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# Breast cancer highlights from 2023: Knowledge to guide practice and future research

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A B S T R A C T

This narrative work highlights a selection of published work from 2023 with potential implications for breast cancer practice. We feature publications that have provided new knowledge immediately relevant to patient care or for future research. We also highlight guidelines that have reported evidence-based or consensus recommendations to support practice and evaluation in breast cancer diagnosis and treatment. The scope of selected highlights represents various domains and disciplines in cancer control, from prevention to treatment of early and advanced breast cancer.

## 1. Introduction

The beginning of a new year is a time to reflect on the year that has passed, and from a professional perspective, to consider what knowledge 2023 has brought to help those involved in the care of breast cancer patients. While attempting to review and summarize the most interesting and informative scientific research published in 2023, we were challenged by the amount of publications in 2023 (in English language) and including "Breast Cancer" in the title, brings around 15 000 titles in PubMed. Attempting to filter the search by restricting to "trial" we attain around 500 new publications in that year.

It goes without saying that the majority of these will not translate into a global or immediate impact, and many will represent incremental knowledge laying ground for the next phase of research efforts.

In this paper, we present to readers of the journal the 'Breast Cancer Highlights from 2023' offering our view on publications that deserve a special mention from the vast amount of knowledge published in 2023, focusing predominantly on full-length papers (with brief mention of noteworthy studies reported as abstracts).

The selection of featured work, whilst not taking a systematic or exhaustive process, attempts to highlight papers from the various disciplines that stood out, for one of several reasons, including, but not exclusively, a clinical trial that led or can lead to practice change, an update or insight into a topic that introduces a new concept, or a consensus approach or new guideline that has the potential to be widely adopted and to improve patients' care. Tables 1 and 2 enumerate respectively the guidelines and consensus publications and the highlights (original studies).

The guidelines and consensus publication (Table 1) represent collaborative efforts aimed at improving the standard of diagnosis and treatment for breast cancer patients both in early and metastatic breast cancer. These could be integrated in the routine clinical practice of breast units and teams and can help to guide difficult decisions, in the case of expert consensus recommendations, mainly when level I or 2 evidence is not available, filling the gaps of evidence-based guidelines.

The highlights (Table 2) are the main focus of the current paper, hence we comment briefly only on the most interesting papers or abstracts (based on our views), that were reported in 2023.

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### 1.1. Guidelines and consensus (Table 1)

Although many countries discuss and formulate national (locally-relevant) guidelines and consensus or position statements, international collaborative efforts that aggregate recommendations according to levels of evidence, or expert consensus where high-level evidence is limited, represent important a2e that can translate into more standardized care and potentially better patient outcomes. In this regard, we note from 2023 the St Gallen consensus [1] and also the Lucerne Toolbox [2] concerning the challenges in locoregional axillary approaches.

The ESMO effort in publishing guidelines produced in 2023 a consensus paper on the definition of HER2-low Breast Cancer [3]; the management of Breast Cancer during Pregnancy [4] and the awaited update of the Early Breast Cancer guidelines [5].

**Table 1**
Guidelines and consensus.

| TITLE | JOURNAL | DATE | IF[a] | AUTHORS | DOI |
|---|---|---|---|---|---|
| Understanding breast cancer complexity to improve patient outcomes: The St Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023 [1] | Ann Oncol | Nov 2023 | 51,77 | Curigliano G, Burstein HJ, Gnant M, Loibl S, Cameron D, Regan MM, Denkert C, Poortmans P, Weber WP, Thürlimann B; St Gallen Consensus Conference Panelists 2023 | 10.1016/j.annonc.2023.08.017 |
| The Lucerne Toolbox 2 to optimise axillary management for early breast cancer: a multidisciplinary expert consensus [2] | EClinicalMedicine | Jul 2023 | 17,03 | Kaidar-Person O, Pfob A, Gentilini OD, Borisch B, Bosch A, Cardoso MJ, Curigliano G, De Boniface J, Denkert C, Hauser N, Heil J, Knauer M, Kühn T, Lee HB, Loibl S, Mannhart M, Meattini I, Montagna G, Pinker K, Poulakaki F, Rubio IT, Sager P, Steyerova P, Tausch C, Tramm T, Vrancken Peeters MJ, Wyld L, Yu JH, Weber WP, Poortmans P, Dubsky P | 10.1016/j.eclinm.2023.102085 |
| ESMO expert consensus statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer [3] | Ann Oncol | Aug 2023 | 51,77 | Tarantino P, Viale G, Press MF, Hu X, Penault-Llorca F, Bardia A, Batistatou A, Burstein HJ, Carey LA, Cortes J, Denkert C, Diéras V, Jacot W, Koutras AK, Lebeau A, Loibl S, Modi S, Mosele MF, Provenzano E, Pruneri G, Reis-Filho JS, Rojo F, Salgado R, Schmid P, Schnitt SJ, Tolaney SM, Trapani D, Vincent-Salomon A, Wolff AC, Pentheroudakis G, André F, Curigliano G | 10.1016/j.annonc.2023.05.008 |
| ESMO Expert Consensus Statements on the management of breast cancer during pregnancy (PrBC) [4] | Ann Oncol | Oct 2023 | 51,77 | Loibl S, Azim HA Jr, Bachelot T, Berveiller P, Bosch A, Cardonick E, Denkert C, Halaska MJ, Hoeltzenbein M, Johansson ALV, Maggen C, Markert UR, Peccatori F, Poortmans P, Saloustros E, Saura C, Schmid P, Stamatakis E, van den Heuvel-Eibrink M, van Gerwen M, Vandecaveye V, Pentheroudakis G, Curigliano G, Amant F. | 10.1016/j.annonc.2023.08.001 |
| Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up [5] | Ann Oncol | Dec 2023 | 51,77 | S. Loibl, F. André, T. Bachelot, C. H. Barrios, J. Bergh, H. J. Burstein, M. J. Cardoso, L. A. Carey, S. Dawood, L. Del Mastro, C. Denkert, E. M. Fallenberg, P. A. Francis, H. Gamal-Eldin, K. Gelmon, C. E. Geyer, M. Gnant, V. Guarneri, S. Gupta, S. B. Kim, D. Krug, M. Martin, I. Meattini, M. Morrow, W. Janni, S. Paluch-Shimon, A. Partridge, P. Poortmans, L. Pusztai, M. M. Regan, J. Sparano T. Spanic, S. Swain, S. Tjulandin, M. Toi, D. Trapani, A. Tutt, B. Xu, G. Curigliano & N. Harbeck, on behalf of the ESMO Guidelines Committee | 10.1016/j.annonc.2023.11.016 |
| Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO-College of American Pathologists Guideline Update [6] | JCO | Aug 2023 | 50,7 | Wolff AC, Somerfield MR, Dowsett M, Hammond MEH, Hayes DF, McShane LM, Saphner TJ, Spears PA, Allison KH | 10.1200/JCO.22.02864 |
| Designing clinical trials based on modern imaging and metastasis-directed treatments in patients with oligometastatic breast cancer: a consensus recommendation from the EORTC Imaging and Breast Cancer Groups [7] | Lancet Oncology | Aug 2023 | 51,1 | Pasquier D, Bidaut L, Oprea-Lager DE, deSouza NM, Krug D, Collette L, Kunz W, Belkacemi Y, Bau MG, Caramella C, De Geus-Oei LF, De Caluwé A, Deroose C, Gheysens O, Herrmann K, Kindts I, Kontos M, Kümmel S, Linderholm B, Lopci E, Meattini I, Smeets A, Kaidar-Person O, Poortmans P, Tsoutsou P, Hajjaji N, Russell N, Senkus E, Talbot JN, Umutlu L, Vandecaveye V, Verhoeff JJC, van Oordt WMH, Zacho HD, Cardoso F, Fournier L, Van Duijnhoven F, Lecouvet FE | 10.1016/S1470-2045(23)00286-3 |
| European Society of Breast Cancer Specialists/ Advanced Breast Cancer Global Alliance quality indicators for metastatic breast cancer care [8] | Eur J Cancer | Jul 2023 | 8,4 | Cardoso F, McCartney A, Ponti A, Marotti L, Vrieling C, Eniu A, Sousa B, Ripamonti C, Travado L, Spitz S, Jolly E, Curigliano G, Penault-Llorca F, Lecouvet F, Rubio IT, Biganzoli L. | 10.1016/j.ejca.2023.03.028 |
| EUSOMA quality indicators for non-metastatic breast cancer: An update [9] | | | | Isabel T. Rubio, Lorenza Marotti, Laura Biganzoli, Cynthia Aristei, Alexandra Athanasiou, Christine Campbell, Fatima Cardoso, Maria Joao Cardoso, Charlotte E. Coles, Manuela Eicher, Nadia Harbeck, Andreas Karakatsanis, Birgitte V. Offersen, Ruud Pijnappel, Antonio Ponti, Peter Regitnig, Donatella Santini, Francesco Sardanelli, Tanja Spanic, Zsuzsanna Varga, Marie Jeanne T.F.D. Vrancken Peeters, Yvonne Wengström, Lynda Wyld, Giuseppe Curigliano | 10.1016/j.ejca.2023.113500 |

[a] *IF – Impact Factor.

**Table 2**
Highlights.

| | JOURNAL | DATE | IF* | AUTHORS | DOI |
|---|---|---|---|---|---|
| **EARLY BREAST CANCER** | | | | | |
| IMAGING/SCREENING | | | | | |
| Artificial intelligence-supported screen reading versus standard double reading in the Mammography Screening with Artificial Intelligence trial (MASAI): a clinical safety analysis of a randomised, controlled, non-inferiority, single-blinded, screening accuracy study (10) | Lancet Oncol | Aug, 2023 | 51 | Lång K, Josefsson V, Larsson AM, Larsson S, Högberg C, Sartor H, Hofvind S, Andersson I, Rosso A. | 10.1016/S1470-2045(23)00298-X. |
| Comparison of Contrast-enhanced Mammography with MRI Utilizing an Enriched Reader Study: A Breast Cancer Study (CONTRRAST Trial) (11) | Radiology | Nov, 2023 | 29 | Jordana Phillips, Tejas S. Mehta, Leah H. Portnow, Michael D. C. Fishman, Zheng Zhang, and Etta D. Pisano | 10.1148/radiol.230530 |
| PREVENTION | | | | | |
| Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Recurrence in Breast Noninvasive Neoplasia: A 10-Year Follow-Up of TAM-01 Study (12) | JCO | Jun, 2023 | 50,7 | Lazzeroni M, Puntoni M, Guerrieri-Gonzaga A, Serrano D, Boni L, Buttiron Webber T, Fava M, Briata IM, Giordano L, Digennaro M, Cortesi L, Falcini F, Serra P, Avino F, Millo F, Cagossi K, Gallerani E, De Simone A, Cariello A, Aprile G, Renne M, Bonanni B, DeCensi A. | 10.1200/JCO.22.02900 |
| GENETICS | | | | | |
| Contralateral Breast Cancer Risk Among Carriers of Germline Pathogenic Variants in ATM, BRCA1, BRCA2, CHEK2, and PALB2 (13) | JCO | Mar, 2023 | 50,7 | Yadav S, Boddicker NJ, Na J, Polley EC, Hu C, Hart SN, Gnanaolivu RD, Larson N, Holtegaard S, Huang H, Dunn CA, Teras LR, Patel AV, Lacey JV, Neuhausen SL, Martinez E, Haiman C, Chen F, Ruddy KJ, Olson JE, John EM, Kurian AW, Sandler DP, O'Brien KM, Taylor JA, Weinberg CR, Anton-Culver H, Ziogas A, Zirpoli G, Goldgar DE, Palmer JR, Domchek SM, Weitzel JN, Nathanson KL, Kraft P, Couch FJ | 10.1200/JCO.22.01239. |
| PATHOLOGY/MOLECULAR BIOLOGY | | | | | |
| Characterisation of luminal and triple-negative breast cancer with HER2 Low protein expression (14) | Eur J Cancer | Dec, 2023 | 10,2 | Atallah NM, Haque M, Quinn C, Toss MS, Makhlouf S, Ibrahim A, Green AR, Alsaleem M, Rutland CS, Allegrucci C, Mongan NP, Rakha E | 10.1016/j.ejca.2023.113371 |
| SURGERY | | | | | |
| Effect of Peritumoral Infiltration of Local Anesthetic Before Surgery on Survival in Early Breast Cancer (15) | JCO | Jun, 2023 | 50,7 | Badwe RA, Parmar V, Nair N, Joshi S, Hawaldar R, Pawar S, Kadayaprath G, Borthakur BB, Rao Thammineedi S, Pandya S, Balasubramanian S, Chitale PV, Neve R, Harris C, Srivastava A, Siddique S, Vanmali VJ, Dewade A, Gaikwad V, Gupta S. | 10.1200/JCO.22.01966 |

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| Local Recurrence After Breast-Conserving Therapy in Patients With Multiple Ipsilateral Breast Cancer: Results From ACOSOG Z11102 (Alliance) (16) | JCO | Jun, 2023 | 50,7 | Boughey JC, Rosenkranz KM, Ballman KV, McCall L, Haffty BG, Cuttino LW, Kubicky CD, Le-Petross HT, Giuliano AE, Van Zee KJ, Hunt KK, Hahn OM, Carey LA, Partridge AH | 10.1200/JCO.22.02553 |
| Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial (17) | JAMA Oncol | Sept, 2023 | 33 | Gentilini OD, Botteri E, Sangalli C, Galimberti V, Porpiglia M, Agresti R, Luini A, Viale G, Cassano E, Peradze N, Toesca A, Massari G, Sacchini V, Munzone E, Leonardi MC, Cattadori F, Di Micco R, Esposito E, Sgarella A, Cattaneo S, Busani M, Dessena M, Bianchi A, Cretella E, Ripoll Orts F, Mueller M, Tinterri C, Chahuan Manzur BJ, Benedetto C, Veronesi P; SOUND Trial Group. | 10.1001/jamaoncol.2023.3759 |
| RADIATION THERAPY | | | | | |
| Dose-escalated simultaneous integrated boost radiotherapy in early breast cancer (IMPORT HIGH): a multicentre, phase 3, non-inferiority, open-label, randomised controlled trial (18) | Lancet | Jun, 2023 | 168,9 | Coles CE, Haviland JS, Kirby AM, Griffin CL, Sydenham MA, Titley JC, Bhattacharya I, Brunt AM, Chan HYC, Donovan EM, Eaton DJ, Emson M, Hopwood P, Jefford ML, Lightowlers SV, Sawyer EJ, Syndikus I, Tsang YM, Twyman NI, Yarnold JR, Bliss JM; IMPORT Trial Management Grou | 10.1016/S0140-6736(23)00619-0 |
| Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14324 women in 16 trials (19) | Lancet | Nov, 2023 | 168,9 | Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Electronic address: bc.overview@ctsu.ox.ac.uk; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). | 10.1016/S0140-6736(23)01082-6 |
| Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer (20) | N Engl J Med | Feb, 2023 | 176,2 | Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM | 10.1056/NEJMoa2207586 |
| Omitting Radiotherapy after Breast-Conserving Surgery in Luminal A Breast Cancer. LUMINA Trial (21) | N Engl J Med | Aug, 2023 | 176,2 | Whelan TJ, Smith S, Parpia S, Fyles AW, Bane A, Liu FF, Rakovitch E, Chang L, Stevens C, Bowen J, Provencher S, Théberge V, Mulligan AM, Kos Z, Akra MA, Voduc KD, Hijal T, Dayes IS, Pond G, Wright JR, Nielsen TO, Levine MN; LUMINA Study Investigators. | 10.1056/NEJMoa2302344 |
| SYSTEMIC TREATMENT | | | | | |
| KEYNOTE-756: Phase III study of neoadjuvant pembrolizumab (pembro) or placebo (pbo) + chemotherapy (chemo), followed by adjuvant pembro or pbo + endocrine therapy (ET) for early-stage high-risk ER+/HER2e breast Cancer (22) | Ann Onc LBA 21 | Oct, 2023 | 51,77 | F. Cardoso, H.L. McArthur, P. Schmid, J. Cortés, N. Harbeck, M.L. Telli, D.W. Cescon, J. O'Shaughnessy, P. Fasching, Z. Shao, D. Loirat, Y.H. Park, M.E. González Fernández, Z. Liu, H. Yasojima, Y. Ding, L. Jia, V.V. Karantza, K.E. Tryfonidis, A. Bardia | 10.1016/j.annonc.2023.10.011 |

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| Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials. (23) | Lancet | April, 2023 | 168,9 | Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Electronic address: bc.overview@ctsu.ox.ac.uk; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). | 10.1016/S0140-6736(23)00285-4 |
| Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. (24) | Lancet Oncol | Jan, 2023 | 54,4 | Johnston SRD, Toi M, O'Shaughnessy J, Rastogi P, Campone M, Neven P, Huang CS, Huober J, Jaliffe GG, Cicin I, Tolaney SM, Goetz MP, Rugo HS, Senkus E, Testa L, Del Mastro L, Shimizu C, Wei R, Shahir A, Munoz M, San Antonio B, André V, Harbeck N, Martin M; monarchE Committee Members. | 10.1016/S1470-2045(22)00694-5 |
| A randomized, double-blind trial of nivolumab (NIVO) vs placebo (PBO) with neoadjuvant chemotherapy (NACT) followed by adjuvant endocrine therapy (ET) ± NIVO in patients (pts) with high-risk, ER+ HER2L primary breast cancer (BC) CheckMate 7FL (25) | Ann Onc LBA 20 | Oct, 2023 | 51,77 | S. Loi, G. Curigliano, R.F. Salgado, R.I. Romero Diaz, S. Delaloge, C. Rojas, M. Kok, C. Saura Manich, N. Harbeck, E.A. Mittendorf, D. Yardley, L. Pusztai, A. Suarez Zaizar, A. Ungureanu, F. Ades, R. Chandra, R. Nathani, M. Pacius, J.Q. Wu, H.L. McArthur | 10.1016/j.annonc.2023.10.010 |
| Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2− early breast cancer: Primary results from the phase III NATALEE trial (26) | JCO LBA500 | Jun, 2023 | 50,7 | Dennis J. Slamon, Daniil Stroyakovskiy, Denise A. Yardley, Chiun-Sheng Huang, Peter A. Fasching, John Crown, Aditya Bardia, Stephen Chia, Seock-Ah Im, Miguel Martin, Sherene Loi, Binghe Xu, Sara A. Hurvitz, Carlos Barrios, Michael Untch, Rebecca L. Moroose, Fran Visco, Rodrigo Fresco, Tetiana Taran, Gabriel N. Hortobagyi | 10.1200/JCO.2023.41.17_suppl.LBA500 |
| QoL | | | | | |
| Significantly longer time to deterioration of quality of life due to CANKADO PRO-React eHealth support in HR+ HER2- metastatic breast cancer patients receiving palbociclib and endocrine therapy: primary outcome analysis of the multicenter randomized AGO-B WSG PreCycle trial (27) | Ann Oncol | Aug 2023 | 51,77 | Harbeck N, Fasching PA, Wuerstlein R, Degenhardt T, Lüftner D, Kates RE, Schumacher J, Räth P, Hoffmann O, Lorenz R, Decker T, Reinisch M, Göhler T, Staib P, Gluz O, Schinköthe T, Schmidt M; AGO-B WSG PreCycle investigators | 10.1016/j.annonc.2023.05.003 |

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|---|---|---|---|---|---|
| Pregnancy After Breast Cancer in Young BRCA Carriers (28) | JAMA | Dec 2023 | 120,7 | Lambertini M, Blondeaux E, Agostinetto E, Hamy AS, Kim HJ, Di Meglio A, Bernstein Molho R, Hilbers F, Pogoda K, Carrasco E, Punie K, Bajpai J, Ignatiadis M, Moore HCF, Phillips KA, Toss A, Rousset-Jablonski C, Peccatori FA, Renaud T, Ferrari A, Paluch-Shimon S, Fruscio R, Cui W, Wong SM, Vernieri C, Ruddy KJ, Dieci MV, Matikas A, Rozenblit M, Villarreal-Garza C, De Marchis L, Del Mastro L, Puglisi F, Del Pilar Estevez-Diz M, Rodriguez-Wallberg KA, Mrinakova B, Meister S, Livraghi L, Clatot F, Yerushalmi R, De Angelis C, Sánchez-Bayona R, Meattini I, Cichowska-Cwalinska N, Berlière M, Salama M, De Giorgi U, Sonnenblick A, Chiodi C, Lee YJ, Maria C, Azim HA Jr, Boni L, Partridge AH; BRCA BCY Collaboration | 10.1001/jama.2023.25463 |
| Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer (29) | N Engl J Med | May, 2023 | 176,2 | Partridge AH, Niman SM, Ruggeri M, Peccatori FA, Azim HA Jr, Colleoni M, Saura C, Shimizu C, Sætersdal AB, Kroep JR, Mailliez A, Warner E, Borges VF, Amant F, Gombos A, Kataoka A, Rousset-Jablonski C, Borstnar S, Takei J, Lee JE, Walshe JM, Ruíz-Borrego M, Moore HCF, Saunders C, Bjelic-Radisic V, Susnjar S, Cardoso F, Smith KL, Ferreiro T, Ribi K, Ruddy K, Kammler R, El-Abed S, Viale G, Piccart M, Korde LA, Goldhirsch A, Gelber RD, Pagani O; International Breast Cancer Study Group; POSITIVE Trial Collaborators. | 10.1056/NEJMoa2212856 |
| **ADVANCED BREAST CANCER** | | | | | |
| Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial (30) | Lancet | Oct, 2023 | 168,9 | Rugo HS, Bardia A, Marmé F, Cortés J, Schmid P, Loirat D, Trédan O, Ciruelos E, Dalenc F, Gómez Pardo P, Jhaveri KL, Delaney R, Valdez T, Wang H, Motwani M, Yoon OK, Verret W, Tolaney SM | 10.1016/S0140-6736(23)01245-X |
| Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC) (31) | JCO 2023 Suppl, LBA1000 | Jun, 2023 | 50,7 | Gabe S. Sonke, Annemiek Van Ommen - Nijhof, Noor Wortelboer, Vincent van der Noort, Astrid C. P. Swinkels, Hedwig M. Blommestein, Aart Beeker, Karin Beelen, Lisanne C. Hamming, Joan B. Heijns, Aafke H. Honkoop, Paul C. De Jong, Quirine C. Van Rossum-Schornagel, Christa van Schaik-van de Mheen, Jolien Tol, Cathrien Tromp-Van Driel, Suzan Vrijaldenhoven, A. Elise Van Leeuwen-Stok, Inge Konings, Agnes Jager | 10.1200/JCO.2023.41.17_suppl.LBA1000 |

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| Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer (32) | N Engl J Med | Jun, 2023 | 176,2 | Nicholas C Turner, Mafalda Oliveira, Sacha J Howell, Florence Dalenc,, Javier Cortes, Henry L Gomez Moreno, Xichun Hu , Komal Jhaveri, Petr Krivorotko, Sibylle Loibl, Serafin Morales Murillo, Meena Okera, Yeon Hee Park, Joohyuk Sohn , Masakazu Toi, Eriko Tokunaga, Samih Yousef, Lyudmila Zhukova, Elza C de Bruin, Lynda Grinsted, Gaia Schiavon, Andrew Foxley, Hope S Rugo; CAPItello-291 Study Group | 10.1056/NEJMoa2214131 |
| **CONTROLLED CLINICAL TRIAL PROTOCOLS** | | | | | |
| Protocol for the T-REX-trial: tailored regional external beam radiotherapy in clinically node-negative breast cancer patients with 1-2 sentinel node macrometastases - an open, multicentre, randomised non-inferiority phase 3 trial (33) | BMJ Open 2023 | Sep, 2023 | 2,9 | Alkner S, de Boniface J, Lundstedt D, Mjaaland I, Ryden L, Vikstrom J, Bendahl PO, Holmberg E, Sackey H, Wieslander E, Karlsson P | 10.1136/bmjopen-2023-075543 |
| CONFIDENT-trial protocol: a pragmatic template for clinical implementation of artificial intelligence assistance in pathology (34) | BMJ Open 2023 | Jun, 2023 | 2,9 | R. N. Flach, N. Stathonikos, T. Q. Nguyen, N. D. Ter Hoeve, P. J. van Diest and C. van Dooijeweert | 10.1136/bmjopen-2022-067437 |
| Evaluating the ability of an artificial-intelligence cloud-based platform designed to provide information prior to locoregional therapy for breast cancer in improving patient's satisfaction with therapy: The CINDERELLA trial (35) | Plos One | Aug, 2023 | 3,8 | Kaidar-Person O, Antunes M, Cardoso JS, Ciani O, Cruz H, Di Micco R, Gentilini OD, Gonçalves T, Gouveia P, Heil J, Kabata P, Lopes D, Martinho M, Martins H, Mavioso C, Mika M, Montenegro H, Oliveira HP, Pfob A, Rotmensz N, Schinköthe T, Silva G, Tarricone R, Cardoso MJ; CINDERELLA Consortium. | 10.1371/journal.pone.0289365. eCollection 2023 |
| Neo-train: study protocol and feasibility results for a two-arm randomized controlled trial investigating the effect of supervised exercise during neoadjuvant chemotherapy on tumour response in patients with breast cancer (36) | BMC Cancer 2023 | Aug, 2023 | 4,4 | Kjeldsted E, Ammitzbøll G, Jørgensen LB, Lodin A, Bojesen RD, Ceballos SG, Rosthøj S, Lænkholm AV, Skou ST, Jack S, Gehl J, Dalton SO | 10.1186/s12885-023-11284-5 |
| Movement and health beyond care, MoviS: study protocol for a randomized clinical trial on nutrition and exercise educational programs for breast cancer survivors (37) | Trials | Feb, 2023 | 2,5 | Natalucci V, Ferri Marini C, De Santi M, Annibalini G, Lucertini F, Vallorani L, Panico AR, Sisti D, Saltarelli R, Donati Zeppa S, Agostini D, Gervasi M, Baldelli G, Grassi E, Nart A, Rossato M, Biancalana V, Piccoli G, Benelli P, Villarini A, Somaini M, Catalano V, Guarino S, Pietrelli A, Monaldi S, Sarti D, Barocci S, Flori M, Rocchi MBL, Brandi G, Stocchi V, Emili R, Barbieri E. | 10.1186/s13063-023-07153-y |
| Psychosocial outcomes and health service use after notifying women participating in population breast screening when they have dense breasts: a Breast Screen Queensland randomised controlled trial (38) | Med J Aust | Nov, 2023 | 9,2 | Nickel B, Ormiston-Smith N, Hammerton L, Cvejic E, Vardon P, Mcinally Z, Legerton P, Baker K, Isautier J, Larsen E, Giles M, Brennan ME, McCaffery KJ, Houssami N. | 10.5694/mja2.52117 |
| ProFertil study protocol for the investigation of gonadotropin-releasing hormone agonists (GnRHa) during chemotherapy aiming at fertility protection of young women and teenagers with cancer in Sweden-a phase III randomised double-blinded placebo-controlled study (39) | BMJ Open 2023 | Dec, 2023 | 2,9 | Rodriguez-Wallberg KA, Nilsson HP, Bergh J, Malmros J, Ljungman P, Foukakis T, Stragliotto CL, Friman EI, Linderholm B, Valachis A, Andersson A, Harrysson S, Vennström L, Frisk P, Mörse H, Eloranta S | 10.1136/bmjopen-2023-078023 |

Publications in Table 2 are listed in alphabetic order/Abstract only publications are shaded in grey; * IF – Impact Factor.

ASCO and the American College of Pathologists also updated the important guidelines for Her2 receptor testing [6].

EORTC's Imaging and Breast Cancer Groups wrote an insightful article, in a topic where guidance was lacking, for the purpose of helping the design of trials for oligometastatic disease with the use of new imaging techniques [7].

We also mention the recent consensus papers from EUSOMA (the European Society of Medical Specialists) on the upgraded quality indicators for the accreditation of Breast Units in Early Breast Cancer [8] and the new quality indicators for Metastatic Breast Cancer [9]. Although several accreditation systems are available for early breast cancer the proposed standardized approach had not been attempted in metastatic breast cancer.

### 1.2. Highlights (Table 2)

The table aims at highlighting all those studies or trials that have contributed new knowledge to the breast cancer field. Some of these are reported as abstracts but are highlighted because their novelty or importance justifies their inclusion in our commentary. Table 2 lists more studies than what we comment on next – we opted to focus on studies that in our view are exemplary highlights of 2023.

We added to the highlights a list of promising Randomized Clinical trial protocols published in 2023 that we hope will, in the near future, contribute new knowledge to improve the care of breast cancer patients.

## 2. Early breast cancer

### 2.1. Imaging, screening [10,11]

Artificial intelligence-supported screen reading versus standard double reading in the Mammography Screening with Artificial Intelligence trial (MASAI): a clinical safety analysis of a randomised, controlled, non-inferiority, single-blinded, screening accuracy study (Lång et al.) [10].

This RCT showed that amongst 80 033 women having population-based screening (in Swedish program), AI-supported screening detected 244 cancers (cancer detection rate, CDR 6·1/1000), while standard double-(human)-reading detected 203 (CDR 5·1/1000)– a CDR ratio of 1·2 (95 % CI: 1·0–1·5; p = 0·052). Recall rates were 2·2 % in the intervention group and 2·0 % in the control group. The screen-reading workload was reduced by 44·3 % using the AI-supported approach.

This pivotal trial represents the highest-level evidence on AI for early detection and is critical in supporting the planning of additional

prospective trials in real-world screening practice. While current findings show the effectiveness and efficiency of AI-supported screen-reading, the RCT's primary endpoint, effect on interval cancer rates (which entails follow-up of participants), is eagerly awaited and will provide a key outcome on AI's effectiveness for population screening programs.

Comparison of Contrast-enhanced Mammography with MRI Utilizing an Enriched Reader Study: A Breast Cancer Study (CONTRRAST Trial) (Philips et al.) [11].

### 2.2. Prevention [12]

Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Recurrence in Breast Non-invasive Neoplasia: A 10-Year Follow-Up of TAM-01 Study (Lazzeroni et al.) [12].

This RCT reported long-term follow-up of women with atypical ductal hyperplasia, lobular carcinoma in situ, or hormone-sensitive or unknown DCIS (with the latter representing the largest group in the trial), treated with low-dose tamoxifen or administered placebo. After a median follow-up of 9.7 years, 66 breast cancers (15 in situ; 51 invasive) were diagnosed: 25 in the *low-dose tamoxifen* group and 41 in the placebo group (annual rate per 1,000 person-years, 11.3 with tamoxifen *v* 19.5 with placebo; hazard ratio = 0.58; 95 % CI: 0.35–0.95; log-rank *P* = 0.03). Most recurrences were invasive (77 %) and ipsilateral (59 %).

This trial highlights the importance of primary and tertiary prevention, showing that low-dose Tamoxifen (5 mg per day) taken for 3 years has a sustained effect in preventing breast cancer and breast cancer recurrence in those with breast intraepithelial proliferations and non-invasive malignancy, respectively, without substantial long-term adverse events.

### 2.3. Genetics [13]

Contralateral Breast Cancer Risk Among Carriers of Germline Pathogenic Variants in ATM, BRCA1, BRCA2, CHEK2, and PALB2 (Yadav et al.) [13].

The study included 15 104 women from Cancer Risk Estimates Related to Susceptibility (CARRIERS) consortium treated with ipsilateral surgery for invasive breast cancer. Included prospective studies reported on contralateral breast cancer (CBC) after a breast cancer diagnosis in women with a germline pathogenic variant (BRCA1, BRCA2, PALB2, CHEK2 and ATM) and breast cancer survivors without a pathogenic variant matched for age of diagnosis, race/ethnicity, menopausal status, histology, estrogen receptor status of the first breast cancer, and use of endocrine therapy to estimate the risk of CBC.

Results showed that BRCA1, BRCA2, and CHEK2 PV carriers with breast cancer were at significantly elevated risk of CBC (HR 1.9) whereas among the PALB2 PV carriers only those with ER-negative breast cancer had elevated risks (HR, 2.9). By contrast, ATM PV carriers did not have significantly increased CBC risks. The 10-year cumulative incidence of CBC was substantially higher in pre-menopausal patients.

The study provides important information that can be applied in practice for surveillance and risk reducing strategies of these women. The work highlights that carriers of germline PVs in BRCA1/2, CHEK2, PALB2 are at substantially increased risk of CBC although age can have a striking impact on future risk. Information should be passed on to patients adding also what the authors of the paper stated, that the impact of risk reducing strategies on overall survival is still controversial.

### 2.4. Pathology [14]

Characterisation of luminal and triple-negative breast cancer with HER2 Low protein expression (Atallah et al.) [14].

### 2.5. Surgery [15–17]

Effect of Peritumoral Infiltration of Local Anaesthetic Before Surgery on Survival in Early Breast Cancer (Badwe et al.) [15].

This is a surprising trial using the recently explored concept that local anesthesia seems to block voltage-gated sodium channels, present in cancer cells, hindering the activation of pro-metastatic pathways.

The RCT tested the impact of presurgical, peritumoral infiltration of local anesthesia on disease-free survival (DFS) and overall survival (OS). Women with breast cancer planned for upfront surgery received either peritumoral injection of 0.5 % lidocaine, 7–10 min before surgery (local anesthetics [LA] arm) or surgery without lidocaine (no LA arm). 1,583 patients were included in this analysis (LA, 796; no LA, 804). 5-Year DFS rates were 86.6 % and 82.6 % (hazard ratio [HR], 0.74; 95 % CI, 0.58 to 0.95; P = 0.017) and 5-year OS rates were 90.1 % and 86.4 %, respectively (HR, 0.71; 95 % CI, 0.53 to 0.94; P = 0.019) in LA vs no LA. Using competing risk analyses, in LA and no LA arms, 5-year cumulative incidence rates of locoregional recurrence were 3.4 % and 4.5 % (HR, 0.68; 95 % CI, 0.41 to 1.11), and distant recurrence rates were 8.5 % and 11.6 %, respectively (HR, 0.73; 95 % CI, 0.53 to 0.99). Authors concluded that peritumoral injection of lidocaine before breast cancer surgery significantly increases DFS and OS at 5 years follow-up.

A word of caution needs to be said as the molecular mechanisms related to the observed benefit in the trial are not yet clear. Surprisingly the same benefit was observed in breast conservation and mastectomy patients questioning the vicinity of the surgical incision to the tumour as a possible vehicle of dissemination.

Local Recurrence After Breast-Conserving Therapy in Patients With Multiple Ipsilateral Breast Cancer: Results From ACOSOG Z11102 (Alliance). (Boughey et al.) [16].

Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial (Gentilini et al.) [17].

The SOUND (Sentinel node vs Observation after axillary ultrasoUND) trial was a prospective randomized non-inferiority study comparing sentinel node biopsy (SLNB) vs no axillary surgery in patients with breast cancer up to 2 cm receiving breast conserving therapy after a preoperative ultrasound with negative axillary lymph nodes. The primary outcome was distant disease-free survival (DDFS), analysed by intention to treat. Between February 6, 2012 and June 30, 2017, 1,463 women were enrolled: 727 were randomly assigned to receive SLNB and 736 were assigned to no axillary surgery. 19 and 39 patients were excluded in the SLNB group and in the no axillary surgery group, respectively. Overall, median tumor size was 1·1 cm (IQR 0.8–1.5), median age 60 years (IQR 52–68) and 1,234 (87·8 %) patients had estrogen receptor-positive HER2-non-overexpressing BC. In the SLNB group, 97 patients (13.7 %) had positive axillary nodes. The median follow-up was 5.7 years (IQR 5.0–6.7 years). Five-year DDFS was 97.7 % in the SLNB arm and 98.0 % in the no axillary surgery arm (Log-rank test P = 0.665; HR 0.84; 90 % CI 0.45–1.54; non-inferiority P = 0.024). 12 (1.7 %) loco-regional relapses, 13 (1.8 %) distant metastases and 21 (3.0 %) deaths were observed in the SLNB group, whereas 11 (1.6 %) loco-regional relapses, 14 (2.0 %) distant metastases and 18 (2.6 %) deaths were observed in the no axillary surgery group. In this trial the omission of axillary surgery was non-inferior to SLNB in patients with small breast cancer and a negative ultrasound of the axillary lymph nodes. The authors concluded that patients with these features can be safely spared any axillary surgery whenever the lack of pathologic information is not affecting the postoperative treatment plan.

### 2.6. Radiation therapy [18–21]

Dose-escalated simultaneous integrated boost radiotherapy in early breast cancer (IMPORT HIGH): a multicentre, phase 3, non-inferiority, open-label, randomised controlled trial (Coles et al.) [18].

An increased "boost" dose to the primary tumour bed following whole-breast irradiation (WBI) halves the risk for local recurrences. However, it increases the total number of treatment fractions and has a negative impact on the cosmetic outcome.

The IMPORT HIGH trial (ISRCTN47437448) compared 2 dose levels of a simultaneous integrated boost, adding no extra fractions, with a sequential boost consisting of extra fractions following WBI:

- Control group: 40 Gy in 15 fractions WBI, followed by a sequential boost consisting of 16 Gy in 8 fractions on the primary tumourbed.
- Test group 1: 36 Gy in 15 fractions WBI, with concomitant 40 Gy in 15 fractions to a partial breast volume and 48 Gy in 15 fractions to the primary tumourbed.
- Test group 2: 36 Gy in 15 fractions WBI, with concomitant 40 Gy in 15 fractions to a partial breast, volume and 53 Gy in 15 fractions to the primary tumourbed.

A total of 2617 patients after breast-conserving surgery for non-metastasised invasive breast carcinoma participated between March 2009 and September 2015, equally assigned over the 3 randomisation groups. The primary endpoint was ipsilateral breast tumour recurrence (IBTR), non-inferiority of the test arms if a less than 3 % increased risk for 5-years IBTR was seen above the estimated 5 % for the control group. Side events were assessed by clinicians, patients, and photographs.

Importantly, the median boost clinical target volume was only 13 cm3. After a median follow-up of 74 months, a total of 76 IBTR were reported, 20 for the control group, 21 for test group 1, and 35 for test group 2, resulting in a 5-year IBTR rate of 1.9 % (control), 2.0 % (test 1), and 3.2 % (test 2). These differences were not significant and didn't pass the pre-set estimations, confirming non-inferiority for test group 1, 36-40-48 Gy simultaneous boost technique. Also, the cumulative 5-year incidence of clinician-reported moderate or marked breast induration was similar for test group 1 (10.6 %) and the control group (11.5 %) for the control group, whereas it was higher for test group 2 (15.5 %) ($p = 0{\cdot}015$ vs control group).

Conclusion: Local control rates were better in all groups than expected and side effects were limited, likely thanks to the small boost volumes. Increasing the (simultaneous) boost dose didn't result in improved control while it increased side effects. The scheme from test group 1 is safe, both in terms of local control as in side effects, and limits the total number of fractions from 23 to 15.

Note: a simultaneous integrated boost combined with the 1-weekly 26 Gy in 5 fractions schedule from the FAST-FORWARD trial is subject of a new study.

Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14324 women in 16 trials (EBCTCG) [19].

Regional nodal irradiation (RNI) reduces risks of recurrence and death in patients with risk factors, but was associated with increased non-cancer related mortality.

In this meta-analysis, 16 trials evaluating RNI were evaluated, 8 ($n = 2157$) starting between 1961 and 1978, and 8 ($n = 12167$) between 1989 and 2008. In the older trials, RNI had no significant effect on breast cancer mortality ($RR = 1.04$, $p = 0{\cdot}55$), while non-breast-cancer mortality was significantly increased ($RR = 1.42$, $p = 0{\cdot}00023$), especially after longer follow-up, leading to an increased overall mortality ($RR = 1.17$, $p = 0{\cdot}0067$). In sharp contrast to this, in the newer trials, RNI significantly reduced recurrence rates ($RR = 0.88$, $p = 0{\cdot}0008$). This was especially seen for distant recurrence, and only few lymph node recurrences were reported. Moreover, RNI significantly reduced breast cancer-related mortality ($RR = 0.87$, $p = 0{\cdot}0010$), and no increased non-breast-cancer-related mortality was seen ($RR = 0.97$, $p = 0{\cdot}63$), finally resulting in a significantly reduced all-cause mortality ($RR = 0.90$, $p = 0{\cdot}0022$). The estimated absolute reductions in 15-year breast cancer-related mortality were 1.6 % for pN0 disease, 2.7 % for pN1 stage, and 4.5 % for pN2-3 staged patients.

Conclusion: Regional nodal irradiation significantly reduced breast cancer-related mortality and overall mortality in trials which started after 1989, in contrast to older trials. This might be explained by the introduction of a combination of technical improvements in radiation therapy in the second half of the eighties.

Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer (Kunkler et al.) (20)

Omitting Radiotherapy after Breast-Conserving Surgery in Luminal A Breast Cancer. LUMINA Trial (Whelan et al.) (21)

### 2.7. Systemic Treatment [22–26]

KEYNOTE-756: Phase III study of neoadjuvant pembrolizumab (pembro) or placebo (pbo) + chemotherapy(chemo), followed by adjuvant pembro or pbo + endocrine therapy (ET) for early-stage high-risk ER+/HER2e breast

Cancer (Cardoso et al.) [22].

Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials by EBCTCG [23].

This is an individual patient-level meta-analysis of trials in early breast cancer, comparing efficacy of taxane regimens with versus without anthracycline, based on the data from 15 trials, which included 18103 patients and of 23 anthracycline regimens with versus without taxane, based on 35 trials of 52976 patients.

Across all trials assessing the effect of anthracyclines a 14 % relative reduction in recurrence rates was observed among patients treated with an anthracycline, albeit the benefit was limited to patients treated with concurrent docetaxel plus anthracycline versus same dose docetaxel plus cyclophosphamide, or taxane plus anthracycline versus higher cumulative dose taxane with or without capecitabine.

For the assessment of taxane effect, an overall 13 % relative reduction in the risk of recurrence was observed among patients administered a taxane. Larger recurrence reductions were seen from adding taxane to anthracycline regimens when the same cumulative dose of anthracycline was used than in trials with higher cumulative doses of non-taxane (mostly anthracycline) in the control group. Direct comparisons between anthracycline and taxane regimens demonstrated higher efficacy of higher cumulative dose and more dose-intense schedules. Importantly, the relative benefits from taxanes and anthracyclines were similar across estrogen receptor status, age, nodal status, or tumour size or grade.

Albeit the results of this meta-analysis support use of higher cumulative dose and more dose-intense schedules, potentially questioning the current tendency to omit anthracyclines and/or decrease the duration of chemotherapy, they should be interpreted with caution, given the years the contributing trials were conducted and the tremendous progress in the understanding of biology of breast cancer, resulting in better selection of patients and more active systemic therapies available today.

Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial

(Johnston SRB et al.) (24)

In this Phase 3 RCT 5637 patients were randomly assigned; 2808 received abemaciclib plus endocrine therapy and 2829 received endocrine therapy alone. At a median follow-up of 42 months, median invasive disease-free survival was not reached in either group, and the invasive disease-free survival benefit previously reported was sustained: HR 0·664 (nominal $p < 0•001$). At 4 years, the absolute difference in invasive disease-free survival between the groups was 6.4 % (85.8 % in the abemaciclib plus endocrine therapy group vs 79.4 % in the endocrine therapy alone group). Similarly, a sustained benefit in distant relapse-free survival was observed, with absolute improvement in 4-year dRFS of 5.9 % (88.4 % vs 82.5 %, HR 0. 659, nominal $p < 0.001$). Overall survival data are immature, but significantly less patients have developed and are alive with metastatic disease in the abemaciclib arm (125 vs 249), raising hopes for overall survival benefit.

These results further support the use of abemaciclib in patients with high-risk hormone receptor-positive, HER2-negative early breast cancer, albeit further follow-up is needed to establish whether overall survival can be improved with abemaciclib plus endocrine therapy in these patients.

A randomized, double-blind trial of nivolumab (NIVO) vs placebo (PBO) with neoadjuvant chemotherapy (NACT) followed by adjuvant endocrine therapy (ET) ± NIVO in patients (pts) with high-risk, ER + HER2L primary breast cancer (BC) CheckMate 7FL (Loi et al.) [25].

Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2− early breast cancer: Primary results from the phase III NATALEE trial (Slamon et al.) [26].

The results of the NATALEE trial were presented at ASCO 2023. NATALEE is a phase 3 RCT which assessed the efficacy and toxicity of CDK4/6 inhibitor ribociclib in patients receiving adjuvant endocrine therapy for intermediate/high risk disease with luminal HER2-negative non-metastatic breast cancer. The study enrolled 5101 patients who were randomly allocated to an Aromatase Inhibitor alone or combined with ribociclib 400 mg/d for 3 years. The dosing was reduced to 400 mg/day to improve tolerability and 3 years treatment duration was used with the intention to drive tumor cells into irreversible senescence. Patients were included with stage IIB and III, stage IIA node-positive and stage IIA node-negative disease with additional high-risk features. The primary endpoint of invasive disease-free survival (iDFS) was met with 3.3 % absolute reduction in the frequency of iDFS events (90.4 % vs 87.1 %, HR 0.748, $p = 0.0014$) at median follow up of 27.7 months. The study additionally demonstrated significant improvement in distant disease-free survival (90.8 % vs 88.6 %, HR 0.739, $p = 0.0017$). These results should be analysed with caution as at the data cutoff point only 20 % of patients have completed 3 years of ribociclib treatment. Additionally, the final manuscript is still awaited. Should these early data be confirmed, adjuvant ribociclib could become a new opportunity for improving outcomes for even a larger population of patients treated for early luminal HER2-negative breast cancer.

### *2.8. Quality of life [27–29]*

Significantly longer time to deterioration of quality of life due to CANKADO PRO-React eHealth support in HR + HER2- metastatic breast cancer patients receiving palbociclib and endocrine therapy: primary outcome analysis of the multicenter randomized AGO-B WSG PreCycle trial (Harbeck et al.) [27].

Pregnancy After Breast Cancer in Young BRCA Carriers (Partridge et al.) [28].

Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer (Partridge et al.) [29].

POSITIVE was a prospective international single-group trial evaluating the temporary interruption of adjuvant endocrine therapy to attempt pregnancy in young (≤42 years) women, with previous ER-positive early breast cancer, who received adjuvant hormonal treatment for no less than 18 and no more than 30 months. The primary end point was the number of breast cancer events (local, regional, distant recurrence or new contralateral invasive breast cancer) during follow-up.

From 497 women who were followed for pregnancy 365 babies were born. At 1638 patient-years of follow-up (median 41 months), 44 patients had a breast cancer event, a result that did not exceed the safety threshold. The 3-year incidence of breast cancer events was 8.9 % (95 % confidence interval [CI], 6.3 to 11.6) in the treatment-interruption group and 9.2 % (95 % CI, 7.6 to 10.8) in the control cohort.

The POSITIVE trial represents an admirable joint effort that intends to give reassurance to women desiring a pregnancy after a breast cancer diagnosis. The main limitations of the trial are the single-arm trial design (with an external cohort used as control) and the short follow-up time. However, it still represents the best available evidence on this issue.

## 3. Advanced breast cancer [30–32]

Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial (Rugo et al.) [30].

TROPiCS-02 was originally presented at ASCO 2022, demonstrating a 34 % reduction in the risk of progression or death (HR 0.66, $p < 0.001$) among 543 patients treated with sacituzumab govitecan (SG) vs treatment of physician's choice (capecitabine, vinorelbine, gemcitabine or eribulin) for advanced HR+/HER2-breast cancer that progressed after at least 2 lines of chemotherapy for metastatic disease. Last year we've seen mature overall survival results, demonstrating a prolongation in median OS from 11.2 months in the control arm to 14.4 months in patients treated with SG (HR 0.79, $p = 0.02$). Additionally, SG-treated patients experienced higher overall response rate (21 % vs 14 %; OR 1.63; $p = 0·035$), and prolongation of time to deterioration of global health status/quality of life (HR 0.75; $p = 0.0059$) and fatigue (HR 0.73; $p = 0.0021$).

Presented data confirm the efficacy of SG in this heavily pretreated population (median 3 prior chemotherapy lines, median time form MBC diagnosis of approximately 48 months), where treatment options are limited.

Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017–03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC) (Sonke et al.) [31].

CDK4/6 inhibitors have greatly improved outcome for patients with advanced ER+/HER2-breast cancer. Studies have shown survival benefits when CDK4/6 inhibitors added to either first-line or second-line endocrine treatment. In the absence of direct comparisons, there was uncertainty whether a first-line or a second-line strategy has the optimal balance for patients between benefits and risks. The SONIA trial (NCT03425838) included 1050 patients with advanced ER+/HER2-breast cancer who had not received treatment for advanced disease. All patients received first-line aromatase inhibitor follow by second-line fulvestrant upon disease progression. Patients were randomized to receive any of the three available CDK4/6 inhibitors either in first or in second line. Primary endpoint was progression-free survival after both protocol-defined treatment lines (PFS2). Overall survival, toxicity and quality-of-life were key secondary endpoints. PFS2 did not differ between the treatment arms (hazard ratio 0.87; 95 % CI 0.74–1.03). OS (HR 0.98; 95 % CI 0.80–1.20) and QoL (FACT-B total score p-value 0.4) were also similar. A first-line strategy, however, was associated with 16.5 months longer duration of CDK4/6 inhibitor use, leading to 74 %

more grade 3-4 adverse events. Therefore, SONIA possibly challenges the need for CDK4/6 inhibitor use in first-line, albeit the clinical significance of this result in view of available targeted therapy options in 2nd line setting and use in the trial of possibly less biologically active CDK4/6 inhibitor seems rather questionable. Biomarkers should try to identify patients that could benefit from first-line use. Trials like SONIA can significantly reduce the toxicity of effective drugs and make them accessible to those who would otherwise find them unaffordable. These trials are self-funded as the costs are covered by the savings achieved through the less expensive treatments used in the trial.

Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer (Turner et al.) [32].

CAPItello-291 was phase 3, randomized, double-blind trial conducted in patients with HR+/HER2–advanced breast cancer who developed disease progression during or after treatment with an aromatase inhibitor, with or without CDK4/6 inhibitor. 708 patients were randomly assigned to receive fulvestrant combined with capivasertib or placebo. PFS prolongation was found both in the overall population (median 7.2 vs 3.6 months, HR 0.6, $p < 0.001$) and in patients with AKT pathway–altered tumors (median 7.3 vs 3.1 months, HR 0.5, $p < 0.001$). Overall survival results are immature. The most frequent adverse events of grade $\geq$3 in patients treated with capivasertib were rash (in 12.1 % vs. in 0.3 %) and diarrhea (in 9.3 % vs. 0.3 %). 13 % of patients in the capivasertib arm (vs 2.3 % in the placebo arm) discontinued treatment due to toxicity.

Capivasterib creates a new treatment option in the difficult-to-treat patients failing endocrine therapy combined with a CDK4/6 inhibitor. Being active in both overall population and in AKT pathway–altered tumors it potentially creates an alternative to both everolimus and alpelisib and we need to learn, how to best select/sequence these agents, as well as how to manage their sometimes non-trivial toxicities.

## 4. Controlled clinical trial protocols [33–39] these are listed in Table 2

### 4.1. Conclusion

The above-tabulated and narrated work has discussed selected studies and recommendations relevant to breast cancer care from the year that has passed. Highlighted original work was dominated by RCTs, but also featured cohort studies and individual patient data meta-analyses leveraging the collective data from multiple trials. Published clinical trial protocols, while not discussed, provide an opportunity for early sharing of research concepts and methods. We look forward to findings from these studies and other research as we begin a new year of learning and practice in breast cancer.

## Disclosure

The selection is the full responsibility of the authors.

## Revision note

The change was the inclusion of an extra reference that altered the following reference sequence.

Along the text – nothing major was changed.

As such we opted to upload a new version without marking.

## CRediT authorship contribution statement

**Maria-Joao Cardoso:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Philip Poortmans:** Writing – original draft. **Elżbieta Senkus:** Writing – review & editing, Writing – original draft. **Oreste D. Gentilini:** Writing – review & editing, Writing – original draft. **Nehmat Houssami:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

## Declaration of competing interest

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**Elżbieta Senkus** honoraria: AstraZeneca, Cancérodigest, Curio Science, Egis, Eli Lilly, Exact Sciences, Gilead, high5md, MSD, Novartis, Pfizer, Pierre Fabre, Roche; travel support: AstraZeneca, Egis, Gilead, Novartis, Pfizer, Roche; contracted research: Amgen, AstraZeneca, Daiichi Sankyo, Eli Lilly, Novartis, OBI Pharma, Pfizer, Roche, Samsung; grants: Pfizer (Stowarzyszenie Różowy Motyl); medical writing: Astellas, AstraZeneca, Eli Lilly; royalties: Springer; leadership or fiduciary role: Stowarzyszenie Różowy Motyl; stock: AstraZeneca, Eli Lilly, Pfizer.

**Philip Poortmans** no conflicts no disclose.

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