HER2 positive metastatic breast cancer

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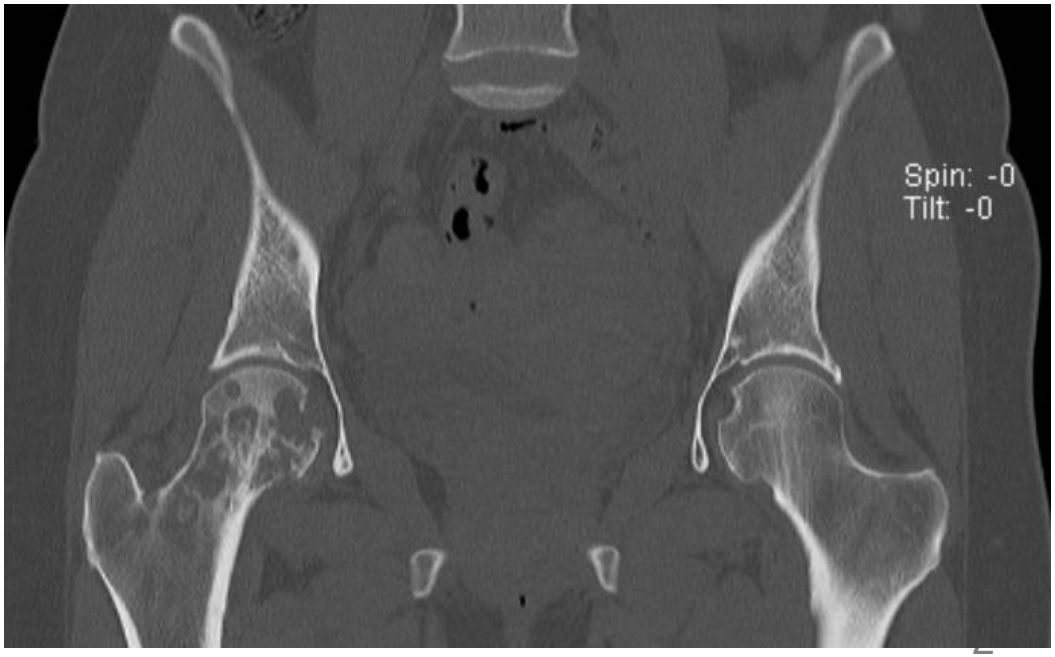
UNIVERSITY HOSPITALS LEUVEN

Case 1: Karen* born 1963

- 9-2006: cT4bN1M0 ER+ PR- HER2+ grade III IDA
  Neoadj **Docetaxel capecitabine trastuzumab**
- 3-2007: Mastectomy and AD, ypT2N1a
  Adjuvant 4x **FEC**, RT, tamoxifen, trastuzumab

- 2-2011: (43y of age)
  - CA15,3 increase
  - pain right hip -> RT 39 Gy
  - diagnosis of bone metastases right hip
  - no other metastases



What would be your treatment? (if you saw patient today)

Castration, taxane, trastuzumab, pertuzumab

Taxane, trastuzumab, pertuzumab

Castration, letrozole, trastuzumab

Castration, letrozole, trastuzumab, pertuzumab

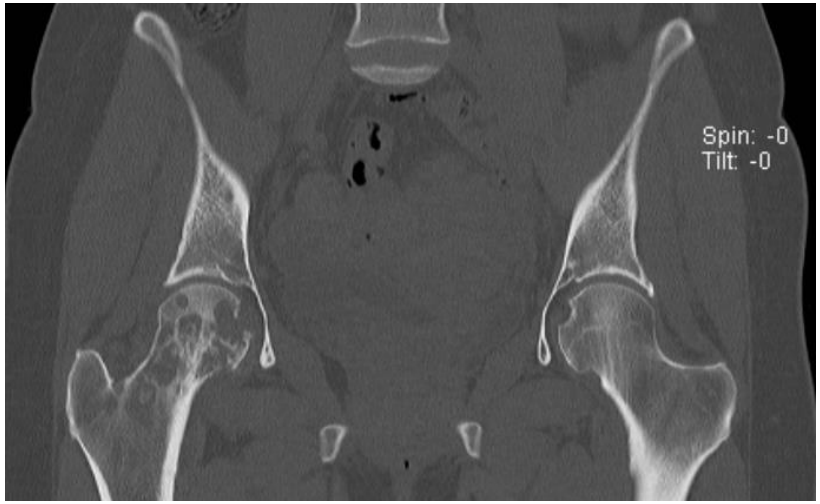
Castration, letrozole, lapatinib

Castration, letrozole, trastuzumab, lapatinib

Other

Case 1: Karen* born 1963

- 2-2011: CA15,3 increase, pain right hip, bone metastases right hip: no other metastases
  - RT right hip
  - radiocastration
  - **letrozole**
  - bisphosphonate



Case 1: Karen* born 1963

- 2-2012: minor progression (right hip, L3, S1, lung?), **trastuzumab** added to letrozole

- 5-2014: minor PD in bone (and CA15,3 ↑)

What would be your systemic treatment choice? (if you saw the patient today)

Taxane trastuzumab pertuzumab

fulvestrant trastuzumab

capecitabine trastuzumab

fulvestrant trastuzumab pertuzumab

letrozole trastuzumab lapatinib

Other

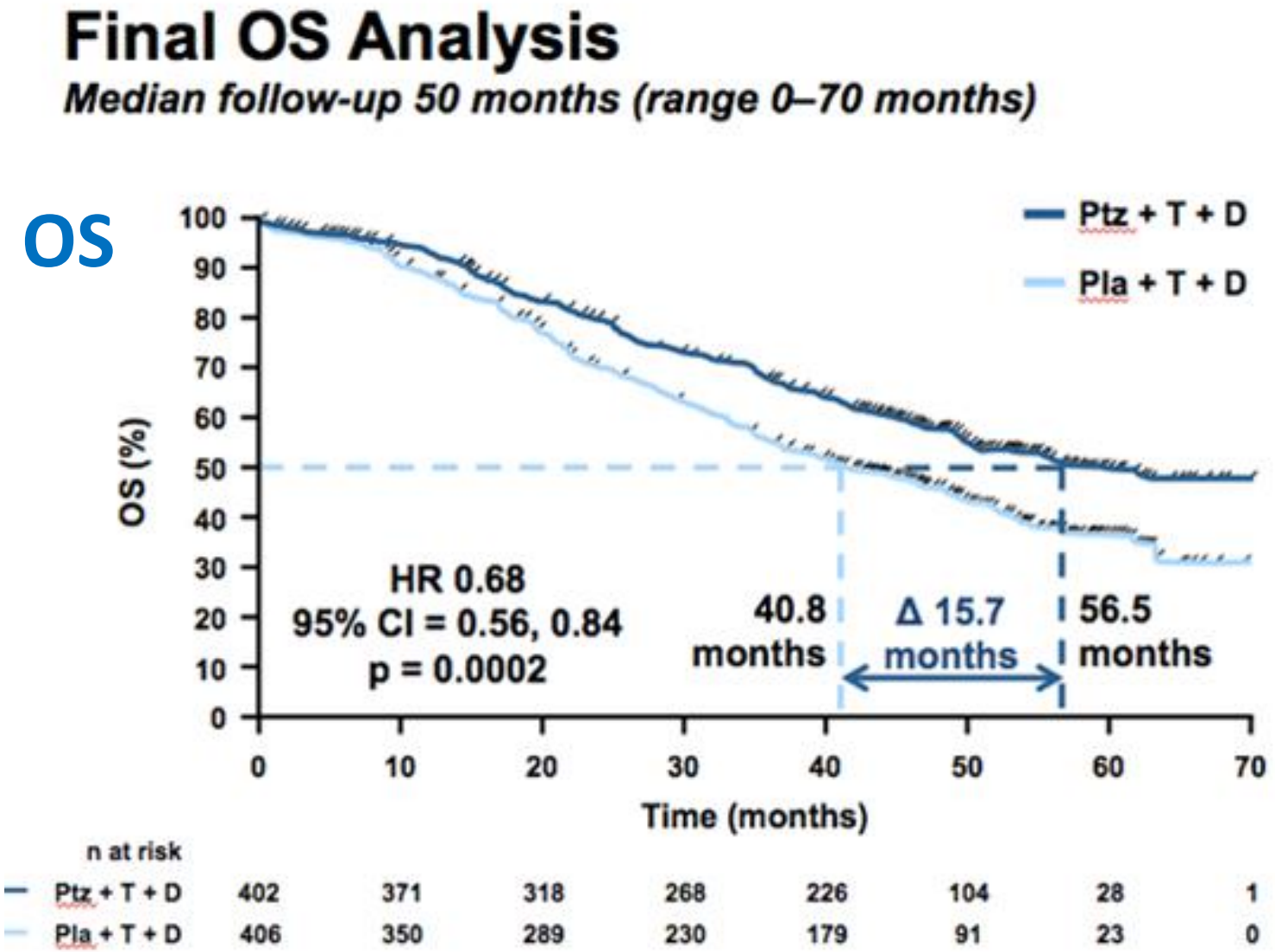
Case 1: Karen* born 1963

- 2-2012: minor progression (right hip, L3, S1, lung?), **trastuzumab** added to letrozole

- 5-2014: minor PD in bone (and CA15,3 ↑), **fulvestrant** and trastuzumab

- 11-2014: PD (bone and lung), **paclitaxel pertuzumab trastuzumab**
- 4-2015: maintenance **exemestane** + Pert/Trast

CLEOPATRA (pertuzumab): OS benefit 15.7 months
first line docetaxel trastuzumab +/- pertuzumab



D, docetaxel; PFS, progression-free survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Baselga NEJM 2012

Vinorelbine as chemo agent? **(in first line HER2+ MBC)**

- Vinorelbine (30-35 mg/m2) –T vs Docetaxel (100 mg/m2) –T

TTP	15.3	vs	12.4 md
OS	38.8	vs	35.7 md
FN	10 %	vs	36 % (p <0.05)

- Vinorelbine-Trastuzumab-Pertuzumab (phase II single arm)
  - 107 pts, first line, vinorelbine (25 mg/m2) d1-8 q3w + Trast + Pert
  - ORR 64%, median PFS 11,5 months
  - 17% pretreated with (neoadjuvant) trastuzumab

Vinorelbine instead of taxane is an option, but not standard

TTP = Time To Progression ; OS = Overall Survival ; FN = Febrile Neutropenia

Andersson JCO 2011; Andersson Oncologist 2017

T-DM1 first line?

MARIANNE study: Pertuzumab +/- T-DM1

- HER2-positive (central) LABC[a] or MBC
- No prior chemotherapy for LABC/MBC
- >6 months from prior neo-/adjuvant vinca alkaloid or taxane chemotherapy

N = 1095

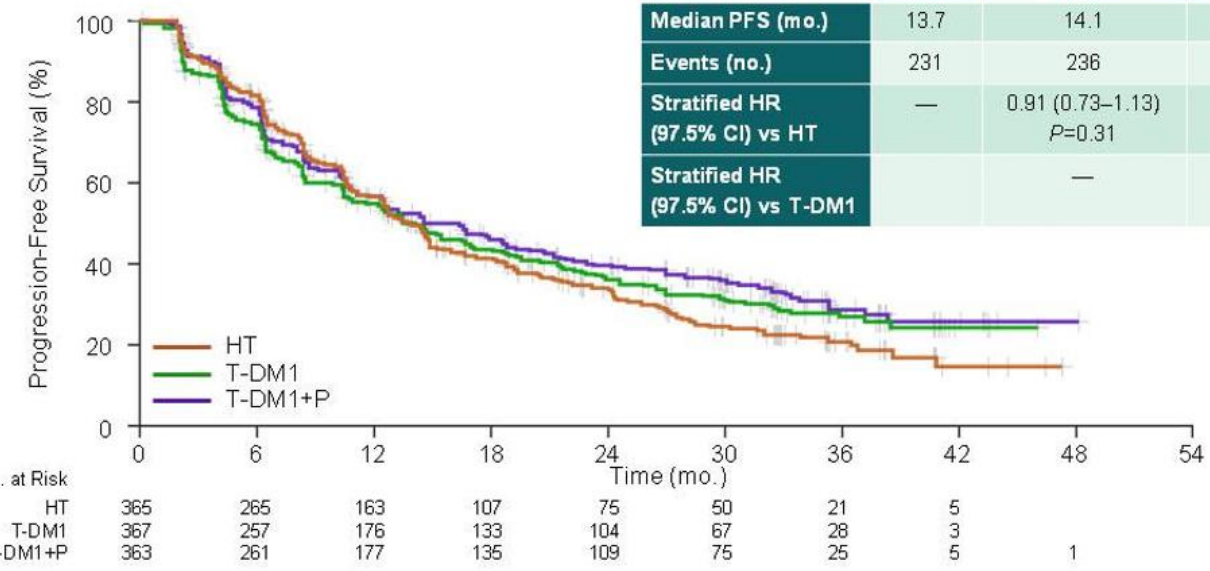
Trastuzumab + docetaxel
(8 mg/kg LD then 6 mg/kg + 100 or 75 mg/m² q3w) **OR**
Trastuzumab + paclitaxel
(4 mg/kg LD then 2 mg/kg + 80 mg/m² qw)

T-DM1 + placebo[b]
(3.6 mg/kg + 840 mg LD then 420 mg q3w)

T-DM1 + pertuzumab
(3.6 mg/kg + 840 mg LD then 420 mg q3w) *

Progression-Free Survival by IRF

	HT	T-DM1	T-DM1+P
Median PFS (mo.)	13.7	14.1	15.2
Events (no.)	231	236	217
Stratified HR (97.5% CI) vs HT	—	0.91 (0.73–1.13) *P*=0.31	0.87 (0.69–1.08) *P*=0.14
Stratified HR (97.5% CI) vs T-DM1		—	0.91 (0.73–1.13)



No new standard

Perez J Clin Oncol 2017

ER+ HER2+ MBC

- First **chemo** with Trast-Pert, and then **maintenance antihormonal** therapy : often best choice

- **Antihormonal** therapy in ER pos ?
  - Tamoxifen: relative resistance?
  - **Anastrozole ± Trast**: PFS 4.8 vs 2.4 mo*
  - **Letrozole ± Lapatinib**: PFS 8.2 vs 3.0 mo* PFS in HER2+ (no benefit in HER2 neg)

Antihormone therapy + antiHER2 therapy not very powerful

Kaufman JCO 2009 ; Johnston JCO 2009 ; Andersson JCO 2011

ER+ HER2+ MBC

Study	Regimens	PFS	Remarks
Pertain 'Pertuzumab' n=258	Endocrine R/ + T Endocrine R/ + TP	11,8 Mo 15,8 Mo*	Diarrhea 36% Diarrhea 55% Induction chemo (taxane) in 57%
Alternative 'Lapatinib' n=369	Endocrine R/ + T Endocrine R/ + L Endocrine R/ + TL	5,7 Mo 8,3 Mo 11 Mo*	Diarrhea 9% Diarrhea 51% Diarrhea 69%

Antihormone therapy + doublet antiHER2 therapy is interesting, but not enough data

T = Trastuzumab ; P = Pertuzumab ; L = Lapatinib

Arpino G et al SABCS 2016 abstract S3-04

Gradishar et al ASCO 2017 abstract 1004

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- 5-2014: minor PD in bone (and CA15,3 ↑), **fulvestrant** and trastuzumab
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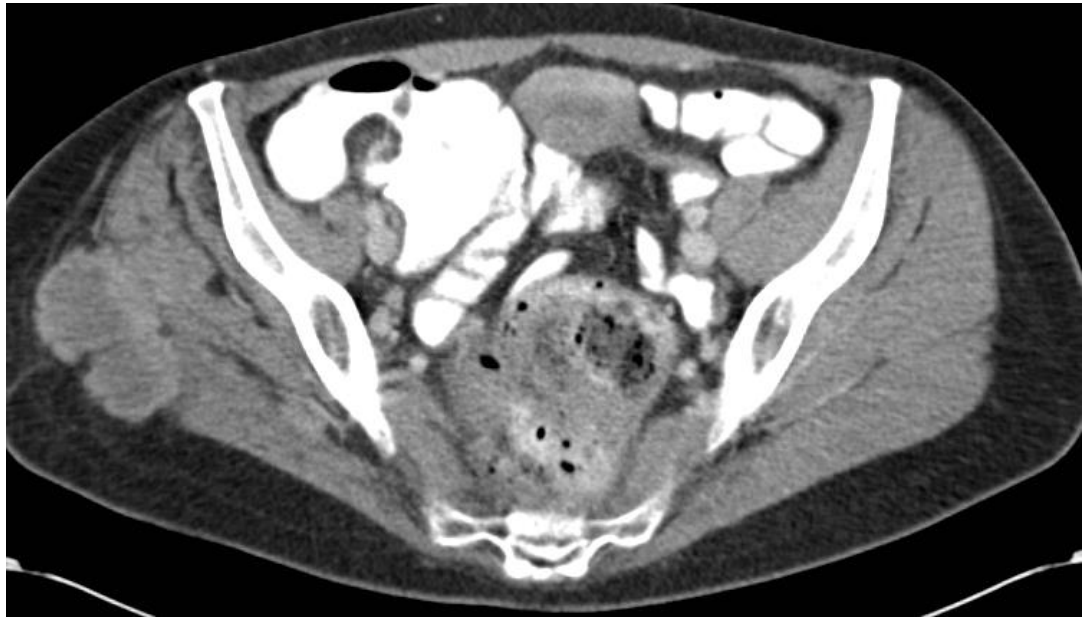
- 9-2015: progression right gluteal region

  biopsy ER 2+1, PR–, HER2+.



What would be your systemic treatment choice?

Capecitabine lapatinib

Capecitabine tratuzumab

T-DM1

Vinorelbine trastuzumab

Other

Case 1: Karen* born 1963

- 9-2015: start **T-DM1**

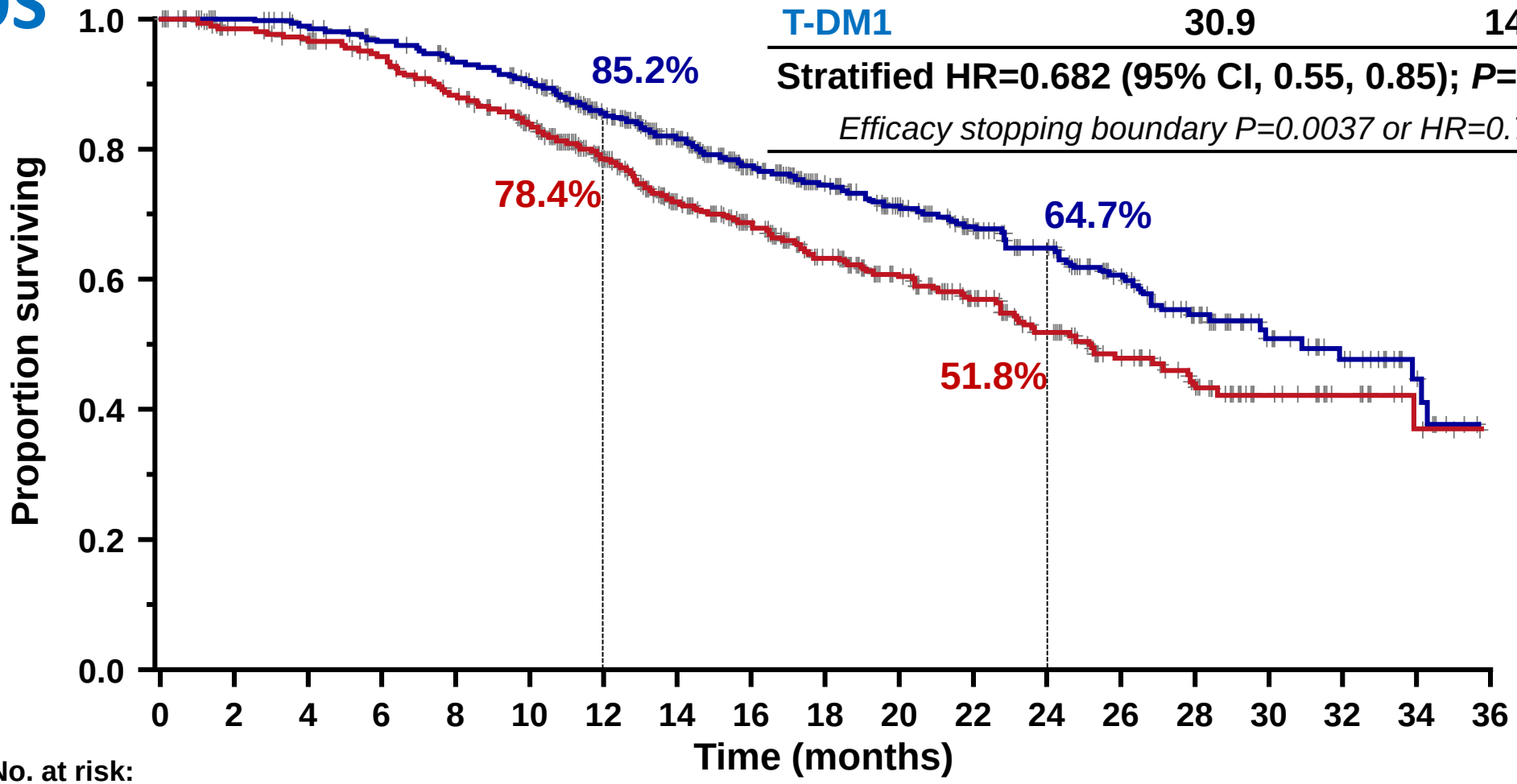
EMILIA: T-DM1 as second line standard

OS

	Median (months)	No. of events
Capecitabine + Lapatinib	25.1	182
T-DM1	30.9	149

Stratified HR=0.682 (95% CI, 0.55, 0.85); *P*=0.0006

Efficacy stopping boundary P=0.0037 or HR=0.727



No. at risk:

Cap + Lap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

Data cut-off July 31, 2012; Unstratified HR=0.70 (*P*=0.0012).

Verma NEJM 2012

TH3RESA:
T-DM1 in later lines

HER2-positive (central) advanced BC (N=600)

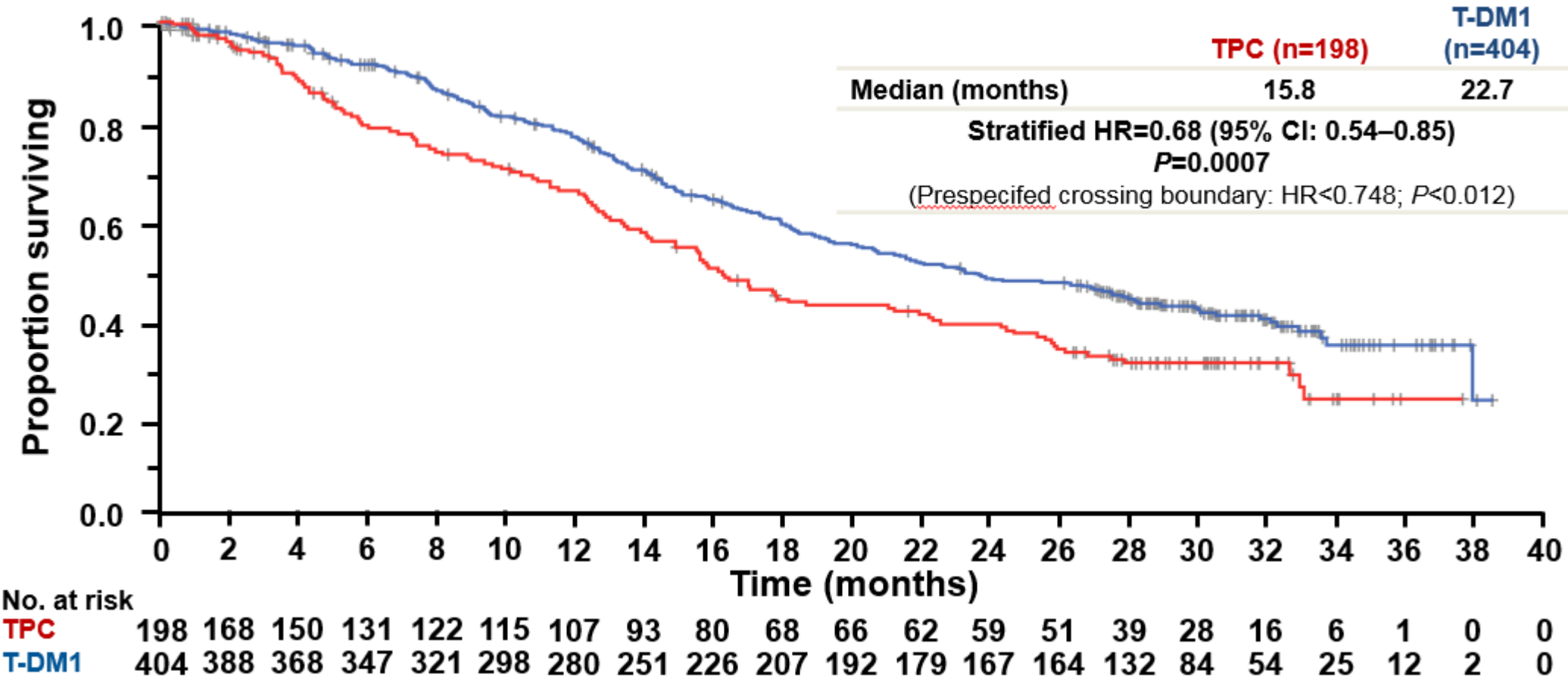
≥2 prior HER2-directed therapies for advanced BC

Prior treatment with trastuzumab, lapatinib, and a taxane

2 → T-DM1 3.6 mg/kg q3w IV

1 → Treatment of physician's choice (TPC)

OS



	TPC (n=198)	T-DM1 (n=404)
Median (months)	15.8	22.7

Stratified HR=0.68 (95% CI: 0.54–0.85)
P=0.0007
(Prespecifed crossing boundary: HR<0.748; *P*<0.012)

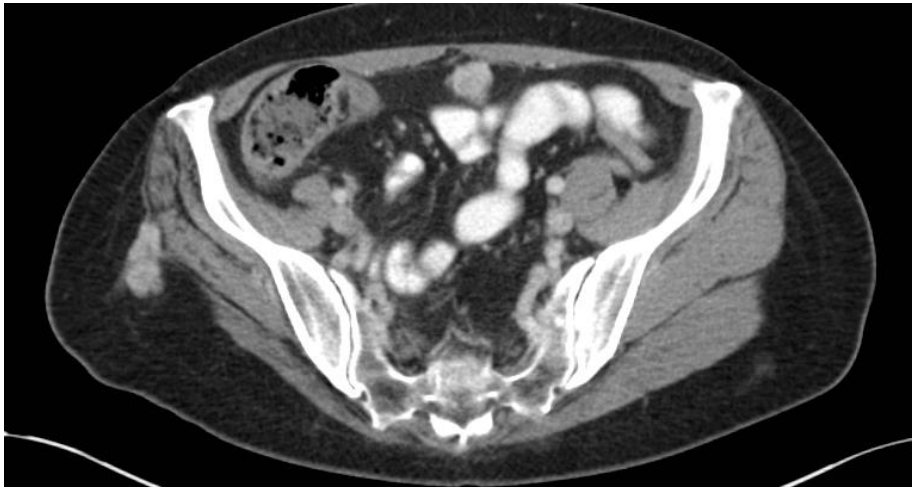
Wildiers SABCS 2015

Case 1: Karen* born 1963

- 9-2015: start **T-DM1**

- 3-2017: PD **Capecitabine Lapatinib**.
- 11-2017: trastuzumab instead of lapatinib (hepatotoxicity)

- 4-2018: PD right gluteal region.

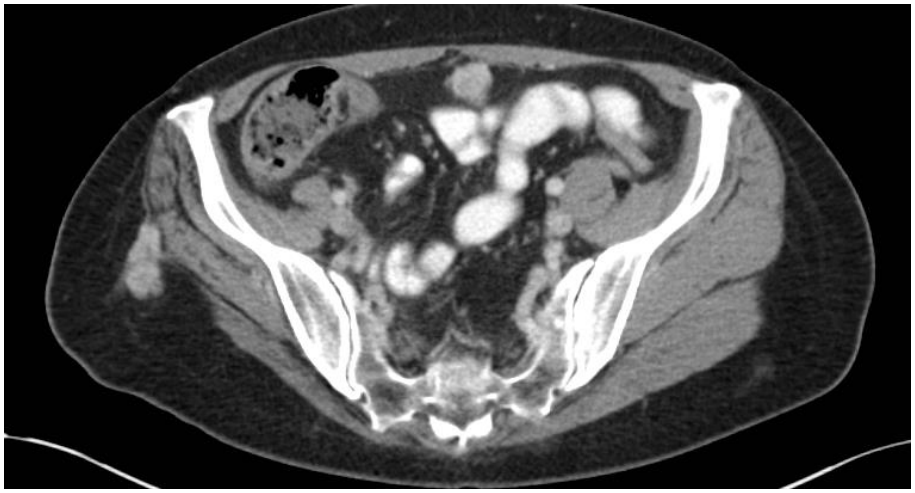


Case 1: Karen* born 1963

- 4-2018: PD right gluteal region.

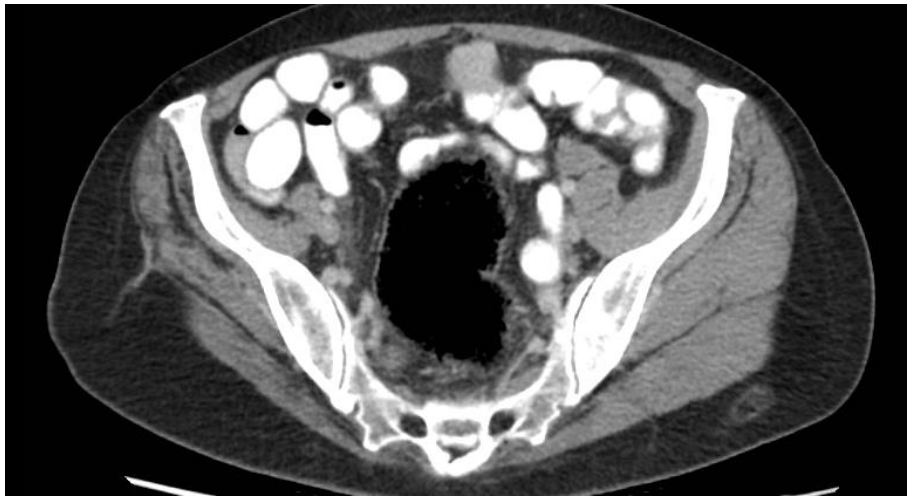
  U201 study with **DS-8201**

  (T-DXd, trastuzumab deruxtecan)



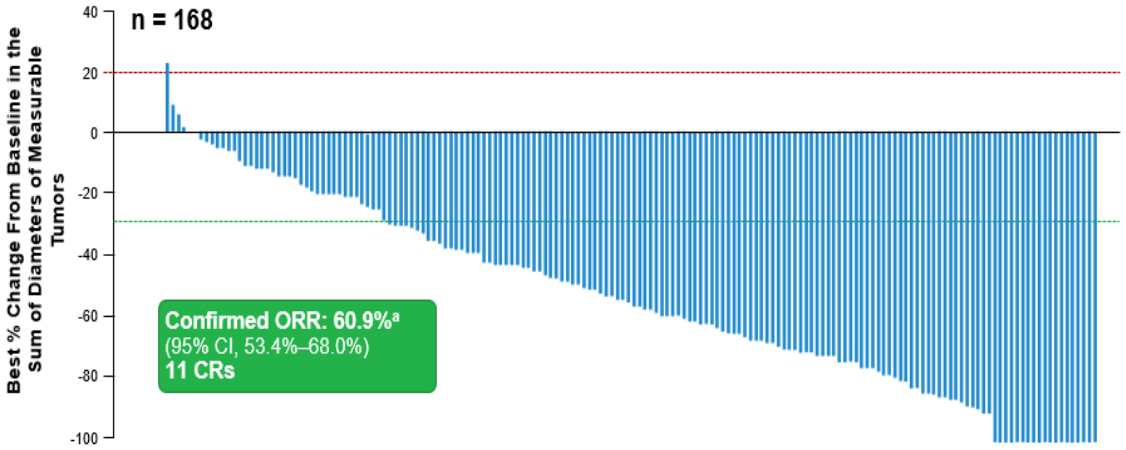
- 2-2021: deep remission

  ECOG 1, only grade 1 toxicity: epistaxis, fatigue, alopecia, tears



DS-8201

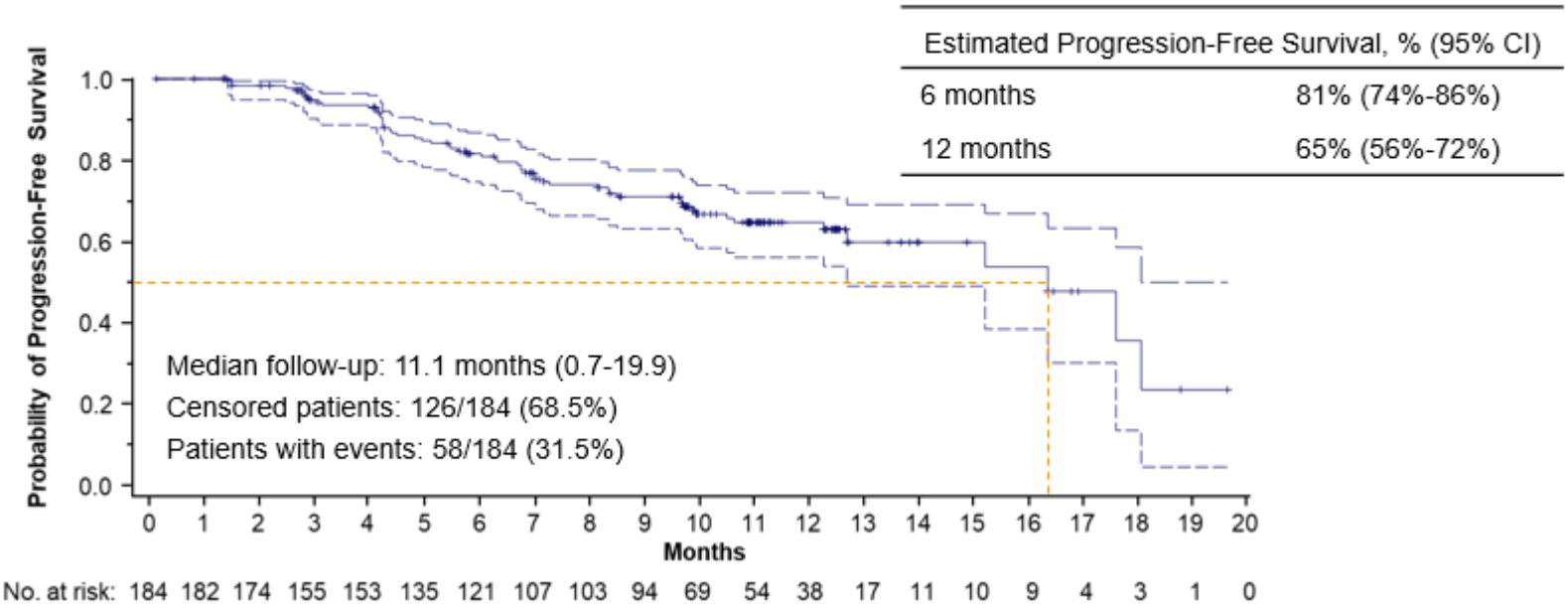
Destiny-Breast01



By independent central review.
The line at 20% indicates progressive disease; the line at −30% indicates partial response.
[a] Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N=184).
Modi S et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N Engl J Med* 2019.

Prior lines of cancer therapy 6 (2-27)
Prior trastuzumab 100%
Prior T-DM1 100%

Median progression-free survival was 16.4 months (95% CI, 12.7-NE)



Estimated Progression-Free Survival, % (95% CI)	
6 months	81% (74%-86%)
12 months	65% (56%-72%)

NEJM 2019 Modi et al

Tucatinib

HER2Climb

Key Eligibility Criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline
  - Previously treated stable brain metastases
  - Untreated brain metastases not needing immediate local therapy
  - Previously treated progressing brain metastases not needing immediate local therapy
  - No evidence of brain metastases

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
(21-day cycle)

Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

N=202

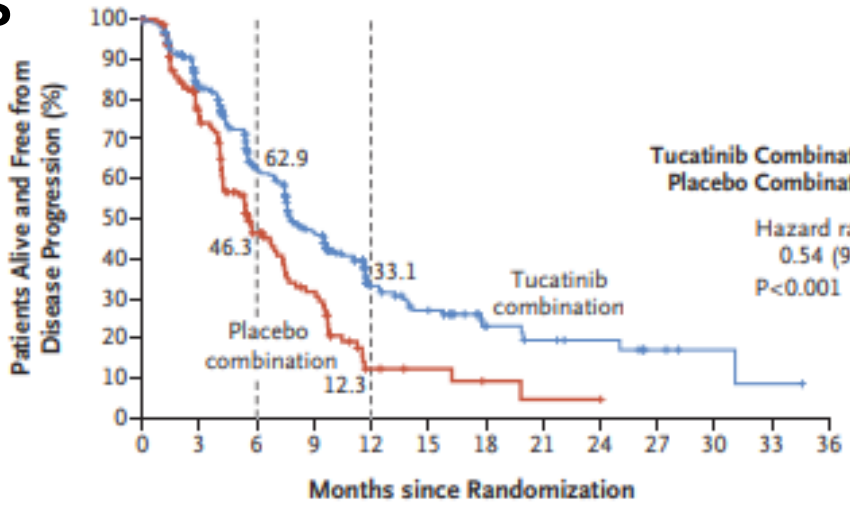
Placebo + Trastuzumab + Capecitabine
(21-day cycle)

Placebo
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

https://clinicaltrials.gov/ct2/show/NCT02614794

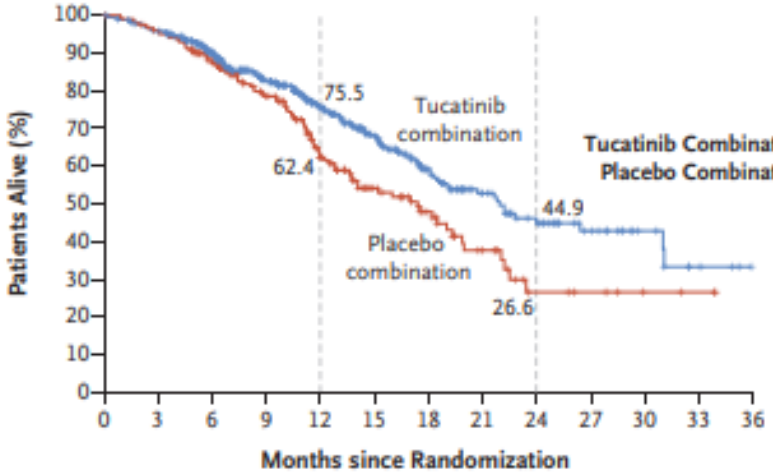
PFS



	No. of Events/ No. of Patients	Median Duration (95% CI) mo
Tucatinib Combination	178/320	7.8 (7.5–9.6)
Placebo Combination	97/160	5.6 (4.2–7.1)

Hazard ratio for disease progression or death, 0.54 (95% CI, 0.42–0.71)
P<0.001

OS

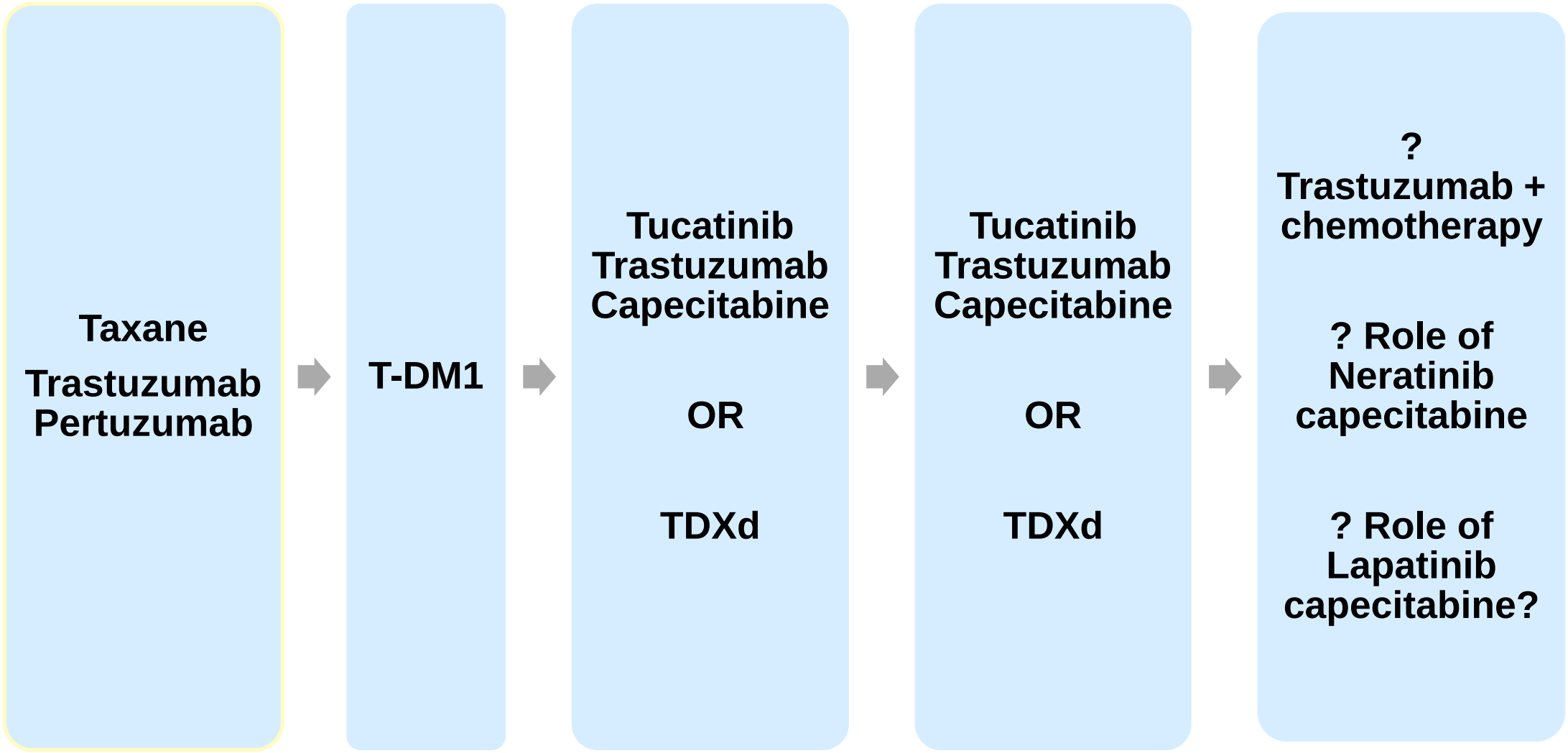


	No. of Deaths/ No. of Patients	Median Duration (95% CI) mo
Tucatinib Combination	130/410	21.9 (18.3–31.0)
Placebo Combination	85/202	17.4 (13.6–19.9)

Hazard ratio for death, 0.66 (95% CI, 0.50–0.88)
P=0.005

NEJM 2020 Murthy et al.

HER2 positive disease: systemic therapy in 2021



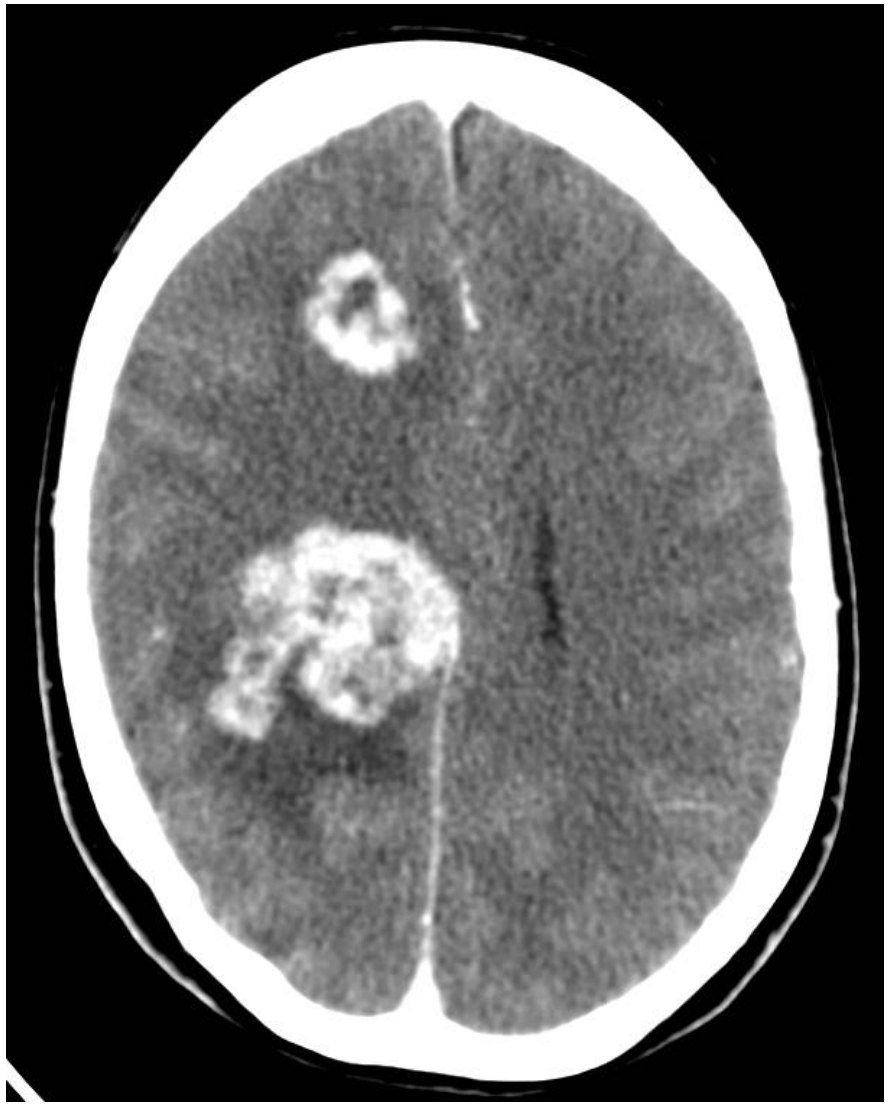
Case 2: Kristel* born 1980

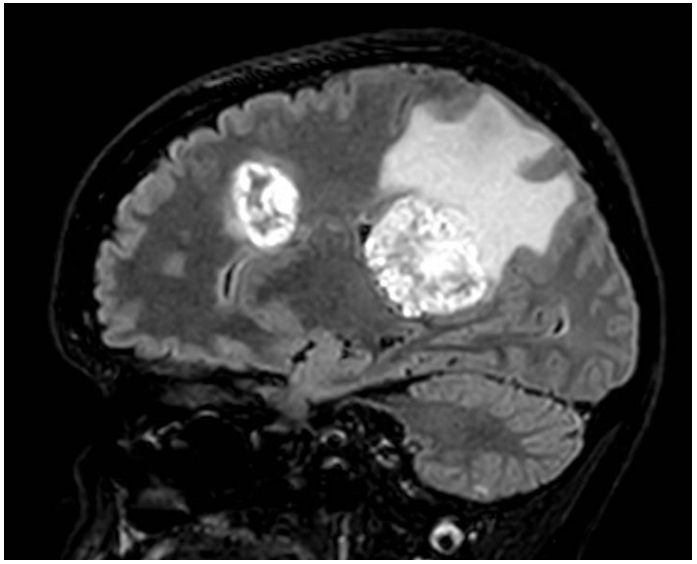
- 10-2018: (38y) liver, bone, lymph node metastatic breast cancer grade III. IDA. ER 7, PR 4 , Her2 + FISH positief.
  - start Paclitaxel + Trastuzumab + Pertuzumab
  - LHRHa followed by ovarectomy ; Denosumab
  - BRCA negative

- 4-2019: major response, stop Paclitaxel, start Letrozole + Trast + Pert.

Case 2: Kristel* born 1980

- 5-2020: nervous, mild headache, CA15,3 6 -> 11





- 2 large metastases with oedema and midline shift
- Multiple subcentimetric brain lesions in cerebellum
- No extracranial progression (only residual bone metastases visible)

What would be your main/first oncological approach? (besides steroids)

Resection of brain metastases

Radiotherapy

Systemic anticancer therapy

Other

Case 2: Kristel* born 1980

- Consult **neurosurgeon**: major risk for post-op deficits (ao. hemiplegia), no clear oncological benefit, so no preference for surgery

- Consult **radiotherapy**: risk of increased oedema and related complications. Preference for tumor load reduction by systemic therapy first.

What would be your systemic therapy choice?

T-DM1

Capecitabine Trastuzumab

Capecitabine Lapatinib

platinum regimen

other

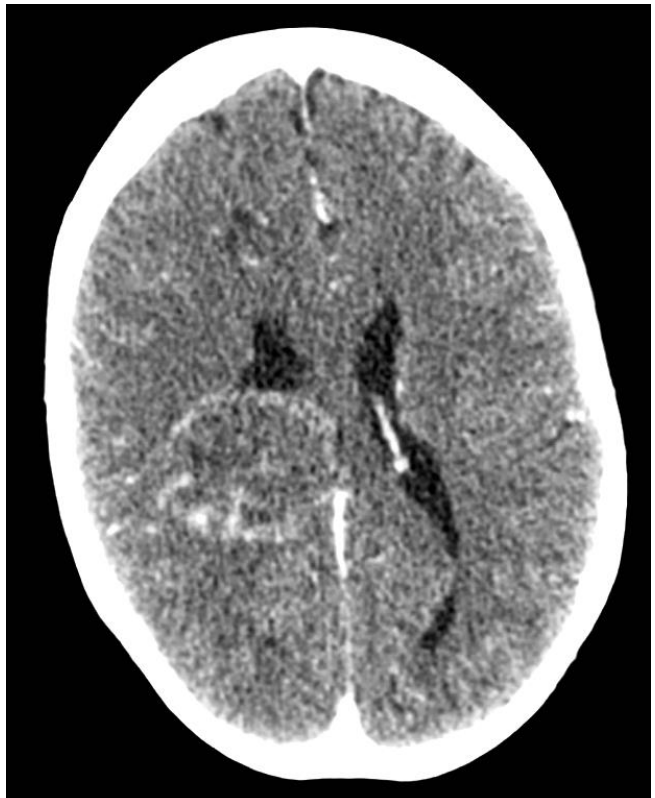
Case 2: Kristel* born 1980

- 29-5-2020:
  - Start steroids (medrol 2x32 mg/d)
  - Start **Lapatinib Capecitabine**

- 9-6-2020:

  Hospitalisation for diarrhea and weakness; dose reduction

- 22-6-2020: response but persistant intolerance, so switch to **T-DM1**



Lapatinib + Capecitabine for HER2+ brain metastases

As a single agent, CNS ORR to lapatinib is only **~ 6%**

In pre-treated patients, **lap-cape** results in CNS ORR **20-38%**

In the upfront setting, **lap-cape** results in CNS ORR **66%**

Study	N	Prior RT	CNS ORR	TTP/PFS	OS
Lin et al CCR 2009	50	**100%**	**20%**	3.6 mo	NR
Sutherland et al, Br J Ca 2010 (LEAP)	34	**94%**	**21%**	5.1 mo	NR
Metro et al, Ann Oncol 2011	22	**86%**	**32%**	5.1 mo	11 mo from start of LC
Lin et al, J Neuro-Oncol 2011	13	**100%**	**38%**	NR	NR
Bachelot Landscape Lancet Oncol 2013	45	**0%**	**66%**	5.5 mo	91% alive at 6 mo

T-DM1 for HER2+ brain metastases

KAMILLA: phase IIIB

- 2003 enrolled patients
- 398 had baseline brain metastases

- In 126 patients with measurable brain metastases, a ≥30% reduction in the sum of the largest diameters of target brain lesions was observed in subgroups
  - **49%** (33/67) of pts who did **not receive brain RT**
  - **33%** (16/49) of pts who **received brain RT ≥30 days** before baseline

Montemurro et al, Ann Oncol 2020

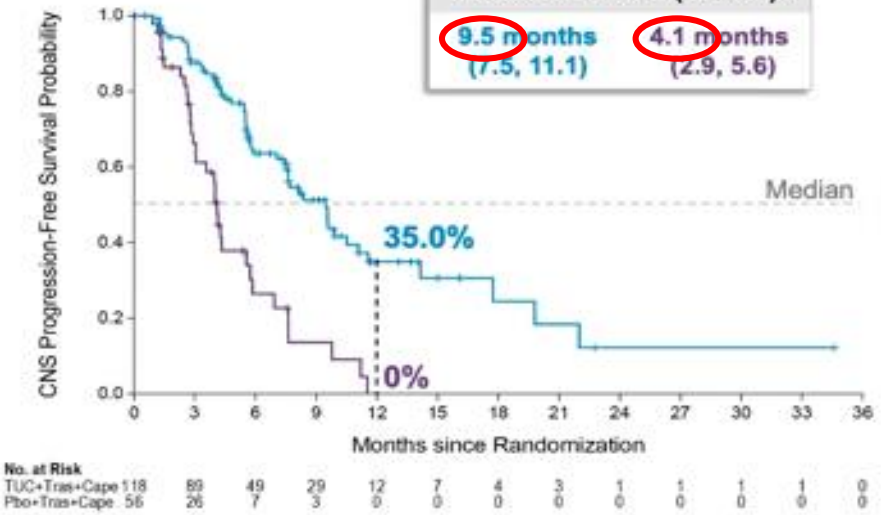
Tucatinib for HER2+ brain metastases

HER2 Climb study

CNS-PFS benefit in pts with ACTIVE brain metastases

	Events N=174	HR (95% CI)	P Value
TUC+Tras+Cape	54/118	0.36 (0.22, 0.57)	<0.0001
Pbo+Tras+Cape	33/56		

Median CNS-PFS (95% CI):	
9.5 months (7.5, 11.1)	4.1 months (2.9, 5.6)

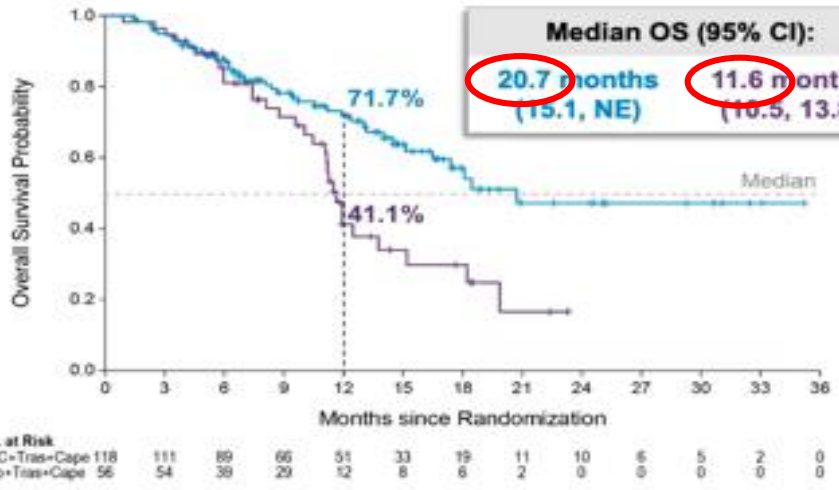


OS benefit in pts with ACTIVE brain metastases

OS Benefit in Patients with Active Brain Metastases

	Events N=174	HR (95% CI)	P Value
TUC+Tras+Cape	39/118	0.49 (0.30, 0.80)	0.004
Pbo+Tras+Cape	30/56		

Median OS (95% CI):	
20.7 months (15.1, NE)	11.6 months (10.5, 13.8)



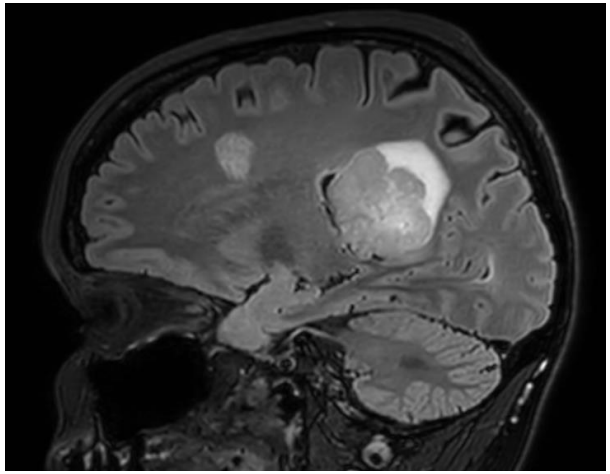
CNS ORR 47% in Tucatinib arm and 20% in control arm in pts with active brain mets and measurable disease (n=75)

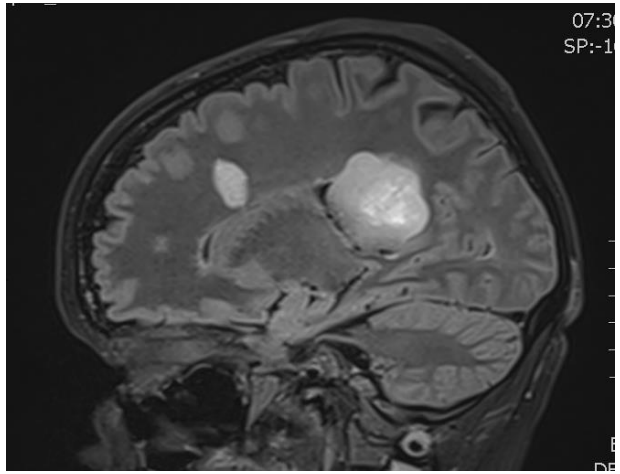
CNS ORR 47% in Tucatinib arm and 17% in control arm in pts without prior RT (n=66)

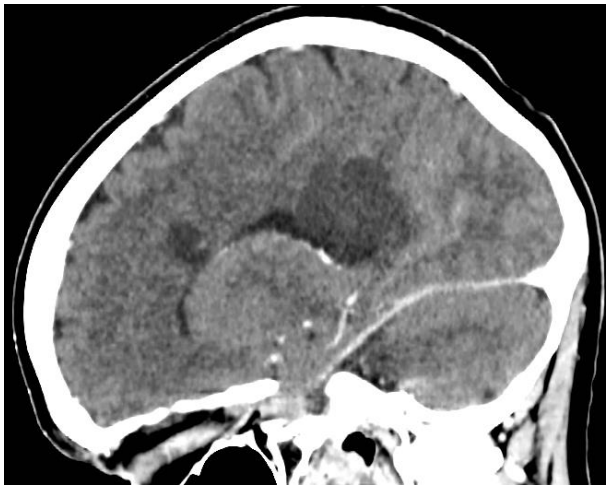
JCO 2020 Lin et al

Case 2: Kristel* born 1980

- 8-2020:
  - Tumor volume decrease but still large
  - oedema ↓↓
  - Decision to proceed T-DM1
- 10-2020:
  - Further tumor volume decrease
  - oedema ↓
  - But growth of small cerebellar mets (4)
  - Stereotactic **RT** of 6 lesions 5x6Gy
  - T-DM1 interrupted during RT
- 12-2020:
  - Good evolution, T-DM1 continued

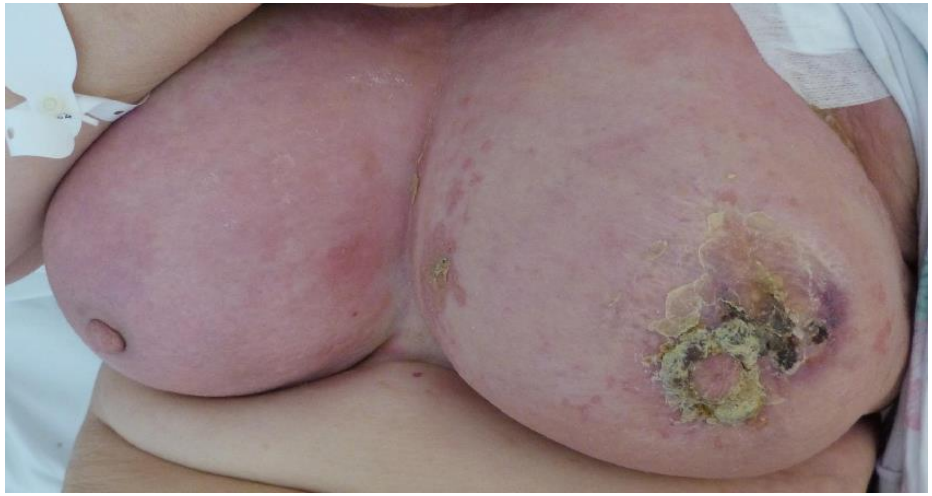


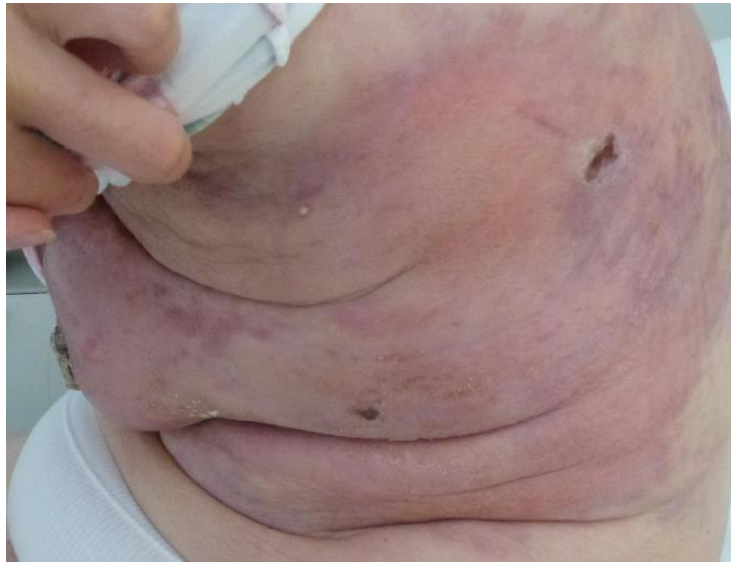




Case 3: Katleen* born 1942

- 7-2014 (72y): Mastitis carcinomatosa left, with extension to right breast and left back.
  - CT: extensive mediastinal ADP.
  - CA15.3 210 kU/l.
  - CNB: IDA gr III, ER 2, PR 0, HER2 3+ FISH pos.





Case 3: Katleen* born 1942

- **Medical history**
  - Hypertension
  - Diabetes mellitus II since 1980, start insuline in 1987
  - Diabetic retinopathy
  - Paroxysmal atrial fibrillation
  - 1997: ankle fracture, osteosynthesis
  - 2009: Burn wounds grade III after syncope during cooking (hospitalized 2 weeks)
  - 2009: hyperthyreoidism
  - 2011: mediale facetectomie L4-L5 left
  - 7-2013: Spiraloid femur fracture after fall.

Case 3: Katleen* born 1942

- **Medication**
  - BURINEX
  - CORUNO
  - MARCOUMAR
  - SOTALEX
  - TRITACE
  - INSULINE 4x/d

- **Clinical examination**
  - W 80 kg H 154 cm BMI 34
  - Sacral decubitis
  - Peripheral bilateral leg oedema, venous insufficiency, venous ulcer
  - Breast cfr previous image

- **Technical investigations**
  - Echocor: EF 55%
  - Lab: Hb 11.1, eGFR 50, CRP 10, Albumine 31, CA15.3 210

- **Social**
  - Lives with her husband and 1 son, no social problems for her
  - Nurse comes 2x/d for washing, cleaning support weekly

Case 3: Katleen* born 1942

- **Geriatric assessment**
  - G8 12/17
  - Lives with husband, no problems for her socially
  - ADL (activities of daily living) 11/24
  - IADL (instrumental ADL) 3/8
  - Falls yes, with hip fracture
  - Mob-T fatigue score 0/6
  - MMSE (mini-mental state) 27/30
  - GDS (geriatric depression) 6/15
  - MNA screening 11 → full scale 22/30 ‘risk for malnutrition’

What would be your anticancer treatment plan?

Docetaxel trastuzumab pertuzumab

Paclitaxel trastuzumab pertuzumab

Vinorelbine trastuzumab pertuzumab

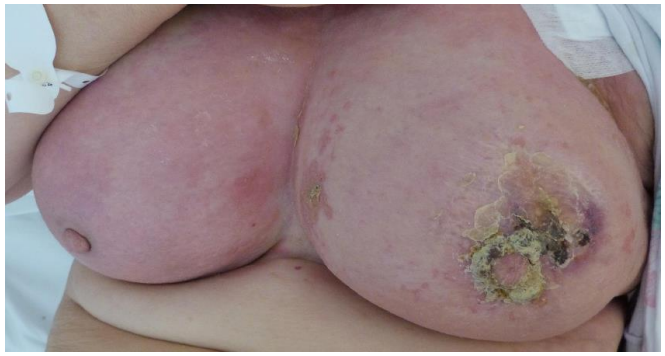
Capecitabine trastuzumab

Oral cyclophosphamide trastuzumab pertuzumab

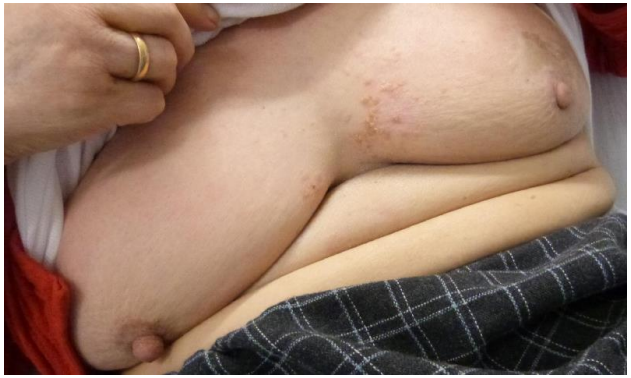
No anticancer therapy

Other

Case 3: Katleen* born 1942



- 7-2014 (72y): Mastitis carcinomatosa left, with extension to right breast and left back.
  - Extensive mediastinal ADP.
  - CA15,3 210.
  - CNB: IDA gr III ER 2 PR0 HER2 3+ FISH pos.
- Therapy plan:
  - Inclusion in EORTC 75111 elderly trial
  - randomisation to arm with Cyclofosfamide + Trast + Pert
  - Allergic reaction after first Trastuzumab, resolved afterwards.
  - Social support: home nurse 3x/d, warm meal by OCMW, washing by sister, transfer with help of son and husband, rolator.
- 12-2014: Partial response, good tolerance



Case 3: Katleen* born 1942

- 7-2014 (72y): Cyclofosfamide + Trast + Pert
- 12-2014: Partial response, good tolerance
- 5-2015: Progressive disease (ADP abdominal and left axilla ; while mastitis remained in remission). Biopsy refused by patient. What now?

What would be your sytemic therapy proposal?

Palliative care

Capecitabine trastuzumab

Capecitabine lapatinib

T-DM1

Anthracycline

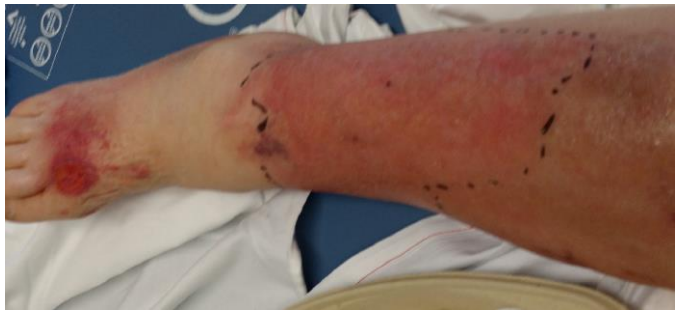
Other

Case 3: Katleen* born 1942

- 7-2014 (72y): **Cyclofosfamide** + **Trast** + **Pert**
- 12-2014: Partial response, good tolerance
- 5-2015: Progressive disease (ADP abdominal and left axilla ; while mastitis remained in remission). Biopsy refused by patient. Switch to **T-DM1** within EORTC 75111 study.

- 4-2016: Major response, good tolerance.

- 5-2016: Hospitalisation for erisypelas right leg,
  UTI, renal insuff, hypoK, diarrhea, decubitus
- 6-2016: Rehospitalisation
- 7-2016: Rehospitalisation
- 8-2016: Rehospitalisation, rapid decline, multiorgan failure, decease 9-2016



Older patients: metronomic chemo as first line chemo backbone?

EORTC 75111 – 10114

N=80

HER2+ MBC

≥ 70 Years (or ≥65/≥60y with co-morbidity)

No prior chemo for MBC

≤1 line of antiHER2 + endocrine therapy

Prior endocrine therapy allowed

Stratification: ER and/or PR pos vs both negative, previous HER2 treatment (none vs adj only vs metastatic), G8< or equal 14 vs G8>14

Primary endpoint:
PFS rate at 6 months

1:1

Pertuzumab + Trastuzumab

Pertuzumab + Trastuzumab + Metronomic Cyclophosphamide

PD →

T-DM1 *(optional)*

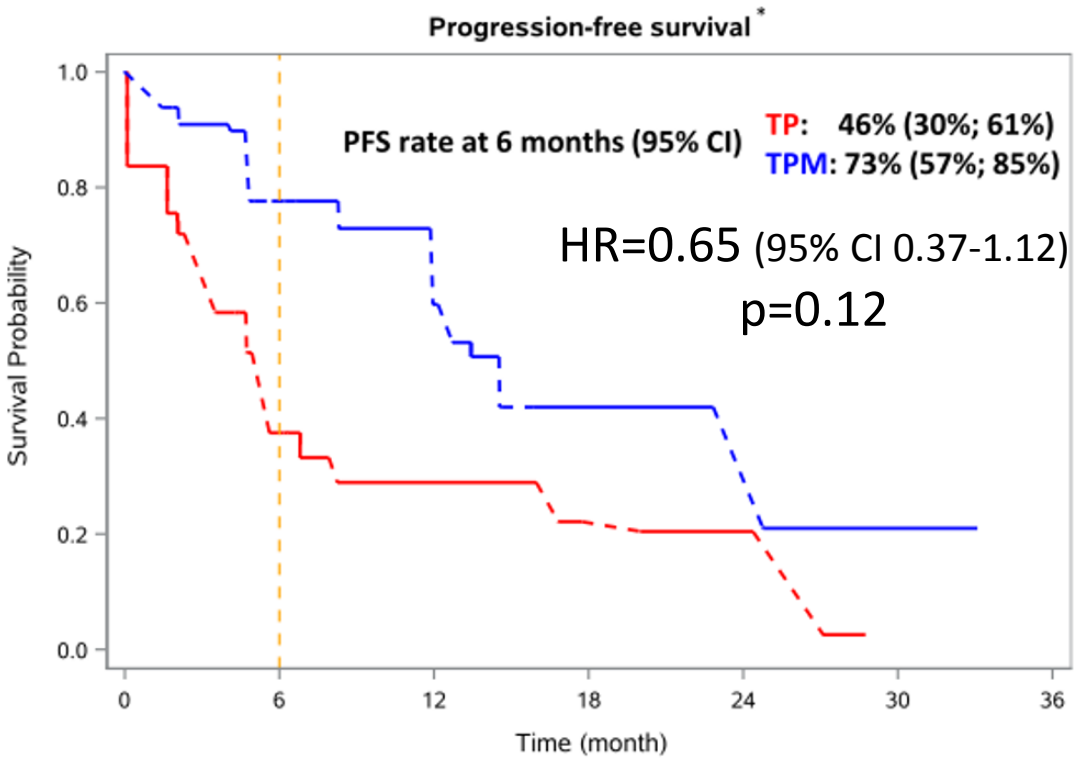
Metronomic CT (chemotherapy): cyclophosphamide 50 mg/d po continuously
On progression: Option to have T-DM1 *(3.6 mg/kg iv q3w)* till progression

	N (%)
Age (years) – Median (Range)	77 (61 - 91)
WHO PS 2-3	19 (23.8)
ER and/or PgR positive	55 (68.8)
No prior anti-HER2 therapy for MBC	72 (91.1)
Prior adjuvant endocrine therapy	24 (30.4)
Visceral involvement	74 (93.3)
G8 score at baseline G8 ≤ 14	56 (70.9)
Frail (SPPB ≤ 7)	37 (52.9)

Wildiers et al. Lancet Oncol 2018

Older patients: metronomic chemo as first line chemo backbone?

EORTC 75111 – 10114



Median PFS was 5.6 months (95% CI 3.6-16.8) versus 12.7 months (95% CI 6.7-24.8)

- 33% grade III-IV lymphopenia for TPM vs 5% for TP, but no febrile neutropenia
- Other toxicities comparable
- No relevant difference in functional evolution between TP and TPM
- 9 (31%) of 29 deaths were not breast cancer related.

- TPM, followed by T-DM1 after progression, may delay or supersede taxane chemotherapy in this population.

TPM is not the new standard, but is a new treatment option

Older patients: Lapatinib Trastuzumab without chemo?

CARG: Lapatinib Trastuzumab phase II single arm

- 39 pts with HER2+ MBC
- 60+ (median age 72)
- ORR 23%
- PFS 2,7 Months
- 43% had lapatinib dose reduction
- 25% hospitalized during or directly after treatment, 5% for events attributed to treatment
- 70% had ≥2 grade toxicity, 20% had ≥ grade 3 toxicity

Lapatinib trastuzumab not first choice in elderly

SABCS P5-21-08 O'Connor

HER2+ metastatic breast cancer in older pts

- Fit older pts can receive standard therapy
- **Deescalation** often possible for
  - Patients who desire to avoid taxane side effects
  - Unfit/frail patients
- Deescalation possibilities
  - TPM (trastuzumab pertuzumab metronomic cyclophosphamide)
  - Vinorelbine trastuzumab pertuzumab
  - Antihormone therapy plus single or doublet antiHER2 therapy
  - …

HER2-targeted treatment for older patients with breast cancer: An expert position paper from the International Society of Geriatric Oncology

Etienne Brain [a,*], Philippe Caillet [b], Nienke de Glas [c], Laura Biganzoli [d], Karis Cheng [e], Lissandra Dal Lago [f], Hans Wildiers [g]

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