HER-2 Borstcarcinoom in het CNS : Systemische opties

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CNS ziekte bij borstkanker

	Risico op HM 10 j	% HM bij M+ ziekte	Mediane tijd tot HM	Mediane overleving sinds diagnose HM
Luminaal A	0.7%	7.6%	47.4/12	10/12
Luminaal B	12%	10.8%	54.4/12	22.9/12
HER2+	12%	25-49%	35.8/12	17.9/12
TN	7%	25-46%	27.5/12	7.3/12

Wat is de beste timing voor systeemtherapie ?

- Primaire preventie
  - Adjuvante therapie tijd tot hersenmetastasen
- Secundaire preventie
  - Bij gemetastaseerde ziekte zonder CNS ziekte
- Samen met WBRT/SRS (radiosensitizer)
- “Tertiaire” preventie na eerdere therapie voor hersenmetastasen (S/WBRT/SRS)
- Na progressie na eerdere WBRT
- In de plaats van enige radiotherapie

Opties van systeemtherapie

- Chemotherapie: platinumzouten, antracyclines en capecitabine
- Trastuzumab
- Pertuzumab
- T-DM1
- Lapatinib
- Neratinib

Veroorzaakt Trastuzumab een risico voor HM ?

	1-year trastuzumab group	Observation group	Overall
Cohort of 3401 enrolled patients			
Number of patients	1703	1698	3401
CNS relapse as first DFS event	37 (2%)	32 (2%)	69 (2%)
Time to CNS relapse (years)	1·31 (0·53–2·03)	1·25 (0·53–2·13)	1·26 (0·53–2·03)
Other first DFS event	326 (19%)	421 (25%)	747 (22%)
Cohort of 413 patients who had died and for whom forms were returned			
Number of patients	186	227	413
Died with CNS relapse	88 (47%)	129 (57%)	217 (53%)
Time to CNS relapse (years)	2·11 (1·34–2·99)	1·89 (1·15–2·92)	2·02 (1·19–2·93)
Died without CNS relapse	98 (53%)	98 (43%)	196 (47%)

Data are n, n (%), or median (IQR). DFS=disease-free survival.

Table 2: **CNS relapse by group**

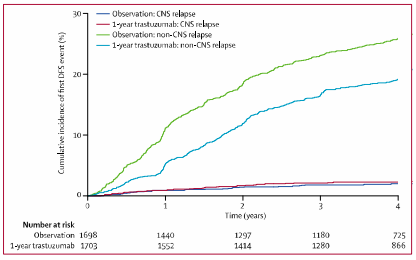
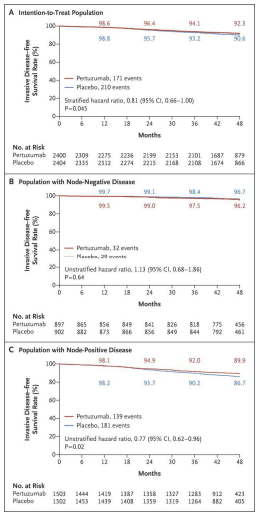


Figure 1: **Competing risks analysis of cumulative incidence of first DFS events for all 3401 patients**
Curves for both groups are shown for the cumulative incidence of the competing events of non-CNS relapses and CNS relapses as the first DFS event. Time axis not drawn beyond 4 years for consistency. DFS=disease-free survival.

Adjuvant Pertuzumab en Trastuzumab



von Minckwitz G et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1703643

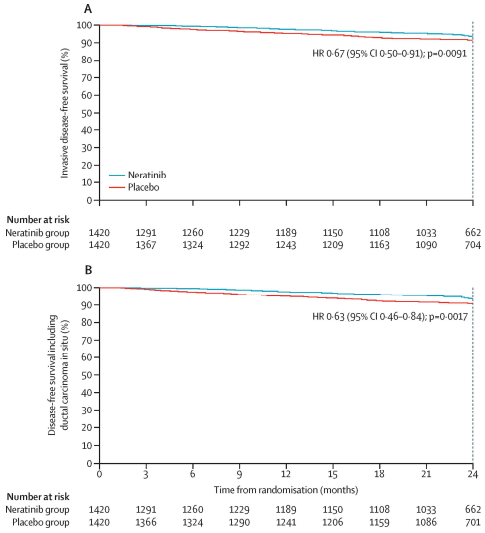
Primaire preventie: adjuvans sensu strictu

- Aphinity EC/AC/FEC gevolgd door Tax + Trastuzumab + Pertuzumab
- Experimentele arm eindpunt IDFS 89.2% versus 91.8%
- Distant recurrence na 3 jaar
  - 112/2400 4.7%
  - 139/2405 5.8%
  - Odds ratio van 0.8
- Hersenmetastasen als eerste event op afstand na 3 jaar
  - 45/2400 1.9%
  - 44/2405 1.8%

Primaire preventie CNS metastasen: the SCLC Approach in HER2 Borstkanker

- Anglo Celtic VII trial
- Stadium IV ptn zonder aangetoonde CNS ziekte
- Randomizering RT vs obs 1/1
- 51 ptn gerandomiseerd 25 RT 26 controle
- Cumulatieve incidentie na 2 jaar 34.4% vs 21.0%

ExteNET Clinical trial



Extenet: Invasive Disease-Free Survival in the ITT population

	Neratinib group (n=1420)	Placebo group (n=1420)
Any event	70 (5%)	109 (8%)
Local or regional invasive recurrence	8 (1%)	25 (2%)
Invasive ipsilateral breast tumour recurrence	4 (<1%)	4 (<1%)
Invasive contralateral breast cancer	2 (<1%)	5 (<1%)
Distant recurrence*	52 (4%)	73 (5%)
Bone	21 (1%)	21 (1%)
Brain	11 (1%)	15 (1%)
Distant lymph node	6 (<1%)	10 (1%)
Liver	13 (1%)	21 (1%)
Lung	5 (<1%)	12 (1%)
Other	5 (<1%)	2 (<1%)
Other abdominal viscera	0	2 (<1%)
Pleura	1 (<1%)	3 (<1%)
Subcutaneous tissue	1 (<1%)	1 (<1%)
Unknown	1 (<1%)	0
Death without previous recurrence	4 (<1%)	2 (<1%)

Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized phase III study CLEOPATRA

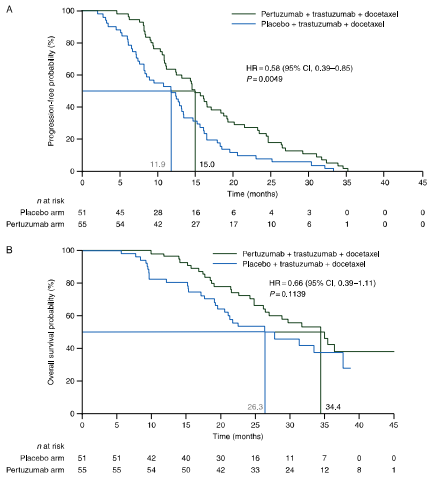


Table 2. Primary and Secondary Efficacy Results

End Point	Lapatinib + Capecitabine	Trastuzumab + Capecitabine	OR*	95% CI	P†
Primary and CNS end points (M-ITT‡)					
No. of patients	251	250			
CNS as first site of relapse			0.65	0.26 to 1.63	.360
No. of patients	8	12			
%	3	5			
95% CI, %	0.89 to 5.11	2.33 to 7.66			
Incidence of CNS progression at any time			1.14	0.52 to 2.51	.8646
No. of patients	17	15			
%	7	6			
95% CI, %	3.84 to 10.16	4.06 to 8.94			
Time to first CNS progression, months					
Median	5.7	4.4			
Range	2-17	2-27			
Secondary end points§ (ITT‖)					
No. of patients	271	269			
ORR			0.80	0.54 to 1.18	.2731
No. of patients	73	85			
%	27	32			
95% CI, %	21.71 to 32.29	26.43 to 37.57			
CR					
No. of patients	8	12			
%	3	4			
PR					
No. of patients	65	73			
%	24	27			
SD					
No. of patients	97	104			
%	36	39			
SD ≥ 24 weeks					
No. of patients	39	33			
%	14	12			
CBR			0.90	0.63 to 1.29	.6106
No. of patients	112	118			
%	41	44			
PD as best response					
No. of patients	49	38			
%	18	14			
DoR, months					
No. of patients	73	85			
Median	6.2	8.4			
95% CI	5.3 to 10.6	6.0 to 21.6			

Abbreviations: CBR, clinical benefit response; CR, complete response; DoR, duration of response; ER, estrogen receptor; IRC, independent review committee; ITT, intent-to-treat population; M-ITT, modified intent-to-treat population; OR, odds ratio; ORR, overall response rate; PD, progressive disease; PgR, progesterone receptor; PR, partial response; SD, stable disease.

*The 95% CI for the incidence of CNS as first site of relapse was computed from the logistic regression model adjusting for prior trastuzumab use, number of prior metastatic treatments, ER status, PgR status, number of metastatic sites at baseline, site of disease at baseline, and age. Exact binomial 95% CIs were computed for the incidence of CNS at any time, ORR, and CBR. 95% CIs for time to first CNS progression and DoR were computed using Greenwood's formula for the standard error of the Kaplan-Meier estimates.

†The *P* value for the incidence of CNS as first site of relapse was computed from the logistic regression model adjusting for prior trastuzumab use, number of prior metastatic treatments, ER status, PgR status, number of metastatic sites at baseline, site of disease at baseline, and age. The *P* values for the incidence of CNS at any time, ORR, and CBR was computed from Fisher's exact test.

‡M-ITT comprised all randomly assigned patients who had no baseline CNS metastases per IRC assessment, regardless of whether treatment was administered.

§The protocol was amended to include confirmed responses for CR and PR.

‖ITT comprised all randomly assigned patients regardless of whether study drug was administered.

From: **Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast CancerThe NEfERT-T Randomized Clinical Trial**

JAMA Oncol. 2016;2(12):1557-1564. doi:10.1001/jamaoncol.2016.0237

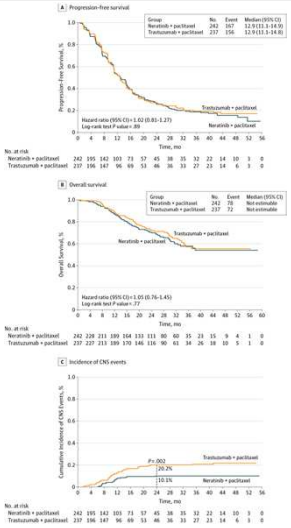


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Table. Efficacy Analyses in the Intent-to-Treat Population[a]

Variable	Neratinib Plus Paclitaxel (n = 242)	Trastuzumab Plus Paclitaxel (n = 237)	Hazard Ratio or Difference (95% CI)	*P* Value
Primary end points				
Patients with PFS event, No. (%)	167 (69.0)	156 (65.8)	1.02 (0.81 to 1.27)	.89[b]
Median PFS, mo	12.9	12.9	...	...
95% CI	11.1-14.9	11.1-14.8	...	...
Secondary end points				
Objective response rate, No. (%)[c]	181 (74.8)	184 (77.6)	-2.8 (-10.5 to 4.8)[d]	.52[c]
95% CI	68.8-80.1	71.8-82.8	...	...
Complete response[e]	4 (1.7)	9 (3.8)	...	...
Partial response[e]	177 (73.1)	175 (73.8)	...	...
Clinical benefit rate, No. (%)	214 (88.4)	202 (85.2)	3.2 (-2.9 to 9.3)[d]	.24[c]
95% CI	83.7-92.2	80.1-89.5		
Median duration of response, mo[f]	13.4	12.9	1.01 (0.78 to 1.32)	.92[b]
95% CI	11.4-16.8	11.0-15.9	...	...
Incidence of symptomatic or progressive CNS events, No. (%)	20 (8.3)	41 (17.3)	0.48 (0.29 to 0.79)[g]	.002[c]
First quartile, 25%, time to CNS events, mo, (95% CI)	Not reached	18.3 (12.3-41.3)	...	...

Abbreviations: CI, confidence interval; CNS, central nervous system; PFS, progression-free survival; ellipses, data not applicable.

[a] All end points by investigator assessment.

[b] Stratified log-rank test.

[c] Adjusted Cochran Mantel-Haenszel test.

[d] Difference.

[e] Confirmed responses.

[f] Assessed in 181 and 184 patients in the neratinib-paclitaxel and trastuzumab-paclitaxel groups, respectively.

[g] Relative risk.

Trastuzumab emtansine (T-DM1) versus lapatinib p capecitabine in patients with HER2-positive metas breast cancer and central nervous system metasta: a retrospective, exploratory analysis in EMILIA†

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Background: We characterized the incidence of central nervous system (CNS) metastases after treatment with trastuzumab emtansine (T-DM1) versus capecitabine–lapatinib (XL), and treatment efficacy among patients with pre-existing CNS metastases in the phase III EMILIA study.

Patients and methods: In EMILIA, patients with human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer previously treated with trastuzumab and a taxane were randomized to T-DM1 or XL until disease progression. Patients with treated, asymptomatic CNS metastases at baseline and patients developing postbaseline CNS metastases were identified retrospectively by independent review; exploratory analyses were carried out.

Results: Among 991 randomized patients (T-DM1 = 495; XL = 496), 95 (T-DM1 = 45; XL = 50) had CNS metastases at baseline. CNS progression occurred in 9 of 450 (2.0%) and 3 of 446 (0.7%) patients without CNS metastases at baseline in the T-DM1 and XL arms, respectively, and in 10 of 45 (22.2%) and 8 of 50 (16.0%) patients with CNS metastases at baseline. Among patients with CNS metastases at baseline, a significant improvement in overall survival (OS) was observed in the T-DM1 arm compared with the XL arm [hazard ratio (HR) = 0.38; $P = 0.008$; median, 26.8 versus 12.9 months]. Progression-free survival by independent review was similar in the two treatment arms (HR = 1.00; $P = 1.000$; median, 5.9 versus 5.7 months). Multivariate analyses demonstrated similar results. Grade ≥3 adverse events were reported in 48.8% and 63.3% of patients with CNS metastases at baseline administered T-DM1 and XL, respectively; no new safety signals were observed.

Conclusion: In this retrospective, exploratory analysis, the rate of CNS progression in patients with HER2-positive advanced breast cancer was similar for T-DM1 and for XL, and higher overall in patients with CNS metastases at baseline compared with those without CNS metastases at baseline. In patients with treated, asymptomatic CNS metastases at baseline, T-DM1 was associated with significantly improved OS compared with XL.

Key words: ado-trastuzumab emtansine, T-DM1, metastatic breast cancer, central nervous system metastasis

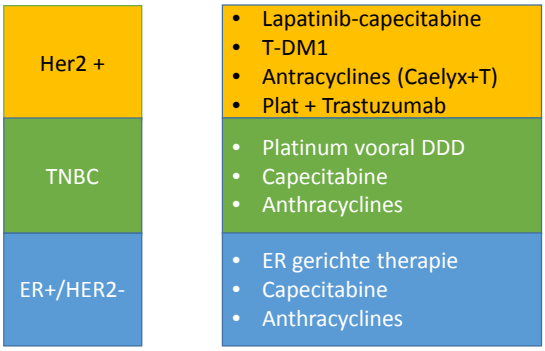
Samen met radiotherapie als sensitizer

- Lapatinib 750 mg - 1000 mg- 1250 mg – 1500 mg q/day
- WBRT 37.5 Gy in 15 fracties 2.5 Gy / fractie. 5/7
- N=35
- 7/26 DLT: 2 graad 3 rash, 2 graad 3 buikloop, 1 graad 3 hypoxie, 2 graad longembolie
- Relatie studie en toxiciteit onduidelijk
- Stop
- RR 80% in CNS

Tertiaire Preventie na therapie CNS

- Weinig gegevens
- Advies : indien regime ziektecontrole behoudt extra-CNS dat regime aanhouden
- Meestal dus Trastuzumab/Pertuzumab/ en evt hormonale therapie

Standaard Systeemtherapie opties bij Hersenmetastasen Borstcarcinoom



Nieuwere opties: Patricia Trial

- CNS ziekte HER2+ post-RT
- Lesies > 10 mm
- RANO criteria
- Pertuzumab standaard + High-Dose Trastuzumab (6mg/kg/wk)
- N=15
- RR 3/15 (20%) alle PR
- SD 9/15 (60%)
- PR + SD > 4/12 = 60%

Nieuwere Opties: Neratinib + Capecitabine

- N= 37 (nagenoeg alle post-RT)
- 65% post WBRT
- Centrale review eindpunt VORR = 50% Volume reductie CNS ziekte
- 18/37 (49%) VORR

Tucatinib + capecitabine + trastuzumab

- ONT-380, a potent, highly selective, orally available inhibitor of HER2
- ONT-380 was evaluated in combination with C and/or T in pts with HER2+ MBC who had been treated with T, a taxane, and ado-trastuzumab emtansine (T-DM1).
- Prior treatment with T, a taxane, and T-DM1 were required; prior pertuzumab, lapatinib, or neratinib were permitted; prior capecitabine exposure was prohibited.
- ORR 61%
- ORR CNS 42%

Conclusie

- HER2-geamplificeerde borstkanker heeft een relatieve hoge prevalentie aan CNS herval
- Er is geen duidelijk direct preventief effect van adjuvant trastuzumab op het risico van eerste herval in het CNS
- In de secundaire preventie lijkt neratinib en paclitaxel te overwegen maar allicht enkel bij intolerantie PTD en T-DM1
- Bij onbehandelde ptn lijkt Capecitabine met Lapatinib een overweegbare keuze
- Nieuwere CNS selectieve middelen lijken beloftevol