 49 |
| Soft tissue | 31 | 29 | 35 | 32 | 218 | 34 | 212 | 33 |
| Other | 18 | 17 | 19 | 17 | 127 | 20 | 125 | 19 |
| Previous therapy | | | | | | | | |
| Endocrine* | 62 | 57 | 60 | 54 | 317 | 49 | 313 | 49 |
| Tamoxifen or toremifene only | 60 | 56 | 59 | 53 | 302 | 47 | 300 | 47 |
| Aromatase inhibitor only | 1 | < 1 | 1 | < 1 | 3 | < 1 | 5 | < 1 |
| Chemotherapy* | 51 | 47 | 61 | 55 | 280 | 43 | 281 | 44 |
| Anthracycline only | 38 | 35 | 41 | 37 | 172 | 27 | 171 | 27 |
| Anthracyclines and taxanes | 9 | 8 | 9 | 8 | 41 | 6 | 42 | 7 |
| Other | 4 | 4 | 11 | 10 | 66 | 10 | 68 | 11 |
| Biologic therapy (any) | 1 | < 1 | 1 | < 1 | 1 | < 1 | 2 | < 1 |
| Interval since prior adjuvant antiestrogen therapy* | | | | | | | | |
| ≥ 6 months or no prior therapy | 67 | 62 | 73 | 66 | 487 | 76 | 501 | 78 |
| < 6 months | 41 | 38 | 38 | 34 | 157 | 24 | 141 | 22 |

Clinical efficacy in human epidermal growth factor receptor 2–positive population.

Progression-Free Survival

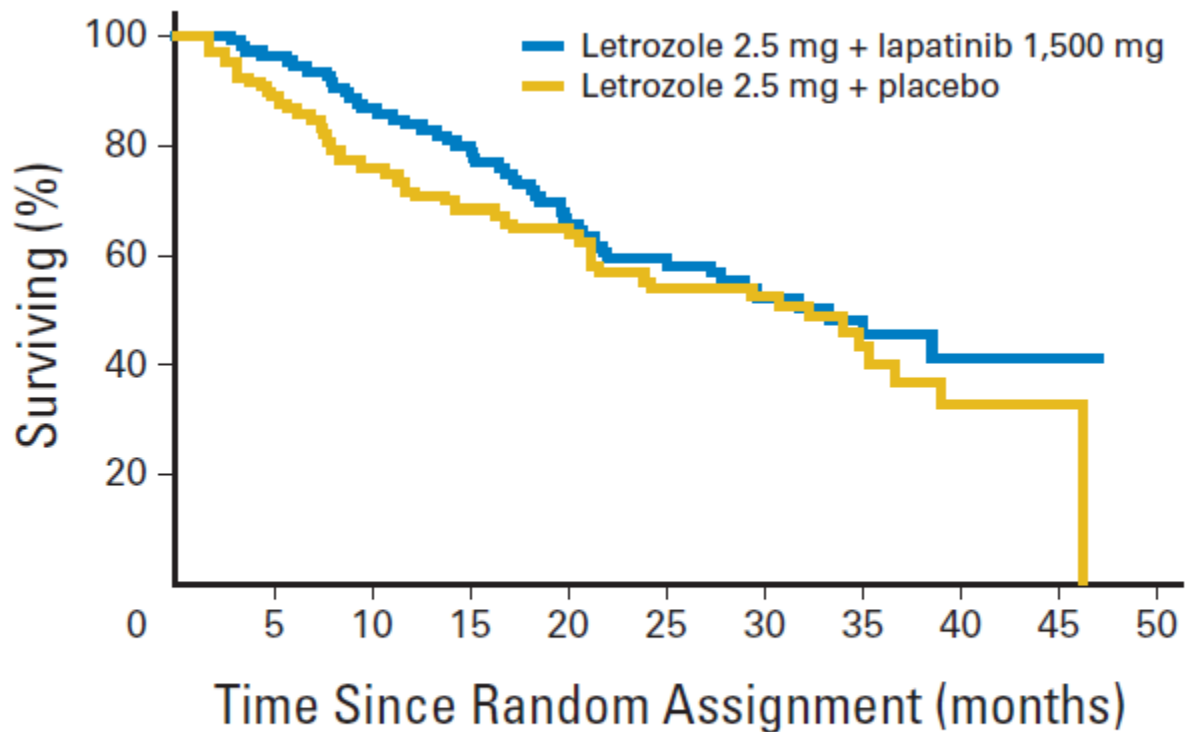


Patients at risk

| | | | | | | | | | |
|-----------------------|-----|----|----|----|----|---|---|---|---|
| Letrozole + lapatinib | 111 | 69 | 33 | 20 | 12 | 8 | 4 | 1 | 1 |
| Letrozole | 108 | 43 | 26 | 18 | 12 | 7 | 5 | 2 | 2 |

Clinical efficacy in human epidermal growth factor receptor 2-positive population.

Overall Survival

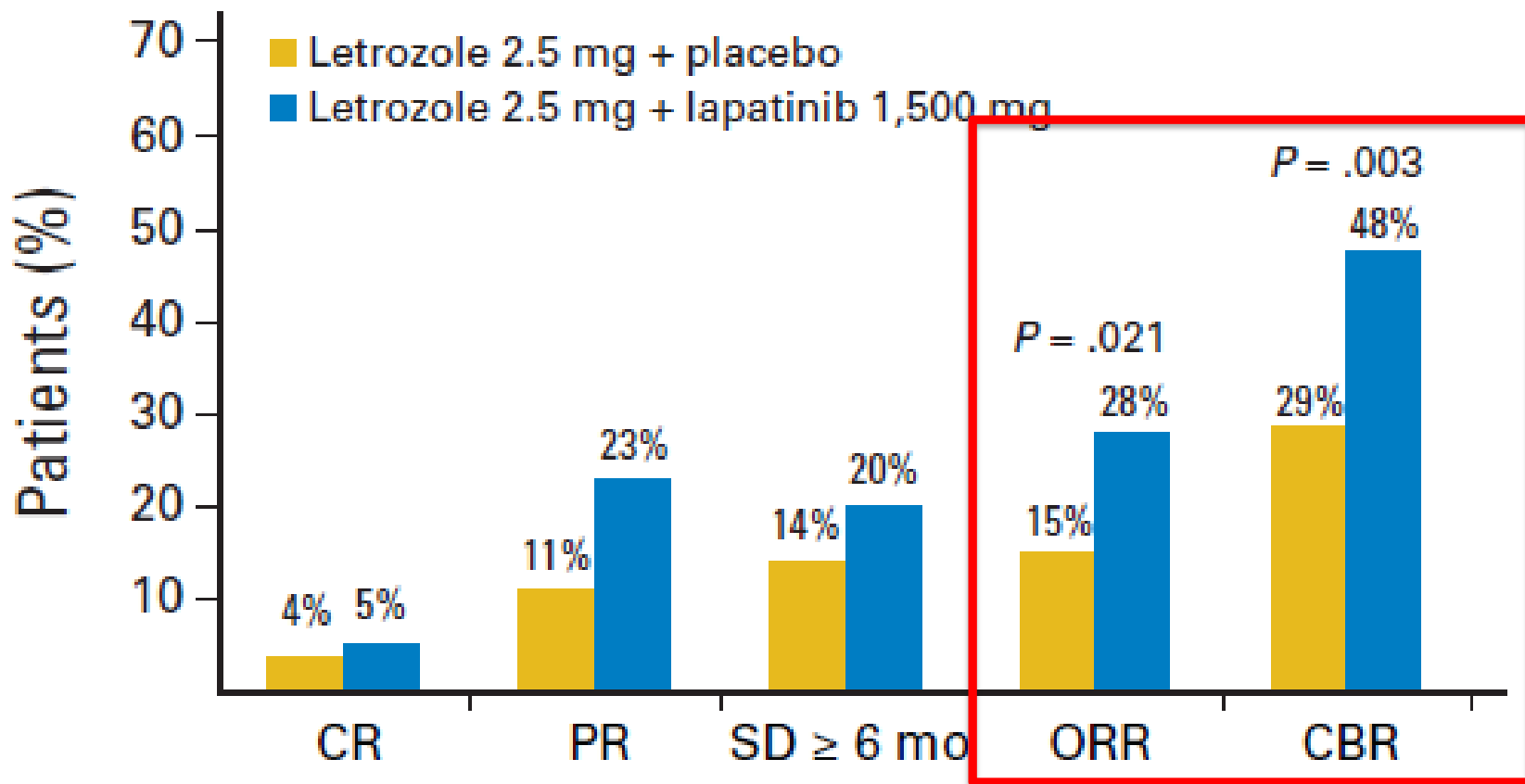


Patients at risk

| | | | | | | | | | | |
|-----------------------|-----|-----|----|----|----|----|----|----|---|---|
| Letrozole + lapatinib | 111 | 104 | 89 | 80 | 64 | 48 | 32 | 19 | 9 | 4 |
| Letrozole | 108 | 93 | 76 | 69 | 59 | 38 | 31 | 15 | 8 | 2 |

Clinical efficacy in human epidermal growth factor receptor 2-positive population.

Overall Response Rate

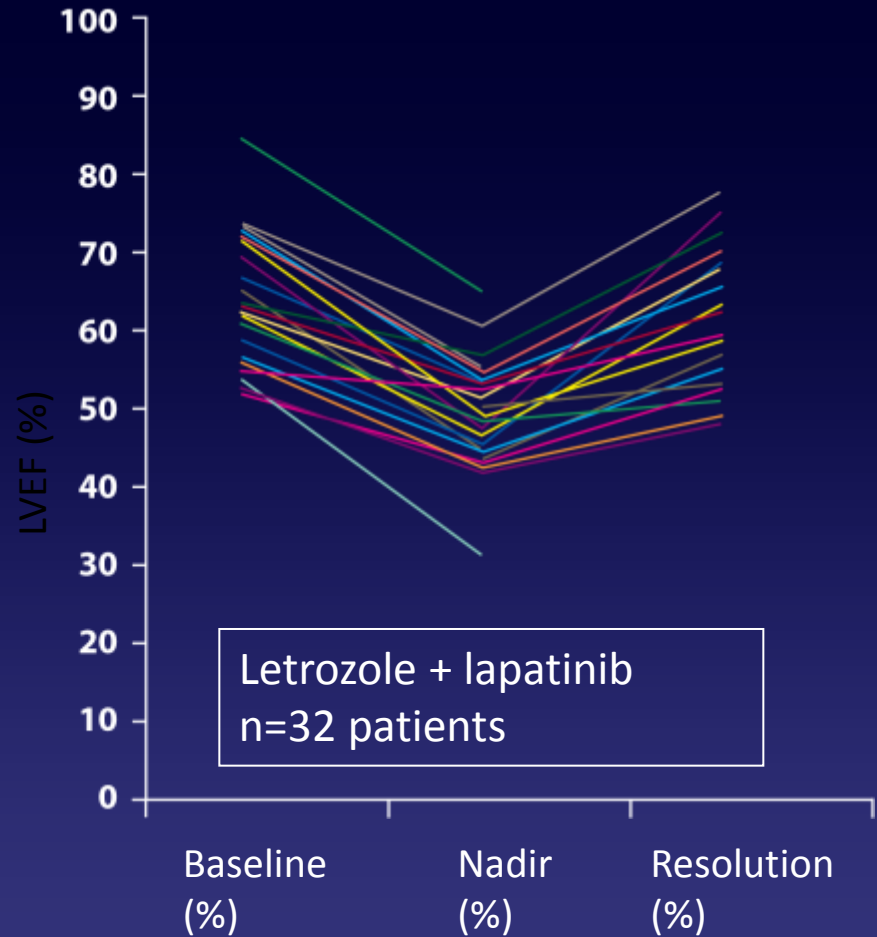
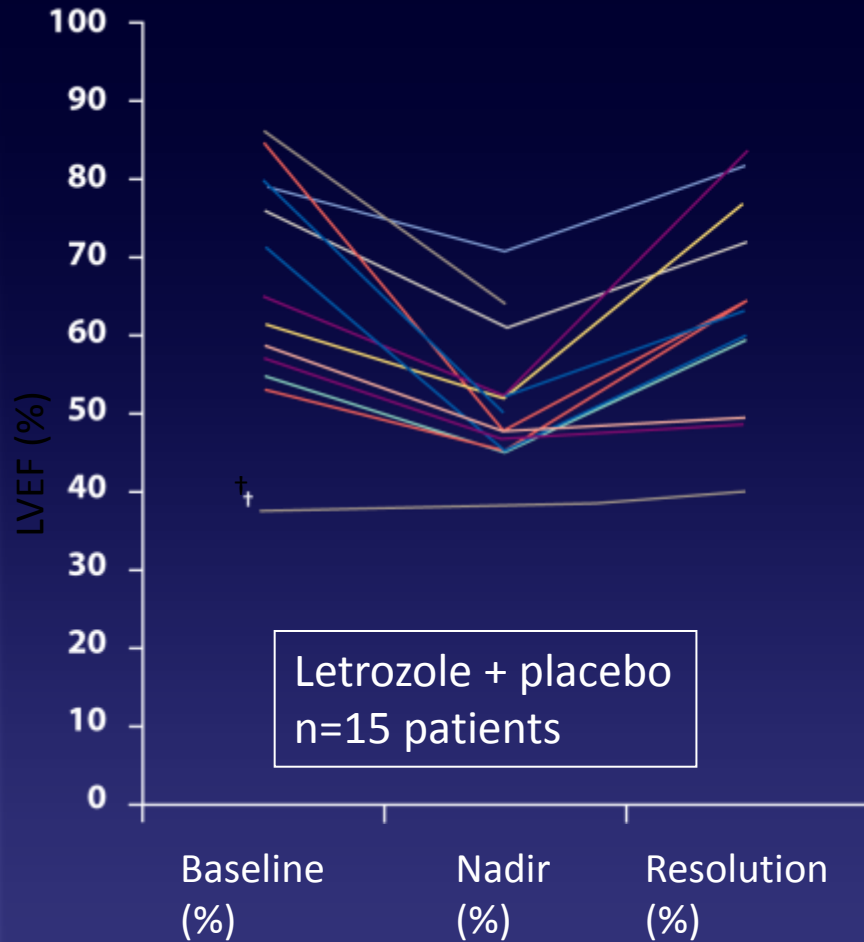


SAEs

| Adverse Event | Letrozole + Placebo (n = 624) | | | | | | | | Letrozole + Lapatinib (n = 654) | | | | | | | |
|-------------------|-------------------------------|-----|---------|-----|---------|-----|---------|-----|---------------------------------|----|---------|-----|---------|-----|---------|-----|
| | Grade 1 | | Grade 2 | | Grade 3 | | Grade 4 | | Grade 1 | | Grade 2 | | Grade 3 | | Grade 4 | |
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Diarrhea* | 91 | 15 | 27 | 4 | 6 | < 1 | 0 | 0 | 210 | 32 | 147 | 22 | 58 | 9 | 2 | < 1 |
| Rash* | 68 | 11 | 15 | 2 | 0 | 0 | 0 | 0 | 186 | 28 | 100 | 15 | 7 | 1 | 0 | 0 |
| Nausea* | 85 | 14 | 40 | 6 | 4 | < 1 | 0 | 0 | 141 | 22 | 53 | 8 | 6 | < 1 | 0 | 0 |
| Arthralgia | 100 | 16 | 37 | 6 | 8 | 1 | 0 | 0 | 81 | 12 | 39 | 6 | 7 | 1 | 0 | 0 |
| Fatigue | 63 | 10 | 42 | 7 | 3 | < 1 | 0 | 0 | 77 | 12 | 47 | 7 | 10 | 2 | 0 | 0 |
| Back pain | 41 | 7 | 42 | 7 | 13 | 2 | 1 | < 1 | 50 | 8 | 42 | 6 | 12 | 2 | 0 | 0 |
| Vomiting* | 42 | 7 | 21 | 3 | 4 | < 1 | 1 | < 1 | 63 | 10 | 38 | 6 | 7 | 1 | 1 | < 1 |
| Headache | 52 | 8 | 28 | 4 | 3 | < 1 | 0 | 0 | 63 | 10 | 26 | 4 | 2 | < 1 | 0 | 0 |
| Cough | 73 | 12 | 15 | 2 | 2 | < 1 | 0 | 0 | 59 | 9 | 19 | 3 | 2 | < 1 | 0 | 0 |
| Hot flush* | 65 | 10 | 27 | 4 | 0 | 0 | 0 | 0 | 54 | 8 | 12 | 2 | 3 | < 1 | 0 | 0 |
| Asthenia | 45 | 7 | 19 | 3 | 5 | < 1 | 0 | 0 | 55 | 8 | 20 | 3 | 5 | < 1 | 0 | 0 |
| Pain in extremity | 42 | 7 | 24 | 4 | 5 | < 1 | 0 | 0 | 39 | 6 | 25 | 4 | 2 | < 1 | 0 | 0 |
| Dyspnea | 36 | 6 | 27 | 4 | 7 | 1 | 2 | < 1 | 31 | 5 | 27 | 4 | 5 | < 1 | 1 | < 1 |
| Pruritus* | 43 | 7 | 11 | 2 | 1 | < 1 | 0 | 0 | 54 | 8 | 23 | 4 | 2 | < 1 | 0 | 0 |
| Alopecia* | 44 | 7 | 1 | < 1 | 0 | 0 | 0 | 0 | 82 | 13 | 2 | < 1 | 1 | < 1 | 0 | 0 |
| Constipation | 48 | 8 | 17 | 3 | 2 | < 1 | 0 | 0 | 54 | 8 | 6 | < 1 | 0 | 0 | 0 | 0 |
| Anorexia | 34 | 5 | 18 | 3 | 2 | < 1 | 0 | 0 | 51 | 8 | 16 | 2 | 5 | < 1 | 0 | 0 |
| Dry skin | 25 | 4 | 2 | < 1 | 0 | 0 | 0 | 0 | 71 | 11 | 15 | 2 | 1 | < 1 | 0 | 0 |
| Epistaxis | 7 | 1 | 3 | < 1 | 1 | < 1 | 0 | 0 | 63 | 10 | 6 | < 1 | 1 | < 1 | 0 | 0 |
| Nail disorder | 5 | < 1 | 1 | < 1 | 0 | 0 | 0 | 0 | 60 | 9 | 11 | 2 | 1 | < 1 | 0 | 0 |

*A statistically significant ($P < .05$) effect was observed between treatment groups for the total incidence of these adverse events.

LVEF assessment values* for individual patients with cardiac events



*LVEF assessments by ECHO or MUGA. †Values for this patient were above this institution's LLN.
Each line on the graph represents LVEF changes for one patient

Chemo or Endocrine therapy +/- antiHER2 agents in HER2+ metastatic BC

| | Regimen | Patients n° | ORR % | Median PFS/TTP (mos) | Median OS (mos) |
|----------------|------------------------------|----------------|----------|-------------------------|--------------------|
| Slamon | Chemo + Trastuzumab | 235 | 50* | 7.4* | 25.1* |
| | Chemo** | 234 | 32 | 4.6 | 20.3 |
| Marty | Doc + Trastuzumab | 92 | 61* | 11.7* | 31.2* |
| | Doc*** | 94 | 34 | 6.1 | 22.7 |
| Andersson M | Doc + Trastuzumab | 143 | 59.3 | 12 | 35.7 |
| | Vnr + Trastuzumab | 141 | 59.3 | 15.3* | 38.8 |
| Kaufmann | Anastrozole + Trastuzumab | 103 | 20.3* | 4.8* | 28.3 |
| | Anastrozole | 104 | 6.8 | 2.4 | 23.9 |
| Johnston | Letrozole + Lapatinib | 111 | 28* | 8.2* | 33.3 |
| | Letrozole + placebo | 108 | 15 | 3.0 | 32.3 |

** 65% cross to trastuzumab

*** 44% cross to trastuzumab

* $p = < 0.05$



OUTLINE

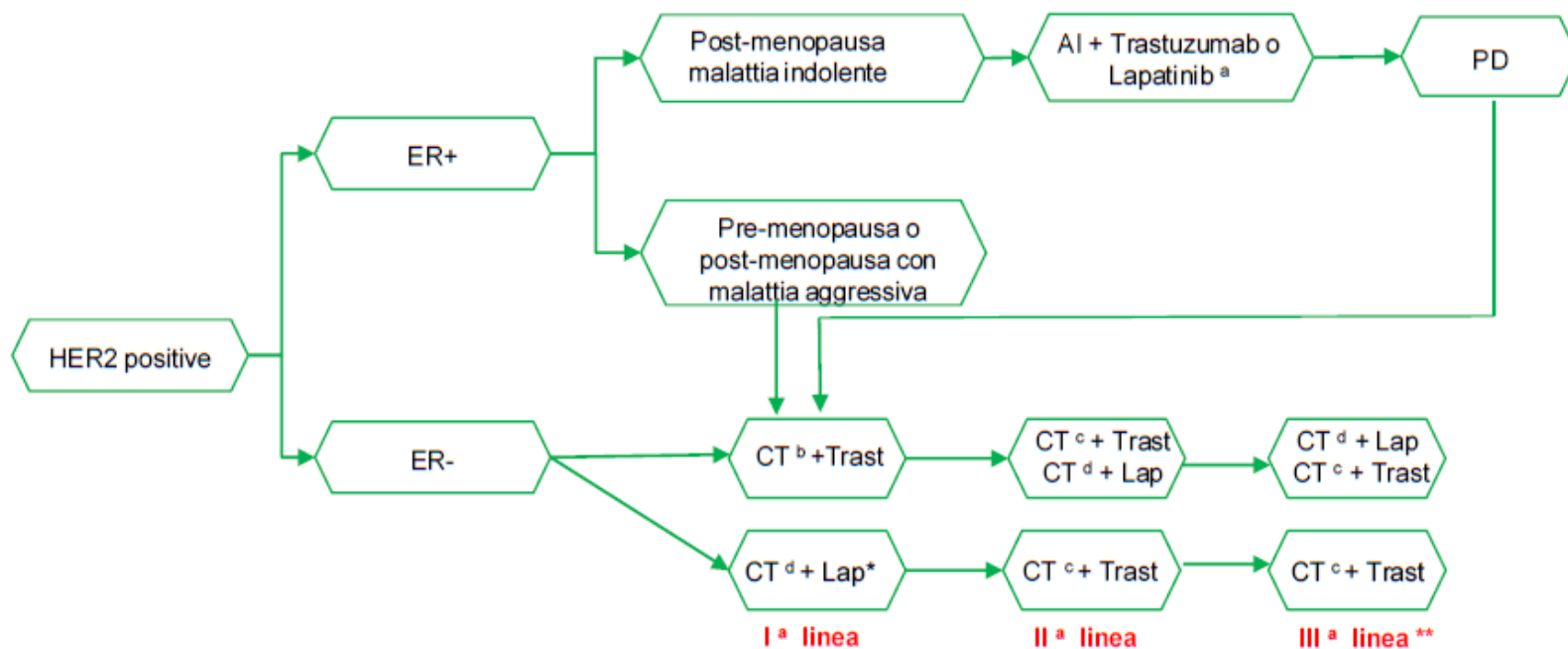
Lapatinib or Trastuzumab in combination with an Aromatase Inhibitor is an Option for:

- **chemo-unfit**
- **chemo-unwilling patients**
- **non Bulky visceral/non visceral metastatic disease**

ALGORITMO 15 – CARCINOMA MAMMARIO METASTATICO



Terapia medica in base alle caratteristiche patologiche e cliniche (I)



Legenda: CT= chemioterapia, Trast= trastuzumab, Lap= Lapatinib, PD= Progressione di malattia.

Nota a- Il trattamento ormonale con un inibitore dell'aromatasi più un farmaco anti HER2 è un'opzione alternativa alla chemioterapia, ma non esistono studi di confronto diretto

Nota b- Chemioterapia con taxano o vinorelbina

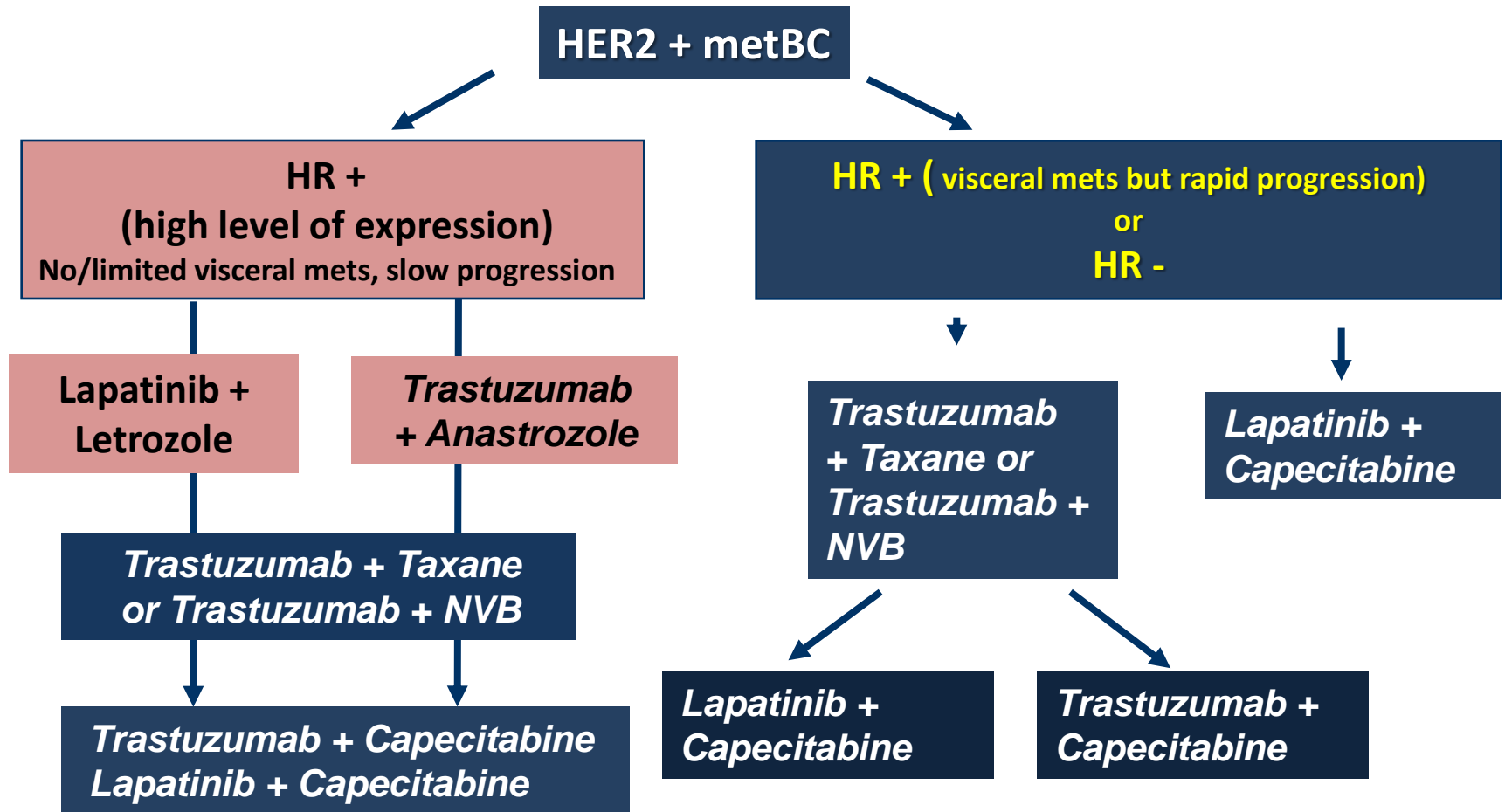
Nota c- Chemioterapia con agente non utilizzato in precedenza

Nota d- Capecitabina.

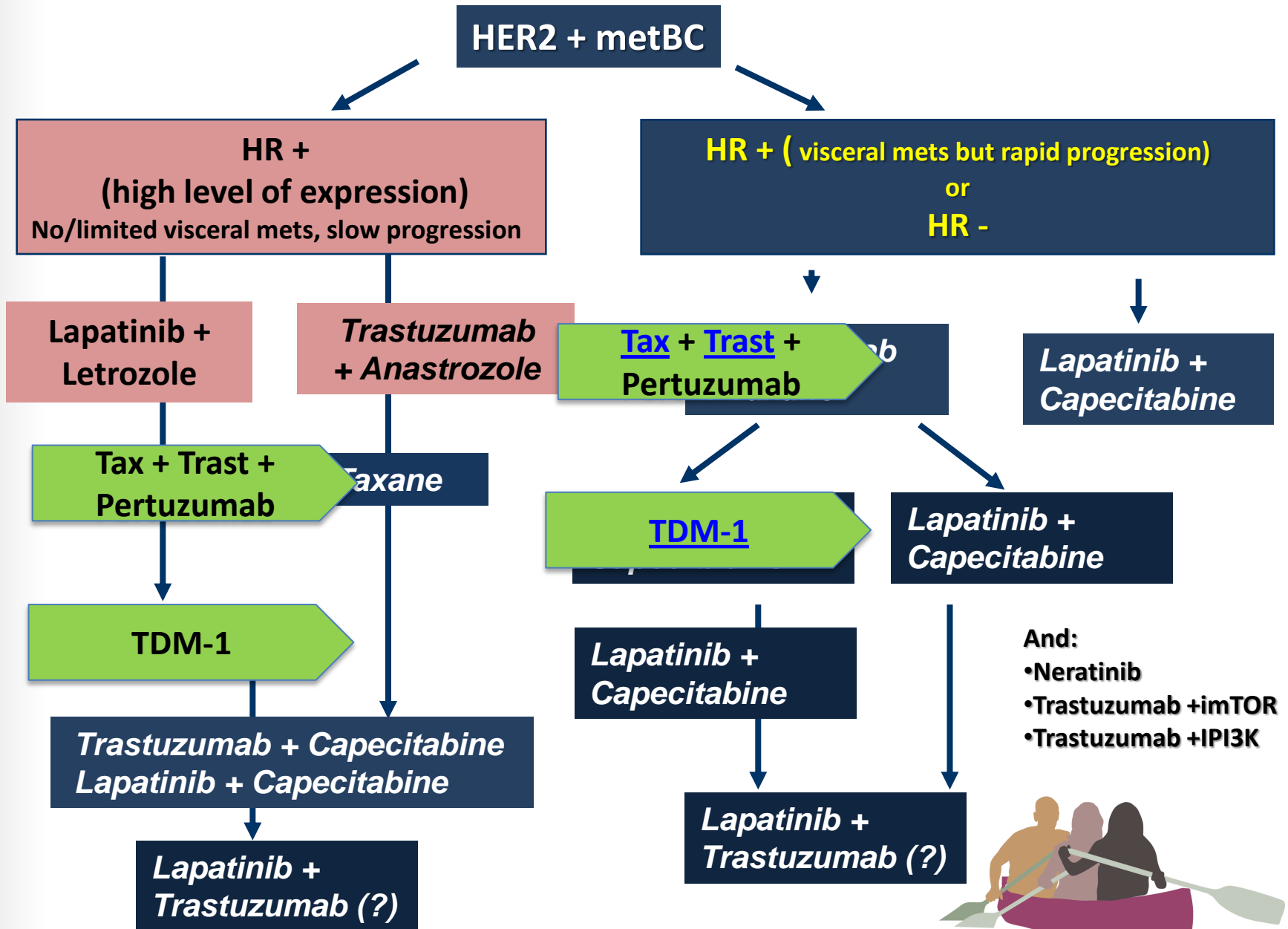
* Pur in assenza di dati da studi prospettici, in caso di progressione durante o entro 6 mesi dalla fine di un trattamento adiuvante con trastuzumab è ammissibile una prima linea con lapatinib e capecitabina (vedere paragrafo 7.2.1b)

** Linee terapeutiche superiori alla III^a sono possibili sulla base delle condizioni cliniche della paziente e sulla presenza di opzioni ragionevoli considerando il rapporto tossicità/efficacia

Algorithm for metastatic HER2+ BC (2013)



Algorithm for mHER2+ BC IN THE NEXT FUTURE



A new *SCENARIO*

- AIs in the adjuvant setting?

| Previous therapy | | | | | | | | |
|------------------------------|----|----|----|----|-----|----|-----|----|
| Endocrine* | 62 | 57 | 60 | 54 | 317 | 49 | 313 | 49 |
| Tamoxifen or toremifene only | 60 | 56 | 59 | 53 | 302 | 47 | 300 | 47 |
| Aromatase inhibitor only | 1 | <1 | 1 | <1 | 3 | <1 | 5 | <1 |
| Chemotherapy* | 51 | 47 | 61 | 55 | 280 | 43 | 281 | 44 |
| Anthracycline only | 38 | 35 | 41 | 37 | 172 | 27 | 171 | 27 |
| Anthracyclines and taxanes | 9 | 8 | 9 | 8 | 41 | 6 | 42 | 7 |
| Other | 4 | 4 | 11 | 10 | 66 | 10 | 68 | 11 |
| Biologic therapy (any) | 1 | <1 | 1 | <1 | 1 | <1 | 2 | <1 |

- Trastuzumab in the adjuvant treatment?
- Maintenance therapy (lack of data)?



An aerial photograph of a university campus, showing various buildings, trees, and parking lots. The text is overlaid in the center of the image.

*Thank you for
your kind attention!*