

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: de Boer M, van Deurzen CHM, van Dijck JAAM, et al. Micrometastases or isolated tumor cells and the outcome of breast cancer. *N Engl J Med* 2009;361:653-63.

Supplementary Table 1. Individuals and Institutions Participating in This Study

Comprehensive Cancer Centre East, Nijmegen - C. Lennards; *Canisius Wilhelmina Hospital, Nijmegen* - C. Wauters, L. Strobbe; *Radboud University Medical Centre, Nijmegen* - Th. Wobbes; *Maas Hospital, Boxmeer* - A. Meersman; *Rijnstate Hospital, Arnhem* - F. van de Molengraft, R. Keus, J. Klinkenbijl; *Gelderse Vallei Hospital, Ede* - E. Balk, J. Kroeze; *Zevenaar Hospital, Zevenaar* - J. van Wijk; *Slingeland Hospital, Doetinchem* - E. Muller; *St. Jansdal Hospital, Harderwijk* - R. Tobon Morales; *Comprehensive Cancer Centre Amsterdam, Amsterdam* - O. Visser, W. Heijbroek-de Clerq; *Academic Medical Centre, Amsterdam* - M. van de Vijver, A. Kluit; *IJsselmeerziekenhuizen, Lelystad* - E. Neefjes-Borst, G. Algie; *Onze Lieve Vrouwe Gasthuis, Amsterdam* - E. Nijhuis, P. Borgstein; *Flevo Hospital, Almere* - M. Regoort; *Medical Centre Alkmaar, Alkmaar* - H.J. van Slooten, B. Langenhorst; *Gemini Hospital, Den Helder* - H. Tjeenk Willink; *Westfries Gasthuis, Hoorn* - J.W. Jansen, M. Govaert; *Zaans Medical Centre, Zaandam* - M. Flens, J. Oomen; *BovenIJ Hospital, Amsterdam* - R. Klicks; *Waterland Hospital, Purmerend* - L. de Widt-Levert; *Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam* - H. van Boven, J. Westerga; *Slotervaart Hospital, Amsterdam* - L. de Kock; *Hospital Amstelland, Amstelveen* - S. Veltkamp; *Spaarne Hospital, Hoofddorp* - J. Burggraaf, A. Tanka; *Sint Lucas Andreas Hospital, Amsterdam* - E. Barbé, E. Steller; *Vrije Universiteit Medical Centre, Amsterdam* - W. Mooi, S. Meijer; *Kennemer Gasthuis, Haarlem* - D. Willebrand, H. Rijna; *Rode Kruis Hospital, Beverwijk* - M. Hunfeld; *Tergooi Hospitals, Blaricum* - M. Prins, P. Bor, A. ten Tije; *Tergooi Hospitals, Hilversum* - J. Juttman, S. Luyck-de Bakker; *Comprehensive Cancer Centre West, Leiden* - P. Krijnen, B. Jongejan; *Bronovo Hospital, Den Haag* - I. Koelma, J. van Esser, O. Guicherit; *Diaconessenhuis, Leiden* - J. Graadt van Roggen, R. Vree, E. Planken; *Rijnland Hospital, Leiderdorp* - J. Calame, A. Zeilemaker, W. Molendijk; *Medical Centre Haaglanden, Den Haag* - E. Ooms, A. Marinelli, R. Brouwer; *Medical Centre Haaglanden, Leidschendam* - I. Groot; *'t Lange Land Hospital, Zoetermeer* - B. Jas, A. Ogilvie; *Groene Hart Hospital, Gouda* - M. Giessen, R. Schmitz, A. van der Torren-Konze; *Haga Hospital Leyenburg, Den Haag* - P. Blok, W. Steup, H. Sleeboom; *Haga Hospital Rode Kruis, Den Haag* - J. Merkus; *Leiden University Medical Centre, Leiden* - V. Smit, B. Bonsing; *Reinier de Graaf Groep, Delft* - A. van Leeuwen, C. Marcoen, E. Maartense; *Comprehensive Cancer Centre Eindhoven, Eindhoven* - M. Janssen-Heijnen, A. van den Eijnden-van Rooijen; *Laboratory for Pathology (PAMM), Eindhoven* - M. van Beek; *Catharina Hospital, Eindhoven* - Y. van Riet, G. Creemers; *Máxima Medical Centre, Eindhoven* - O. Repelaer van Driel, M. Nijziel; *Máxima Medical Centre, Veldhoven* - R. Roumen, G. Vreugdenhil; *Sint Anna Zorggroep, Geldrop* - E. Luiten, A. Smals; *Jeroen Bosch Hospital, 's Hertogenbosch* - J. Broekman, W. Gelderman, J. Wissing, S. Bouwer, T. Smilde; *Hospital Bernhoven, Veghel* - B. Storck, N. van Diemen; *Bernhoven Hospital, Oss* - Y. Paquay, A. Vos; *Amphia Hospital Molengracht, Breda* - P. de Wit, J. Nuytinck, G. Ras; *Amphia Hospital Pasteurlaan, Oosterhout* - O. van West, J. van Wissen; *Amphia Hospital Langendijk, Breda* - A. van Gent; *Sint Elizabeth Hospital, Tilburg* - A. Croonen, J. Roukema, J. van Riel; *Tweesteden Hospital, Tilburg* - S. Brenninkmeijer, H. van Ojik; *Elkerliek Hospital, Helmond* - M. Tutein Nolthenius-Puylaert, B. Lemaire; *VieCuri Medical Centre, Venlo* - R. Schapers, P. Nijhuis, A. van der Wouw; *Comprehensive Cancer Centre Rotterdam, Rotterdam* - R. Damhuis, J. Paulides; *Erasmus Medical Centre, Rotterdam* - M. Kliffen; *Medical Centre Rijnmond-Zuid Zuider, Rotterdam* - S. Henzen-Logmans; *Medical Centre Rijnmond-Zuid Clara, Rotterdam* - H. van den Ingh, W. Meijer; *Laboratory for Pathology (PATHAN), Rotterdam* - J. Ruizeveld de Winter; *Vlietland Hospital, Schiedam* - I. Mares-Engelberts; *Ruwaard van Putten Hospital, Spijkenisse* - R. den Toom; *IJsselland Hospital, Capelle aan de IJssel* - G. Tetteroo; *Sint Fransiscus Hospital, Rotterdam* - H. Strijdhorst; *Ikazia Hospital, Rotterdam* - W. Vles; *Haven Hospital, Rotterdam* - J. van Dam; *Albert Schweitzer Hospital, Dordrecht* - P. Westenend, P. Plaisier; *Laboratory for Pathology Zeeland* - L. de Bruijkere; *Hospital Walcheren, Vlissingen* - J. ten Thijsse; *Oosterschelde Hospitals, Goes* - H. de Morree; *Van Weel-Bethesda Hospital, Dirksland* - R. van der Hul;

Hospital Zeeuw-Vlaanderen, Terneuzen - W. Mostert, K. Ongena; *Hospital Lievensberg, Bergen op Zoom* - V. Potters, E. Slingenbergh; *Franciscus Hospital, Roosendaal* - H. Kemperman; *Comprehensive Cancer Centre Limburg, Maastricht* - J. Bruijnen, S. Adema; *Maastricht University Medical Hospital, Maastricht* - M. von Meyenfeldt, P. Hupperets; *Maasland Hospital, Sittard* - W. Vos, F. van der Ent, F. Erdkamp; *Atrium Medical Centre Parkstad, Heerlen* - M. Nap, J. van der Bijl, M. Pannebakker; *Laurentius Hospital, Roermond* - A. Willig, C. Finaly-Marais, M. den Boer; *Sint Jans Gasthuis, Weert* - F. Limbeek, P. den Haan; *Comprehensive Cancer Centre Midden-Nederland, Utrecht* - M. van der Heiden-van der Loo, A. Koppejan-Rensenbrink; *Sint Antonius Hospital, Nieuwegein* - C. Seldenrijk, R. Koelemij, P. de Jong; *Mesos Medical Centre, Utrecht* - A. van Wieringen, R. Oltmans; *Zuwe Hofpoort Hospital, Woerden* - J. Vente, M. Verhaar-Langereis; *Diakonessenhuis, Utrecht* - J. van Gorp, T. van Dalen, P. Thunnissen; *Meander Medical Centre, Amersfoort* - E. Ahsmann, A. van Overbeeke, C. Rodenburg; *University Medical Centre Utrecht, Utrecht* - R. van Hilligersberg, E. van der Wall; *Hospital Rivierenland, Tiel* - K. Ong, C. Henkens; *Comprehensive Cancer Centre North East, Enschede, Groningen* - S. Siesling, M. Schaapveld, R. Otter, A. Wit; *Laboratory for Pathology Oost Nederland (LPON), Enschede* - M. Brinkhuis; *Medisch Spectrum Twente, Enschede* - W. Mastboom, W. Smit; *Ziekenhuisgroep Twente Twenteborg, Almelo* - D. van der Velde, R. Hoekstra; *Ziekenhuisgroep Twente SMT, Hengelo* - H. Heijmans, H. Dankbaar; *Streekziekenhuis Koningin Beatrix, Winterswijk* - F. Slootmans, P. Schiphorst; *Gelre Hospitals, Apeldoorn* - E. Weltevreden, J. Roussel, S. Radema; *Hospital Spitaal, Zutphen* - J. Ketel, O. van Dobbenburgh; *Deventer Hospital, Deventer* - J. Arends, H. de Vries, A. Imholz; *Laboratory for Pathology (LVF), Leeuwarden* - H. Eggink; *Antonius Hospital, Sneek* - E. Mulder, G. Woolthuis; *Medical Centre Leeuwarden, Leeuwarden* - C. Hoff, H. de Graaf; *Hospital Nij Smellinghe, Drachten* - H. van der Mijle, H. van Kamp; *Hospital Talma Sionsberg, Dokkum* - J. Kaspers, J. de Graaf; *Hospital de Tjongerschans, Heerenveen* - P. Veldman, J. de Boer; *Bethesda Hospital, Hoogeveen* - G. Freling, R. Haasen, J. Haasjes; *Röpke-Zweers Hospital, Hardenberg* - M. Jagers, R. Blankenburgh; *Diaconessenhuis, Meppel* - L. Hanssen, H. de Korte; *Isala Klinieken, Zwolle* - A. Jonker, E. Pierik, J. de Graaf; *Laboratory for Pathology, Winschoten* - C. Schoots; *Sint Lucas Hospital, Winschoten* - M. Klöppner, H. Potthoff; *Refaja Hospital, Stadskanaal* - A. Kemper, J. Jansen; *Delfzicht Hospital, Delfzijl* - J. Ashruf, Z. Erjavec; *Martini Hospital, Groningen* - A. Groote, A. Olieman, R. de Jong; *University Medical Centre Groningen, Groningen* - A. Suurmeijer, J. de Vries, P. Willemse; *Wilhelmina Hospital, Assen* - R. Wijffels, F. Blok; *Scheper Hospital, Emmen* - M. van den Aardweg, E. Weernink – *all in the Netherlands*.

Supplementary Table 2. Number of First Events after 5-Year Follow-Up and 5-Year First Event Rate According to Cohort

Cohort	No. of Patients	Contralateral Breast Cancer		Locoregional Recurrence		Distant Metastases	
		No. of First Events	5-Year First Event Rate (%)	No. of First Events	5-Year First Event Rate (%)	No. of First Events	5-Year First Event Rate (%)
Node-Negative, No Adjuvant Therapy	856	21	2.6	30	3.7	23	2.8
Node-Positive, No Adjuvant Therapy	856	35	5.6	42	6.6	30	4.6
Isolated tumor cells	513	20	5.4	24	6.2	15	3.7
Micrometastases	343	15	5.9	18	6.8	15	6.3
Node-Positive, Adjuvant Therapy	995	11	1.2	20	2.6	20	2.6
Isolated tumor cells	306	4	1.3	8	3.8	3	1.2
Micrometastases	689	9	1.2	12	1.9	17	3.2
All	2707	67	2.9	92	4.1	73	3.2

Supplementary Table 3. Cox Proportional-Hazards Model of the Effect of Variables on Events According to the Presence or Absence of Isolated Tumor Cells or Micrometastases (Axillary Lymph-Node Dissection Included in the Model)

Variable	Node-Negative vs. Isolated Tumor Cells or Micrometastases, All with No Adjuvant Therapy		Node-Negative vs. Isolated Tumor Cells, Both with No Adjuvant Therapy		Node-Negative, No Adjuvant Therapy vs. Micrometastases, Both with No Adjuvant Therapy	
	Hazard Ratio for Events (95% CI)	P Value	Hazard Ratio for Events (95% CI)	P Value	Hazard Ratio for Events (95% CI)	P Value
Node-negative	1.00		1.00		1.00	
Node-positive, isolated tumor cells or micrometastases	1.59 (1.24-2.04)	<0.001	–	–	–	–
Isolated tumor cells	–	–	1.54 (1.17-2.03)	0.002	–	–
Micrometastases	–	–	–	–	1.81 (1.25-2.61)	0.002
Age at diagnosis (year)*	1.01 (1.00-1.02)	0.02	1.02 (1.01-1.03)	0.002	1.01 (1.00-1.02)	0.15
Tumor size†	1.23 (1.03-1.47)	0.02	1.26 (1.03-1.54)	0.02	1.22 (0.98-1.53)	0.08
Tumor grade						
1	1.00		1.00		1.00	
2	1.53 (1.18-1.99)	0.001	1.75 (1.30-2.36)	<0.001	1.50 (1.09-2.06)	0.01
3	2.15 (1.28-3.63)	0.004	2.41 (1.36-4.29)	0.003	2.27 (1.24-4.15)	0.008
Expression of estrogen receptors, progesterone receptors, or both						
Yes	1.00		1.00		1.00	
No	1.52 (1.04-2.23)	0.03	1.63 (1.07-2.48)	0.02	1.34 (0.82-2.20)	0.25
Axillary lymph-node dissection						
Yes	1.00		1.00		1.00	
No	1.16 (0.89-1.51)	0.28	1.13 (0.83-1.55)	0.44	1.31 (0.90-1.90)	0.15

*Age was modeled as continuous variable.

† The hazard ratio is for a doubling of tumor diameter.

Supplementary Table 4. Disease-Free Survival (DFS) Rates According to Type of Systemic Adjuvant Therapy					
Type of Systemic Adjuvant Therapy	Node-Positive, No Adjuvant Therapy		Node-Positive, Adjuvant Therapy		P Value (Compared with No Chemotherapy or Hormonal Therapy)
	N (%)	5 year DFS Rate (%)	N (%)	5 year DFS Rate (%)	
No chemotherapy or hormonal therapy	856 (100)	76.5	0 (0)	NA	NA
Chemotherapy	0 (0)	NA	60 (6.0)	83.4	0.41
Hormonal therapy	0 (0)	NA	627 (63.0)	84.2	0.002
Both chemotherapy or hormonal therapy	0 (0)	NA	308 (31.0)	91.3	<0.001

Supplementary Table 5. Cox Proportional-Hazards Model of the Effects of Type of Systemic Adjuvant Therapy on Events

Variable	Hazard Ratio for Events (95% CI)	P Value
Node-Positive, No Adjuvant Therapy	1.00	
Node-Positive, Adjuvant Therapy		
Chemotherapy	0.82 (0.41-1.61)	0.56
Hormonal therapy	0.60 (0.46-0.80)	<0.001
Both chemotherapy or hormonal therapy	0.34 (0.21-0.55)	<0.001

Age at diagnosis (modeled as a continuous variable), tumor size (the hazard ratio is for a doubling of the tumor diameter), tumor grade, and axillary treatment also included as variables in the Cox proportional-hazards model.