Critical Reviews in Oncology / Hematology 181 (2023) 103900

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Neoadjuvant endocrine therapy for luminal breast tumors: State of the art, challenges and future perspectives

Marianna Sirico [a,1], Alessandra Virga [b,1], Benedetta Conte [c], Milena Urbini [b], Paola Ulivi [b], Caterina Gianni [a], Filippo Merloni [a], Michela Palleschi [a], Marco Gasperoni [d], Annalisa Curcio [d], Debjani Saha [e], Giuseppe Buono [f], Montserrat Muñoz [c,g,h], Ugo De Giorgi [a,2], Francesco Schettini [c,g,h,*,2]

[a] Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy
[b] Biosciences Laboratory, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy
[c] Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain
[d] Breast Surgery Unit, Morgagni-Pierantoni Hospital, AUSL Romagna, Forlì, Italy
[e] Department of Surgery and Cancer, Imperial College London, London, UK
[f] Department of Breast and Thoracic Oncology, National Cancer Institute, Fondazione G. Pascale, Naples, Italy
[g] Medical Oncology Department, Hospital Clinic of Barcelona, Barcelona, Spain
[h] Faculty of Medicine, University of Barcelona, Barcelona, Spain

ARTICLE INFO

Keywords:
Endocrine receptor
Neoadjuvant therapy
Endocrine therapy
Biomarker
Ki67
Breast cancer

ABSTRACT

Neoadjuvant endocrine treatment (NET) associates to satisfactory rates of breast conservative surgery and conversions from inoperable to operable hormone receptor-positive (HR+)/HER2-negative breast cancer (BC), with less toxicities than neoadjuvant chemotherapy (NACT) and similar outcomes. Hence, it has been proposed as a logical alternative to NACT in patients with HR+/HER2- BC candidate to a neoadjuvant approach. Nevertheless, potential barriers to the widespread use of NET include the heterogeneous nature of patient response coupled with the long duration needed to achieve a clinical response. However, interest in NET has significantly increased in the last decade, owing to more in-depth investigation of several biomarkers for a more adequate patient selection and on-treatment benefit monitoring, such as PEPI score, Ki67 and genomic assays. This review is intended to describe the state-of-the-art regarding NET, its future perspectives and potential integration with molecular biomarkers for the optimal selection of patients, regimen and duration of (neo) adjuvant treatments.

1. Introduction

Hormone receptor-positive (HR+) or luminal BC with no over-expression or amplification of HER2 (HER2-) accounts for 65–70% of all breast tumors. In early-stage disease, its mainstay of systemic treatment is represented by endocrine therapy (ET), with chemotherapy (CT) being useful mostly in premenopausal women, men and postmenopausal patients with high-risk of relapse (Cardoso et al., 2019a; Korde et al., 2021a; Schettini et al., 2021). CT can be administered before (neo-adjuvant therapy) or after surgery (adjuvant therapy) for 4–6 months, when indicated, while ET is usually administered as adjuvant therapy for 5–10 years. However, ET can be also started before surgery, in certain circumstances(F. Cardoso et al., 2019a), although there are no clear recommendations for patient selection for neoadjuvant ET (NET). The main aim of this review is to describe the state-of-the-art regarding NET and its future perspectives, especially in light of the increasing interest towards de-escalation therapeutic strategies and implementation of molecular biomarkers for the optimal selection and duration of (neo) adjuvant treatments.

* Corresponding author at: Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain.
[1] These authors contributed equally to the manuscript as co-first author
[2] These authors contributed equally to the manuscript as co-last authors

https://doi.org/10.1016/j.critrevonc.2022.103900
Received 2 May 2022; Received in revised form 16 December 2022; Accepted 19 December 2022
Available online 21 December 2022

1.1. The neoadjuvant paradigm in breast cancer

Neoadjuvant therapy (NAT) presents with several advantages. A reduction of tumor burden can either allow for a more conservative surgery or the surgical resection of an inoperable primary tumor (Bear, 2010; Fisher et al., 1997). In addition, given that the tumor remains in place during the treatment, a pre-surgical approach allows for the monitoring of treatment response and the interruption of inefficient therapies in case of progression, avoiding potentially toxic treatments that offer no clinical benefit (Cain et al., 2017). For the same reason and the possibility of an easy access to pre-/on-/post-treatment tumor tissue (primary site instead of organ/bone metastases), neoadjuvant approaches are also becoming an increasingly popular and invaluable translational research platform (Buono et al., 2018). Beyond all of these considerations, several studies showed that patients who obtain a pathological complete response (pCR), defined as absence of invasive carcinoma in breast and nodes after neoadjuvant therapy and posterior surgery, might experience an improved survival (Cortazar et al., 2014a; Pennisi et al., 2016) or might be treated with additional adjuvant treatments if not obtaining pCR. This is especially true for HER2 positive (HER2+) and triple negative (TN) tumors, but less clear for HR+/HER2- disease (Cortazar et al., 2014b). At the same time the more recent post-neoadjuvant endpoint of residual cancer burden (RCB) was independently validated in multiple studies (Yau et al., 2022). The RCB method allows for a standardized evaluation and quantification of the extent of residual disease in breast and axillary lymph-nodes at surgery, following neoadjuvant chemotherapy (NACT). RCB is a continuous score subdivided into 4 categories ranging from 0 to III. An RCB score of zero represents the achievement of pCR, while RCB categories I-III represent an increasing residual disease burden (Symmans et al., 2007a). In a recent patient-level meta-analysis including more than 5000 patients from 12 Institutions and trials, its prognostic role was confirmed, independently from age, grade, T category, and nodal status at baseline, including for HR+/HER2- BC (Yau et al., 2022).

1.2. NET: Efficacy and optimal duration

While HER2+ and TN BC may achieve pCR in 50–60% of cases, in HR+/HER2- tumors pCR is achieved just in 10–20% of patients (Gianni et al., 2012; Schneeweiss et al., 2013). This has represented an important limitation to the widespread use of a neoadjuvant approach in this BC subtype, so far. However, pCR rates observed with NET are similar to what has been usually observed with NACT in this BC subtype, with significantly better tolerability (Spring et al., 2016a). Moreover, when NET is administered for more than 3 months, the likelihood of breast-conserving surgery (BCS) can range between 40% and 80% (Cain et al., 2017; Fisher et al., 1997) with up to 77% of patients initially non-eligible for BCS, that might become eligible for breast preservation after NET. Though, this rate seems to be lower in those with low progesterone receptor expression levels and positive axillary lymph-nodes (N+) (Suman et al., 2015). For these reasons, NET has been proposed as a logical alternative to NACT in HR+/HER2- BC. In any case, while NACT has already an established role in the European Society Medical Guidelines (ESMO) and American Society of Clinical Oncology (ASCO) guidelines, the role of NET is still underrated, limited to postmenopausal women, and scarcely used in clinical practice (Cardoso et al., 2019b; Korde et al., 2021a). Potential barriers to the widespread use of NET include the heterogeneous nature of patient response coupled with the long duration needed to achieve a clinical response. In fact, several studies have been conducted to define the appropriate duration of NET, generally demonstrating better response rates after longer treatment periods, with overall response rates (ORR) ranging between 20% and 70% with 3–4 months of NET and up to 88% with 12 months and BCS. However, pCR was achieved in 0–17.5% cases (Table 1), increasing with longer drug exposition(Cataliotti et al., 2006; Eiermann et al., 2001; Ellis et al., 2001; Masuda et al., 2012; Smith et al., 2005). Moreover, close tumor burden monitoring must be carried out so to quickly intervene in case of local progression before surgery, which could either make the tumor inoperable or the patient not amenable to BCS.

Importantly, during COVID-19 pandemic, Di Lena et al. performed a multi-institutional matched historical cohort study where BC patients

Table 1
NET duration and clinical efficacy.

Study	No. of patients	Intervention/s	Setting	Phase	Duration Months	Primary endpoint	Results
Krainick-Strobel UE; 2008	32	Letrozole	Stage II–III-IV ER+ /PR+ BC	2/3	4/8	Tumor Regression, BCS	4 mo: ORR: 55.2% BCS: 71% 8 mo ORR: 72.4% BCS: 80%
Dixon JM; 2009	182	Letrozole	HR+/HER2- locally advanced BC	2	3/6/12/24	ORR	3 mo: ORR: 70% BCS: 60% >3 mo: ORR: 83%, BCS: 72%
Llombart-Cussac A; 2012	70	Letrozole	HR+/HER2- early BC	2	4/12	Maximal response	ORR: 76.8% (25% CR and 51.8% PR) BCS: 43%
Hojo T; 2013	50	Exemestane	Stage II-IIIA ER+ and/or PgR+ BC	2	4/6	CR, pCR BCS	4 mo: pCR: 0%; ORR: 42.3%; BCS: 50% 6 mo: pCR: 4%; ORR: 48%; BCS: 48%
Allevi G; 2013	120	Letrozole	Stage II HR+ BC	–	4/8/12	pCR	4 mo: pCR 2.5%; 8 mo: pCR 5%; 12 mo: pCR 17.5%
Fontein DBY; 2014	102	Exemestane	Stage II-III HR+ BC	2	3/6	CR	3 mo ORR: 58.7%; BCS: 61.8% >3 mo ORR: 68.3%; BCS: 70.6%
Rusz O; 2015	42	Letrozole, Goserelin, Tamoxifen	Stage II-III HR+/HER2- BC	–	12	ORR, pCR	pCR: 14.3% ORR: 88% BCS: 45%
Pariser AC; 2019	6584	NET	stage II-III ER+ and/or PgR+ BC	–	≥3	Tumor downstaging	1–3 mo: 20.6% 12–24 mo: 34.9%

Legend. CR: complete response; ER: estrogen receptor; PgR: progesterone receptor; HR: hormone receptor; + : positive; PR: partial response; ORR: overall response rate; BCS: breast conservation surgery; OR: objective response; pCR: pathologic complete response.

with stage I/II BC receiving NET were prospectively identified and matched to a historical cohort of stage I/II HR+/HER2- BC patients treated with upfront surgery in <35 days. Despite 2.5-times longer delays, patients receiving NET did not experience pathologic upstaging during the pandemic(Lena et al., 2021).

In conclusion, while the optimal duration of NET has not been completely established, in the majority of NET trials, patients were treated for 3–6 months before surgery (Abrial et al., 2006; Allevi et al., 2013; Dixon et al., 2008). Thus, all main international guidelines recommend NET to be administered for at least 3–4 months to obtain a relevant clinical response (Burstein et al., 2021b; Cardoso et al., 2019; Korde et al., 2021b).

1.3. NET: Which endocrine agents?

Nowadays, the third-generation aromatase inhibitors (AIs) anastrozole, letrozole, and exemestane (with a gonadotropin releasing hormone [GnRH] analogue [GnRHa] in premenopausal patients) are considered the standard of care for NET. In postmenopausal patients, at least five randomized phase III trials compared AIs to tamoxifen(Cataliotti et al., 2006; Eiermann et al., 2001; Ellis et al., 2001; Masuda et al., 2012; Smith et al., 2005), with results consistently pointing towards the superiority of AIs in response rates. (Table 2). Interestingly, the irreversible, steroidal AI exemestane, showed a similar clinical response rate to the non-steroidal AI anastrozole in a study from Semiglazov et al. (2007) which also compared NET to NACT(Semiglazov et al., 2007). Overall the superiority of AIs vs. tamoxifen was confirmed in a recent meta-analysis, showing better clinical and radiological response rates ($p<0.001$ for both), along with superior BCS rate ($p<0.001$) with AIs (Spring et al., 2016b).

To note, two trials explored the use of the estrogen receptor (ER) degrader (SERD) fulvestrant or anastrozole in the neoadjuvant setting. The latter appeared to be slightly favoured in terms of efficacy and tolerability, although no formal comparison was carried out (Lerebours et al., 2016; Quenel-Tueux et al., 2015) (Table 2).

In the premenopausal setting, the STAGE trial compared AIs vs. tamoxifen in 204 women with iatrogenic menopause induced by the GnRHa goserelin in both treatment arms. This study confirmed the superiority of an AI over tamoxifen in response rates (70.4% v 50.5%, respectively), also in this clinical scenario (Masuda et al., 2012) (Table 2).

2. Biomarkers for patients selection

In the last 2021 St. Gallen International Breast Cancer Conference, 98% of the expert panellists did not consider anymore CT as a treatment of choice for postmenopausal women with clinical and/or genomic low-risk HR+/HER2- tumors (Burstein et al., 2021a). However, there is a need for better selection of patients to whom administer NET.

2.1. Baseline ER expression

Baseline ER levels are predictive of response to ET. The first evidence of this association was obtained from a biomarker analysis of the IMPACT(Smith et al., 2005) and the P024(Eiermann et al., 2001) trials of neoadjuvant AIs vs. tamoxifen. While large adjuvant trials showed that an ER expression of at least 1% is sufficient to derive survival benefit form ET(Hammond et al., 2010), the P024 and IMPACT results indicate that higher baseline levels are associated with increased likelihood of objective response to NET. In light of these results, strong ER staining was subsequently adopted as an eligibility criterion in other NET trials, such as Z103114(Ellis et al., 2017) and ALTERNATE (Suman et al., 2015).

2.2. Baseline Ki67 expression

In the adjuvant setting, the Ki67 expression has been used to discriminate aggressive HR+/HER2- tumors requiring CT from those which are likely to be cured with ET monotherapy (Dowsett et al., 2007; Ellis et al., 2017). However, the reliability of such biomarker has long been under debate for the considerable inter-pathologist variability (Harris et al., 2007), until its use has been replaced by standardized gene expression-based assays (GEA), where available (Cardoso et al., 2016a; Dubsky et al., 2013a; Filipits et al., 2014, 2019a; Gnant et al., 2014; Lænkholm et al., 2018; Sestak et al., 2015, 2019a; Sparano et al., 2018). Similar unsatisfactory results have been observed in the neoadjuvant

Table 2
Randomized clinical trials comparing different endocrine agents in the neoadjuvant setting.

Clinical Trial Identifier	Study Design	Menopausal Status	Intervention/s	Duration	Primary Endpoint and results	Phase
Eiermann W; 2011	337 Participants, randomized, double-blind	Postmenopausal	Letrozole (A) vs. tamoxifen (B)	3 mo	RR by clinical palpation A 55%, B 36% (OR: 2.23, 95%CI: 1.43–3.50, P=0.0005).	3
Ellis MJ; 2001	250 Participants, randomized, double-blind	Postmenopausal	Letrozole (A) vs. tamoxifen (B)	4 mo	RR by clinical palpation A 60%, B 41% (P=0.004).	3
Smith IE; 2005	330 Participants, randomized, double-blind	Postmenopausal	Anastrozole (A) or tamoxifen (B) vs. anastrozole + tamoxifen ©	4 mo	RR by ultrasound A 37%, B 36% (A vs. B OR: 1.05, 95%CI: 0.61–1.81, P=0.87), C 39% (C vs. B OR: 1.15, 95%CI: 0.67–2.00, P=0.61).	3
Cataliotti L; 2006	450 Participants, randomized, double-blind	Postmenopausal	Anastrozole (A) vs. tamoxifen (B)	3 mo	RR by ultrasound A 39.5%, B 35.4% (A vs. B OR: 1.24, 95%CI: 0.84–1.83, P=0.29).	3
Semiglazov VF; 2007	239 Participants, randomized, controlled, open-label	Postmenopausal	NET arm (anastrozole [A] or exemestane [B])	3 mo	RR by clinical palpation in the NET group A 62%, B 67% (no formal comparison).	2
Quenel-Tueux N; 2015	108 Participants, randomized, non-comparative	Postmenopausal	Anastrozole (A) vs. fulvestrant (B)	6 mo	ORR A 58.9% (95%CI: 45.0–71.9%); B 53.8% (95%CI: 39.5–67.8%) BCS A 58.9% (95%CI: 45.0–71.9%); B 50.0% (95%CI: 35.8–64.2%).	2
Lerebours F; 2016	116 Participants, randomized open label, non-comparative	Postmenopausal	Anastrozole (A) vs. fulvestrant (B)	4 or 6 mo	ORR A 52.6% (95%CI: 41.0–64.0%); B 36.8% (95%CI: 25.0–49.0%).	2
Masuda N; 2012	240 Participants, randomized, double-blind, parallel-group	Premenopausal	Anastrozole + goserelin (A) vs. tamoxifen + goserelin (B)	6 mo	CRR with calliper A 70.4%, B 50.5% (A vs. B OR: 2·23, 95% CI 1·22–4·06, p=0·009)	3

Legend. BCS: breast conservative surgery; RR: response rate; CRR: clinical response rate; mo: months; ORR: overall response rate; OR: odds ratio; TTP: time to progression; OS: overall survival; CI: confidence interval.

setting. In the P024 (Eiermann et al., 2001) and IMPACT (Smith et al., 2005) trials, an extremely low baseline Ki67 expression (below 10%) was able to identify a subgroup of patients with outstanding survival rates at 5 years; however, no significant association between baseline Ki67 levels and relapse-free survival (RFS) was observed. Such results suggest that extremely low levels of baseline Ki67 might be a useful biomarker to identify patients who can be safely endorsed for NET without the need for more expensive and complex biomarkers. However, the reliability of baseline Ki67 becomes largely unsatisfactory for levels above 10%, and the use of more proficient biomarkers is needed in these cases.

2.3. GEA

In the last St. Gallen Conference, 73% of the panellists voted in favour of performing genomic assays on core biopsies to select patients with HR+/HER2- BC for NACT vs. NET (Thomssen et al., 2021).

GEA, such as OncotypeDX® (Sparano et al., 2018), Mammaprint® (Cardoso et al., 2016b), EndoPredict® (Dubsky et al., 2013b; Filipits et al., 2019b; Sestak et al., 2019b) and PAM50 (Prosigna®)(Filipits et al., 2014; Gnant et al., 2014; Lænkholm et al., 2018; Sestak et al., 2015), accurately predict the risk of recurrence of HR+/HER2- early BC, allowing to discriminate patients who might not need adjuvant CT from those who are likely to benefit. Although these assays have been validated for the adjuvant setting, their use could be easily translated to the neoadjuvant scenario, to triage patients to either NACT or NET based on their genomic risk scores. This strategy has been tested in a pilot trial (Bear et al., 2017), which assigned 64 HR+/HER2- BC patients not suitable for BCS to NACT or NET based on OncotypeDX Recurrence Score (RS). Similarly to the TAILORx adjuvant trial (Sparano et al., 2018), patients with a midrange RS of 11–25 were randomized to either NET or NACT. The results showed significantly lower ORR in patients with midrange RS randomized to NET vs. NACT; however, high ORR (72%) were observed in patients with RS<11 treated with NET, indicating NET as a potentially effective strategy in this subgroup. A similar approach has been used in the I-SPY program (Barker et al., 2009), where eligible patients had to be affected by HR+/HER2- BC classified as high-risk by the MammaPrint assay.

Recently, a PAM50-based chemo-endocrine score (CES) has been developed and validated to predict sensitivity to NACT and NET (Prat et al., 2017). Patients with high CES showed lower probability of achieving pCR, significantly higher ORR upon NET (75%), and higher survival rates independently of pCR (Prat et al., 2017). These data overall suggest the potential of GEA for tailoring treatment recommendations in the neoadjuvant setting in addition to classic pathology.

2.4. Tumor histology and NET: invasive lobular carcinoma

The efficacy of NET has been explored also in the context of invasive lobular carcinoma (ILC), the second most frequent BC histotype after invasive ductal carcinoma (IDC) (Carbognin et al., 2020). This phenotype accounts for 5–15% of all BC, is usually HR+ and despite showing frequently lower mitotic index and grade than IDC, presents with peculiar molecular features associated to worse long-term survival (Carbognin et al., 2020). In current clinical practice, there are no established differences in the (neo)adjuvant therapeutic approach between IDC and ILC, owing to substantial lack of data. Noteworthy, a single arm study confined to ILC showed a mean reduction in tumor volume at 3 months of 66%, with a clinical response rate of almost 92% with letrozole as NET (Dixon et al., 2011). An ongoing randomized phase 2 trial (NCT02206984) will assess whether fulvestrant is more effective than anastrozole or tamoxifen in reducing Ki67 in ILC. The trial is currently recruiting patients and results might have potential implications for the future management of this BC phenotype.

3. Biomarkers for predicting long-term benefit of NET and defining the adjuvant strategy

The neoadjuvant setting allows to evaluate on-treatment changes of molecular tumor characteristics. This important feature has been extensively exploited by researchers to find early biomarkers of endocrine sensitivity in patients with HR+ BC 21, so to pursuit risk-adapted strategies in the (neo)adjuvant setting. Biomarkers currently available for directing treatment decisions include, among others, on-treatment changes of Ki67 expression, the preoperative endocrine prognostic index (PEPI), the RCB and GEA.

3.1. On-treatment changes of Ki67 expression

In postmenopausal HR+/HER2- BC patients receiving NET, the early suppression of Ki67 seems to be a significant predictor of treatment efficacy and long-term survival. In 2007, the investigators of the IMPACT trial showed that lower levels of Ki67 expression after 2 weeks of NET (assessed with on-treatment tumor biopsies) were significantly associated with higher RFS (Smith et al., 2005). One year later, the investigators of the P024 trial showed that also post-treatment Ki67 levels on surgical specimens after 4 months of NET were significantly associated with RFS and breast cancer-specific survival (BCSS) (Eiermann et al., 2001). Importantly, both trials showed that on-treatment Ki67 expression (either after 2 weeks or after 4 months) was more strongly associated with long-term outcome than Ki67 expression at baseline.

The prognostic role of Ki67 determination after 2–4 weeks of NET was further validated by the Z1031 (Ellis et al., 2017) and POETIC (Smith et al., 2020) trials. The Z1031 was initially designed to compare the neoadjuvant activity of different AIs in postmenopausal HR+/HER2- BC patients. Following the results of IMPACT and P024, the trial was amended to perform a tumor biopsy 2–4 weeks after starting AI and triage those patients with Ki67>10% to NACT. After 4.4 years of median follow-up, patients who remained on NET due to persistent Ki67 suppression (levels ≤10% at biopsy) showed a significantly higher RFS compared to patients that ultimately received NACT. Importantly, this trial settled the Ki67 expression cut-off at 10% to identify those patients who benefit greatly from NET and may not need CT afterwards.

The POETIC trial was specifically designed to validate Ki67 expression after short-term NET as a prognostic biomarker. In this study, 4300 postmenopausal HR+/HER2- BC patients were randomized to receive either an AI for 2 weeks before surgery, or no pre-surgical treatment. This short-course NET allowed to identify three prognostic subgroups of patients in the NET arm, based on surgical Ki67 levels. Namely, patients whose Ki67 was ≤10% both at baseline and after 2 weeks of NET patients whose Ki67 was initially >10% but shrunk down to 10% after 2 weeks of NET and patients whose Ki67 remained >10% upon 2 weeks of NET. Patients from the first group showed the highest survival rates, with a 5-year recurrence risk (RR) of 4.3% (95% confidence interval [CI]: 2.9 – 6.3%); patients from the second group showed an intermediate prognosis, with a 5-year RR of 8.4% (95%CI: 6.8–10.5%), while those whose Ki67 remained >10% displayed the worst prognosis, with a RR at 5 years of 21.5% (95%CI: 17.1 – 27.0%). Furthermore, almost all patients with Ki67≤10% remained Ki67-low at week 2, indicating little value for on-treatment biopsy for this group (Smith et al., 2020).

Taken together, these trials clearly demonstrate that Ki67 assessment after 2–4 weeks of NET is a valuable biomarker of treatment efficacy and long-term survival for those patients with a baseline Ki67>10%. However, its use in clinical practice is currently limited by the lack of pre-analytical and analytical reproducibility, and by a significant inter-observer variability in the interpretation of Ki67 immunohistochemical (IHC) scoring (Dowsett et al., 2011; Harris et al., 2007).

To note, novel cyclin-dependent kinase (CDK)4/6-inhibitors (palbociclib, ribociclib and abemaciclib) in combination with ET have recently become the new standard of care for the first/second-line treatment in HR+/HER2- metastatic BC, following unprecedented

benefit observed in progression-free survival (PFS) and overall survival (OS) (Giuliano et al., 2019; Schettini et al., 2020). Consequently, there is growing interest in exploring the biologic activity and clinical efficacy of CDK4/6-inhibitors in combination with NET. While some preliminary trials have already been published and will be further discussed (Hurvitz et al., 2020; Johnston et al., 2019; Ma et al., 2017), others are currently ongoing. As these agents dramatically suppress tumor cell proliferation, the Ki67 cut-off of 10% might have become out of date. Therefore, most neoadjuvant trials evaluating the efficacy of NET + CDK4/6-inhibitors, have settled a Ki67 expression <2.7% as a new surrogate endpoint for CDK4/6-inhibitors efficacy, indicating a complete cell cycle arrest (CCCE) (Hurvitz et al., 2020; Johnston et al., 2019; Ma et al., 2017). However, Ki67 remains an exploratory biomarker in this setting.

3.2. The preoperative endocrine prognostic index (PEPI) score

The P024 and IMPACT trials have served respectively as the development (Eiermann et al., 2001) and validation (Smith et al., 2005) datasets of the PEPI score, a multivariable prognostic model incorporating post-treatment pathological stage and biomarker status in patients treated with NET. Among baseline and post-treatment variables tested in the P024 trial, only post-treatment Ki67, post-treatment ER, residual tumor size and residual nodal status were independently associated with survival and were therefore selected to derive the PEPI score (Table 3). Then, such score was used to identify three prognostic groups (PEPI score 0, 1–3 and ≥4) that in the P024 trial were associated with a risk of relapse at 5 years of 10%, 23% and 48%, respectively ($p<0.001$), and with a risk of breast cancer-related death of 2%, 11% and 17%, respectively ($p<0.001$). The prognostic performance of PEPI score was then confirmed in the IMPACT trial, where patients achieving a PEPI-0 after NET showed an impressive RFS of 97% at 3 years, while patients with a score ≥4 had a significantly worse RFS of 83% ($p=0.002$). A further validation of the PEPI score was performed in the Z1031 trial (Ellis et al., 2017), where patients achieving a PEPI-0 after NET had a significantly lower relapse rate at 5 years as compared with patients with a PEPI score >0 (3.7% versus 14.4%, $p=0.014$).

On-treatment Ki67 expression and post-treatment PEPI-score may be seen as different turning points in the treatment decision-making of postmenopausal women with HR+/HER2- BC. The Ki67 expression after only 2–4 weeks of NET allows for an early identification of those patients who are extremely unlikely to achieve a PEPI-0 with NET, and should therefore triaged to either NACT or upfront surgery. On the other hand, the PEPI-score, provides a more complete prognostic prediction by integrating multiple clinical and molecular variables from the surgical sample, and allows to identify those patients with an excellent prognosis (PEPI-0 group) who may not need adjuvant CT after NET. The ongoing ALTERNATE trial is aiming to further validate on-treatment Ki67 and post-treatment PEPI-score as biomarkers to guide the (neo)adjuvant therapeutic strategy. This study will treat 1362 postmenopausal stage II-III HR+/HER2- BC patients with either 6-month neoadjuvant anastrozole, fulvestrant or the combination followed by the same treatment in adjuvant setting (Suman et al., 2015). Patients with Ki67>10% on breast biopsy after 4 weeks (mandatory) or 12 weeks (optional) have to switch to NACT. At the same time, women having completed 6 months of NET and found to have positive axillary nodes or Ki67>2.7% in residual disease after surgery will receive adjuvant CT (Suman et al., 2015).

Table 3
The preoperative endocrine prognostic index.

Variable	Points
Pathological tumor size	
pT1/pT2	0
pT3/pT4	3
Pathological nodal status	
Negative	0
Positive	3
Ki67 expression (%)	
0–2.7	0
>2.7–7.3	1
>7.3–19.7	1
>19.7–53.1	2
>53.1	3
ER expression, Allred score	
0–2	3
3–8	0
PEPI groups: 1 (PEPI=0), 2 (PEPI=1–3), 3 (PEPI≥4)	

Legend. ER: estrogen receptor; p: pathological.

As for on-treatment Ki67, few data are currently available on the prognostic role of PEPI score in patients treated with NET + CDK4/6-inhibitors. Surprisingly, the FELINE trial showed no significant benefit from the addition of ribociclib to letrozole in terms of PEPI score(Khan et al., 2020). Follow-up is ongoing, and survival data are awaited to elucidate the prognostic performance of PEPI score following CDK4/6-inhibitors-based NET.

3.3. RCB score

RCB was demonstrated to predict disease recurrence and survival across all breast cancer subtypes (Symmans et al., 2017, 2007b). It includes residual primary tumor size, residual primary tumor cellularity, the number and size of nodal metastases. An RCB of 0 (i.e. equal to pCR) or I proved to be associated with better event-free survival (EFS) than RCB II-III in HR+/HER2- BC (Yau et al., 2022). Unfortunately, little is known about its prognostic value after NET.

In the NeoPAL study, the only trial so far to have adopted the RCB score as efficacy endpoint for NET + CDK4/6-inhibitors, patients treated with neoadjuvant letrozole and palbociclib showed decreased RCB 0/I rates compared with patients treated with NACT (7.7% versus 15.7%, respectively), although clinical response was similar between arms (Cottu et al., 2018).

Recently, the I-SPY Consortium developed a statistical tool, defined Treatment Efficacy Score (TES), to quantify the difference between the entire distribution of pathologic responses in terms of different RCB values observed in trial arms. The authors demonstrated that the higher the TES in a reference arm, the greater the shift to lower RCB values in a corresponding experimental arm. This tool seemed to be able to accurately identify less effective regimens, independently of pCR rate improvement. Furthermore, the correlation between TES and survival was higher than the correlation between the pCR rate difference and survival. Potentially, this tool may become an early surrogate endpoint to predict trial arm level survival differences, but further validation and incorporation in other studies is required (Marczyk et al., 2022).

3.4. GEA

GEA are currently under active investigation in the neoadjuvant setting to assess the prognostic role of molecular downstaging, i.e. the switch from a high genomic risk at baseline to a lower genomic risk following neoadjuvant treatment.

Although data on molecular downstaging are limited, there is a strong rationale supporting the use of this endpoint. First, on-treatment Ki67 and post-treatment PEPI score have been validated only on patients treated with NET monotherapy (Dowsett et al., 2007; Ellis et al., 2008). However, to compare the efficacy of treatment options in the neoadjuvant setting, including NET monotherapy, NACT, and the combination of NET + CDK4/6-inhibitors, a common post-treatment biomarker is needed. Secondly, the negative results of both the neoPAL (Cottu et al., 2018) and FELINE (Khan et al., 2020) trials suggest that neither PEPI nor RCB might be suitable endpoints to assess CDK4/6-inhibitors efficacy. In addition, the lack of adequate reproducibility of pathological-based biomarkers remains an unsolved issued that hampers their use in clinical practice (Dowsett et al., 2011; Harris

et al., 2007). As GEA are standardized and have proven to predict long-term outcomes regardless of treatment received (Lænkholm et al., 2018; Sestak et al., 2015), they seem to overcome all these limitations.

A small analysis conducted on 59 postmenopausal HR+/HER2- BC patients treated with neoadjuvant exemestane for 16 weeks showed that both post-treatment OncotypeDX RS and the combination of baseline and post-treatment RS were superior predictors of long-term survival as compared with PEPI score (Ueno et al., 2019). Another small neoadjuvant trial (n = 20) has evaluated post-treatment changes in postmenopausal women treated with letrozole + palbociclib both in terms of PEPI-score and EndoPredict (EP) score(Chow et al., 2018). Post-treatment PEPI and EP scores showed a significant discordance, with 6 patients with post-treatment intermediate PEPI-score and 3 patients with high PEPI-score showing low genomic risk at the EP assay. Although these trials are exploratory, they provided the first evidence that molecular downstaging might diverge from pathological biomarkers and might be more proficient in predicting prognosis after neoadjuvant treatment.

The CORALEEN trial (Prat et al., 2020) represents the first prospective neoadjuvant trial to adopt molecular downstaging as primary efficacy endpoint. This trial randomized 106 postmenopausal patients with HR+/HER2- BC Luminal B by PAM50 (Schettini et al., 2022) to either standard NACT or letrozole + ribociclib for 24 weeks. Molecular downstaging, defined as the switch from baseline high/intermediate risk-of-relapse (ROR) group to a low ROR group, occurred at similar rates in the ribociclib + letrozole and CT arms (46.9% vs. 46.1%). The survival data are immature, but the long-term outcomes of CORALEEN will be crucial to elucidate the role of molecular downstaging as surrogate endpoint in early-stage HR+/HER2- BC.

Noteworthy, based on the CORALEEN results, the phase II trial RIBOLARIS (NCT05296746), which recently started patients accrual, will test PAM50 molecular downstaging after a ribociclib-based NET as a tool to tailor the post-surgical systemic treatment strategy. Patients with stage II HR+/HER2- BC with grade 2 or 3 and Ki67≥20% will be recruited to receive 24 weeks of letrozole + ribociclib + /- GnRHa. After surgery, patients with a PAM50 ROR considered as low will continue adjuvant ribociclib + ET for 2.5 years and then will only receive ET for ≥2.5 years, with a primary objective of distant metastasis-free survival (DMFS) at 5 years >90.6%. Within the so-called non-responder cohort with a PAM50 ROR-medium or high after NET, adjuvant CT will be administered, followed by 2.5 years of ribociclib + ET and ≥2.5 years of ET.

Finally, gene-expression data collected in post-treatment samples might provide useful insights on the mechanisms of resistance to neoadjuvant treatments and potentially drive post-neoadjuvant therapeutic strategies. In the NeoPalana (Ma et al., 2017) and the NeoMONARCH trials (Hurvitz et al., 2020), patients failing to achieve cell cycle arrest upon neoadjuvant CDK4/6-inhibitors showed significantly higher expression in a set of proliferation genes whose expression is transcriptionally regulated by E2F transcription factor 1 (*E2F1*), indicating a crucial role of persistent *E2F1* activity in CDK4/6 inhibitor-resistant tumors.

Interestingly, the ongoing NCT03900637 trial is a multicenter phase 2 study adopting the genomic assay MammaPrint as a tool to increase the BCS rate by a personalized neoadjuvant strategy. Similarly, Oncotype DX is being used in the DxCARTES trial (NCT03819010) to explore the ability of palbociclib in combination with letrozole to induce global molecular changes measured by either the Oncotype DX Breast Recurrence Score® at time of surgery, after 6 months of treatment.

3.5. Combination of GEA and Ki67 or other molecular and histopathological biomarkers

Interestingly, in the WSG-ADAPT-HR+/HER2– trial, a short-course 3-week NET, integrated with a combination of clinical features, GEA and Ki67 dynamics, proved to be potentially useful for efficiently tailoring the postsurgical therapeutic strategy.

All patients received 3-week NET after diagnostic biopsy, followed by surgery. Then, patients with ≤3 positive lymph-nodes (N0–1) at surgery and an Oncotype DX RS of ≤11 on the excised tumor, or RS 12–25 and Ki67≤10% after 3-week NET (experimental arm) received ET also in the adjuvant setting, without CT. Conversely, patients with N0–1 RS 12–25 and Ki67>10% after 3-week NET (ET non-responders) received adjuvant CT followed by ET, like RS>25 or >3 positive lymph-nodes (N2–3). Long term outcomes did not differ between the experimental arm and ET non-responders for age>50 years, while ET was even superior to CT for age≤50 years (Nitz et al., 2022). Indeed, 5-year-invasive Disease-Free Survival (iDFS) was 92.6% in experimental vs. 93.9% in control arm (non-inferiority p=0.05). Importantly, in case of RS 12–25 and 3-week Ki67>10%, 5-year iDFS was 90.3%, despite receiving both adjuvant ET and CT (Dowsett, 2022).

Recently, new data regarding 10 study arms including 987 patients from the I-SPY2 neoadjuvant study platform were published. All BC IHC subtypes were enrolled, with 38% being HR+/HER2–. Patients had been treated with standard chemotherapy (control), poly (ADP-ribose) polymerase (PARP)-inhibitors, immunotherapy, anti-HER2 agents and other experimental targeted agents, including AK strain transforming (*AKT*)-inhibitors, angiopoietin 1/2 (*ANG1/2*)-, insulin growth factor 1 receptor (*IGF1R*)- and heat shock protein 90 (Hsp90)-inhibitors added to standard NACT(Wolf et al., 2022). A complex integration of baseline mechanism-of-action-based gene expression signatures obtained with microarray assays, proteins/phosphoproteins and standard histopathological biomarkers was carried out, in order to develop different treatment response-predicting subtypes (RPSs). These novel biomarkers provided a better match for the tested drugs than the standard HR/HER2-based subtypes, so to maximize pCR rate for a given drug, or regimen, in each given BC IHC-based subgroup. This strategy led to an improvement in the overall pCR rate from 51% to 63% (Wolf et al., 2022). Given these encouraging data, a prospective evaluation of the response-predictive subtyping scheme will be pursued in an upcoming version of the I-SPY2 trial that includes a sequential multiple assignment randomize trial (SMART) scheme and adapts treatment within individual patients on the basis of biology and response. Unfortunately, standard NET was not tested in this trial, but this approach might be useful to maximize NET efficacy in HR+/HER2- disease and tailor novel NET strategies based on the combination with standard ET agents and novel targeted drugs (as further discussed) and might be pursued in the next future.

3.6. Circulating tumor DNA

Circulating tumor DNA (ctDNA) in blood is a promising biomarker for prognosis and prediction of treatment response, especially in metastatic disease, where levels in blood are higher and can be more easily detected than in early-stage disease(Arpino et al., 2022; Martínez-Sáez et al., 2021). However, recent evidences pointed out a potential ability in detecting tumor relapses earlier compared to standard radiologic imaging, suggesting a potential role for the monitoring of minimal residual disease (MRD) after NAT and posterior surgery, as well as the possibility to anticipate the treatment of tumor relapse, with the potential to improve patients outcomes (Garcia-Murillas et al., 2015; Ignatiadis et al., 2021). In the neoadjuvant setting, several studies have investigated the role of ctDNA in the prediction of disease recurrence in patients treated with standard NACT (Garcia-Murillas et al., 2015; Magbanua et al., 2021; McDonald et al., 2019; Papakonstantinou et al., 2022). In 2020 Magbanua et al. (2021) found out that the lack of ctDNA clearance was a significant predictor of metastatic recurrence, while clearance correlated with improved survival, even in patients who did not achieve pCR (Magbanua et al., 2021). Similarly, Garcillas et al. in a prospective cohort of 55 early-stage BC patients receiving NACT, showed that the detection of ctDNA after NACT was associated to metastatic relapse (Garcia-Murillas et al., 2015). Moreover, tracking tumor

mutations in serial samples increased the sensitivity for relapse prediction compared to clinical/radiologic relapse and the identification of genomic events in MRD could help predicting the genetic events of the metastatic relapse in a more accurate way than by sequencing primary tumor samples (Garcia-Murillas et al., 2015). Consistently, another study showed that post-neoadjuvant ctDNA levels were lower in patients achieving pCR compared to those with residual disease at surgery, with the major on-treatment decrease in ctDNA levels observed in cases ultimately obtaining pCR (McDonald et al., 2019). Recently this year another small trial confirmed the role of ctDNA as a biomarker of early relapse, in a cohort of 44 patients (Cailleux et al., 2022). Moreover, they found out a significant correlation between ctDNA detection at baseline and both higher tumor proliferation index and more aggressive subtype (Cailleux et al., 2022).

A systematic review and meta-analysis investigating the prognostic value of ctDNA in patients with early BC receiving NACT found out that the detection of ctDNA correlated with worse RFS and worse OS, but not with the achievement of pCR (Papakonstantinou et al., 2022).

Although evidences are promising, few is known with regard to ctDNA and prediction of response to NET. Finally, it is worth mentioning that different methods for ctDNA analysis exist, with no clear gold standard.

Taken together, these data suggest the ctDNA assessment in early disease, although promising, requires further evaluation in prospective trials, an optimization of detection methods and more evidence in early-stage HR+/HER2- BC, especially in cohorts treated with NET before entering the clinical practice scenario.

4. Improving the efficacy of NET: Combination treatments

CDK4/6-inhibitors have been tested in the neoadjuvant setting in combination with NET (Chow et al., 2018; Cottu et al., 2018; Curigliano et al., 2016; Hurvitz et al., 2020; Khan et al., 2020; Ma et al., 2017; Prat et al., 2020). Several studies provided evidence of activity for these combinations, although clinical results have been disappointing up to this point.

The PALLET trial showed that the addition of palbociclib to letrozole over 14 weeks led to a significant Ki67 reduction, suggesting an anti-proliferative effect. Clinical response rate was not improved, though (Johnston et al., 2019). Similarly, in the NeoPalAna trial, palbociclib enhanced cell cycle control over anastrozole monotherapy. Nevertheless, palbociclib should be given continuously up to surgery in order to maintain the anti-proliferative effect (Ma et al., 2017). In the NeoPAL trial, the combination of letrozole and palbociclib led to a profound decrease in Ki67 levels, at least equivalent to that obtained by NACT, translating into very encouraging BCSS and RFS. Nevertheless, pCR was low with both NET and NACT (Cottu et al., 2018). In addition, Chow et al. tried to test the efficacy of neoadjuvant palbociclib through the assessment of complete cell cycle arrest (CCCA) as well as changes in the EP assay clinical score (EPclin) before and after the treatment (Chow et al., 2018). They found a statistically significant decrease in Ki67 and EPclin after treatment, associated with an effective clinical response. Moreover, the authors suggested that the EPclin score may be more accurate than the PEPI score in estimating prognosis, as it is unlikely to rebound during the drug washout period before surgery (Chow et al., 2018).

The neo-MONARCH trial revealed that abemaciclib, alone or in combination with anastrozole, may obtain a significant decrease in Ki67 expression, leading to a potent CCCA after 2 weeks of treatment compared with anastrozole alone (Hurvitz et al., 2020).

The MONALEESA-1 trial showed a decrease in the percentage of cells expressing the Ki67 proliferation marker, following treatment with letrozole in combination with ribociclib(Curigliano et al., 2016). The CORALLEEN randomized phase II trial validated the hypothesis that patients with PAM50 Luminal B/HR+/HER2- BC may obtain a molecular downstaging of their disease with ribociclib + letrozole, similar to what observed with CT, but with less toxicity(Prat et al., 2020). Further confirmation is seek with the ongoing RIBOLARIS trial (NCT05296746).

The FELINE trial found that the addition of ribociclib to ET did not result in any difference in term of BCS rate or PEPI score at the time of surgery. However, survival analysis has not been published yet(Khan et al., 2020).

Overall, these studies used different surrogate endpoints to evaluate efficacy of the tested treatments and none of the biomarkers adopted has demonstrated a clear correlation with survival, so far. Moreover, none of these trials directly showed a clear improvement in OS for such combinations, if compared to NET alone or NACT and, lastly, follow-up was not adequate to draw meaningful conclusions.

The mammalian target of rapamycin (mTOR)-inhibitor everolimus, as well as some phosphatidylinositol-3-kinase (PI3K)-inhibitors, when combined to ET showed higher efficacy than ET alone in the metastatic setting (Giuliano et al., 2019; Schettini et al., 2021).

In 2009 Baselga et al. evaluated the efficacy of the mTOR inhibitor everolimus in 270 postmenopausal women with operable HR+/HER2- BC, who were randomly assigned to receive 4 months of NET with letrozole and either everolimus or placebo (Baselga et al., 2009). The everolimus-based combination increased clinical response by palpation (68.1% vs. 59.1%, p=0.062, significant with alfa level 0.1), at the cost of higher toxicity (Baselga et al., 2009). Two trials involving stage I–III postmenopausal HR+/HER2- BC patients, investigated the addition of the α-selective PI3K-inhibitors taselisib and alpelisib to a NET strategy. The addition of taselisib to letrozole was associated with higher ORR compared to ET alone in all patients (50% vs. 39%, p=0.049) as well as in the phosphatidylinositol-3-kinase catalytic alpha (*PIK3CA*)-mutant subset (56% vs. 38% p=0.033), but no significant differences were observed in pCR between the two groups, with higher toxicity in the taselisib arm (Saura et al., 2019). Alpelisib in combination with letrozole did not improve ORR both in the overall (43% vs. 45%, respectively) and *PIK3CA*-mutant (63% vs. 61%, respectively) populations, with higher toxicity compared to ET alone and comparable low pCR rates in both arms. In addition, the decrease in Ki67 was similar across treatment arms and cohorts (Mayer et al., 2019). Considering poor results in tumor downstaging and pCR rates, along with unfavorable risk-benefit balance, mTOR- and PI3K-inhibitors do not seem to be a suitable therapeutic partner for ET in the neoadjuvant setting. Study results are resumed in Table 4.

Other trials exploring new drugs or combinations are currently ongoing (Table 5). Immunotherapy with anti-programmed death (PD)1/PD-ligand(PD-L)1 immune-checkpoint inhibitors are being studied in combination with NET. The ULTIMATE trial (NCT02997995) is an open label, phase 2 trial, investigating the use of anti–PD-L1 human monoclonal antibody durvalumab associated with AIs in patients with CD8 + T cell infiltration obtained with an immune-attractant. Similarly, the NCT03874325 trial is exploring the efficacy and the safety of the same combinations using the PEPI score after 6 months as a primary endpoint. The ImmunoADAPT trial (NCT03573648) is a pilot study of avelumab, palbociclib, and ET aiming to evaluate the number of patients with a response to treatment by breast magnetic resonance imaging (MRI). Moreover, other target agents, such as tyrosine kinase inhibitors, anti-vascular endothelial growth factor receptor (*VEGF*) and ROS proto-oncogene 1 (*ROS1)*-inhibitors are also under investigation. The rearranged during transfection (*RET*)-inhibitor lenvatinib, combined with ET, is being evaluated in the NCT02562118 trial, as preclinical studies showed a cross-talk between *RET* and ER which might have potential therapeutic implications(Spanheimer et al., 2014).

The ROSALINE trial (NCT04551495) is a neoadjuvant study focusing on the use of a *ROS1* inhibitor in combination with ET in ILC, as *ROS1*-inhibitors have been found to produce profound anti-tumor effects in multiple models of E-cadherin-defective BC. Furthermore, the NeoTEE phase 2 trial (NCT04465097) will assess the efficacy of tucidinostat, an oral subtype-selective histone deacetylase (HDAC)-inhibitor, in association to exemestane, following promising results in the advanced setting

Table 4
Clinical trials with CDK4/6-, mTOR- and PI3K-inhibitors in combination with endocrine agents in the neoadjuvant setting.

Clinical Trial Identifier	Study Design and menopausal status	Intervention/s	Duration	Primary Endpoint and results	Phase
Johnston S; 2019	307 Participants, randomized, multinational, postmenopausal	Letrozole + palbociclib (A) vs. letrozole (B)	14 w	CRR A 54.3% vs. B 49.5% (*P*=0.20) Ki-67 changes: A 2.2 (IQR: −3.4 to −1.0), B 4.1 (IQR: −5.0 to −2.8) (P<0.001)	2
Ma CX; 2017	50 Participants, randomized, postmenopausal	Anastrozole + palbociclib (A) vs. anastrozole (B)	5–6 mo	CCCA after 15 days: A 87%, B 26% (*P*<0.001)	3
Sa H; 2020	223 Participants, randomized, open-label, postmenopausal	Anastrozole + abemaciclib (A) vs. anastrozole (B)	14 w	Ki-67 reduction rate: A 92.6% (90%CI, −95 to −90) vs. B 63.2% (90% CI, −73 to −49)	2
Cottu P; 2018	106 Participants, randomized, prospective, parallel, non-comparative, postmenopausal	Letrozole + palbociclib (A) vs. letrozole (B)	19 w	RCB (0/1) A 7.7% (95%CI 0.4–14.9) vs. B 15% (95%CI 5.7–25.7)	2
Curigliano G; 2016	14 Participants, randomized, postmenopausal	Letrozole + ribociclib 400 mg (A) vs. letrozole + ribociclib 600 mg (B) vs. letrozole (C)	N/A	Ki-67 reduction rate A 96% (range 78–100%; n = 6), B 92% (range 75–100%; n = 3), C 69% (range 38–100%; n = 2)	2
Prat A; 2020	106 Participants, randomized, open-label, postmenopausal	Letrozole + ribociclib (A) vs. AC → Paclitaxel (B)	24 w	Low-ROR risk after surgery A 46.9% (95%CI 32·5–61·7) vs. B 46.1% (95%CI 32·9–61·5)	2
SOLTI Cooperative Research Group	530 Participants, non-randomized, open-label, pre/postmenopausal and men	Letrozole + ribociclib + /- GnRHa → Surgery → Letrozole + ribociclib + /- GnRHa for 2.5 years, then standard ET completion in PAM50 ROR-low (A), or adjuvant CT → Letrozole + ribociclib for 2.5 years, then standard ET completion in PAM50 ROR-med/high (B)	24 w	5-year DMFS in molecular responders (i.e. post-surgery ROR-low)	2
Chow LWC; 2018	20 Participants, open-label, single-arm, postmenopausal	Letrozole (A) + palbociclib (B)	16 w	CRR 85%; CR 40% (*P*<0.0001); PEPI score categories: 0 = 1 patient, 1–3 = 7 patients, >4 = 12 patients	2
Khan QJ; 2020	116 Participants, randomized, biomarker-based, postmenopausal	Letrozole + ribociclib (A) vs. letrozole (B)	24 w	PEPI score 0 after surgery: A 25.4% vs. B 25.8% (*P*=0.96)	2
Mayer AI; 2014	46 Participants, Interventional, single Group Assignment, Open Label, postmenopausal	Alpelisib (A), letrozole (B)	4–8 w	DLT, MTD (ongoing)	1
Baselga J; 2009	267 Participants, Interventional, Randomized, Parallel Assignment, postmenopausal	Letrozole + everolimus (A) vs. letrozole (B)	4 m	OR A 68.1% (95%CI 60.3–75.9) B 59.1% (95%CI 50.7–67.5), (*P*=0.0616)	2
Saura C; 2019	334 Participants, Interventional, Randomized, Parallel Assignment, postmenopausal	Letrozole + taselisib (A) vs. letrozole (B)	16 w	OR A 83 (50%) vs B 66 (39%); pCR A 2% vs B 1%	2

Legend. BCS: breast conservative surgery; CCCA: complete cell cycle arrest (Ki-67 <2.7%); CI: confidence interval; CRR: clinical response rate; CR: complete response; FEC: 5-fluorouracil, epirubicin and cyclophosphamide; DLT: Dose limiting toxicity; MTD: Maximum tolerated dose; N/A: not available; OR: overall response; w- weeks; mo: months; →: followed by; IQR: interquartile range; ROR: risk of recurrence; PEPI: preoperative endocrine prognostic index; RCB: residual cancer burden; RR: Response Rate; pCR: Pathologic Complete Response; med: medium; GnRHa: gonadotropin releasing hormone analogue; ET: endocrine therapy; CT: chemotherapy; DMFS: Distant Metastasis-Free Survival.

(Jiang et al., 2019).

Finally, as novel selective SERDs alternative to fulvestrant are showing promising efficacy results in metastatic HR+/HER2- BC trials, there is raising interest in assessing the efficacy of these drugs in the neoadjuvant setting, as well (Garcia-Fructuoso et al., 2022).

5. Conclusions

Based on the available evidence, NET may be considered a less toxic but equally effective alternative to NACT, leading to satisfactory rates of BCS and conversions from inoperable to operable HR+/HER2- BC, as well as a way to provide researchers with invaluable translational research opportunities. Duration should be of 3–4 months and preferred agents should be AIs, with a GnRHa in premenopausal women and men. Patients with higher hormone receptor levels and lower Ki67 (<10%) might be more suitable for NET. However, robust conclusions to guide an appropriate patient selection cannot be drawn yet. Moreover, the optimal strategy to evaluate tumor response is still an open challenge, both in terms of timing (i.e. when to carry out the first revaluation and frequency of further controls) and methodology (i.e. physical exploration with calliper, breast ultrasounds or magnetic resonance, mammography). Furthermore, differently from HER2+ and TN BC, pCR has failed to predict prognosis for HR+/HER2- BC, and other biomarkers are needed to identify patients potentially candidate to further escalated or de-escalated strategies in the post-neoadjuvant setting. In this context, the use of genomic and/or transcriptomic approaches (e.g. gene expression assays, gene-expression-based signatures etc.) coupled with the identification of tissue-based and clinical parameters (e.g. on-treatment and post-surgery Ki67, basal and post-surgery ER, post-surgery residual tumor burden etc.), as well as baseline, on-treatment and post-surgical ctDNA levels, could help better selecting patients for NET or NACT and/or tailoring post-surgical therapeutic strategies. Results from the ADAPT trial seem to support this approach (Dowsett, 2022; Nitz et al., 2022). Other results from several phase II and III ongoing studies are eagerly awaited to better elucidate the role of NET in the clinical practice scenario (Spring et al., 2016b).

Funding

This work was partly supported thanks to the contribution of Ricerca Corrente by the Italian Ministry of Health within the research line: Precision, gender and ethnicity-based medicine and geroscience:

Table 5
Selected ongoing trials with targeted agents in neoadjuvant setting.

Experimental Therapeutic Class	Clinical Trial Identifier	Study Design	Intervention/s	Setting	Primary Endpoint	Phase	Status
	NCT02997995 (Ultimate)	61 Participants, Interventional, Single-arm assignment	Durvalumab	Post-menopausal women with Stage II-III, HR+HER2- BC	pCR	2	Completed
Immunotherapy	NCT03573648 (ImmunoADAPT)	40 Participants, Randomized, Parallel Assignment, Open label	Avelumab + Palbociclib + ET	Stage II-III HR+HER2- BC	CCR	2	Recruting
	NCT03874325	17 Participants, Interventional, Sequential Assignment, Open Label	Durvalumab +ET	Stage II-III HR+HER2- BC	PEPI score	2	Active, not recruiting
SERDs	NCT04797728 (ELIPSE)	24 Participants, Interventional, Single-arm assignment	Elacestrant	Early Stage HR+HER2- BC	Ki67≤2.7%	1	Recruting
	NCT04436744 (coopERA Breast Cancer)	221 Participant, Randomized, Parallel Assignmen, Open label	Giredestrant, anastrozole, palbociclib	Early Stage HR+HER2- BC	Ki-67 score	2	Active, not recruting
	NCT04647487, (EMBER-2)	90 Participant, Randomized, Parallel Assignment, Open label	LY3484356	Stage I-III HR+HER2- BC	Change in Estrogen Receptor Expression	1	Recruiting
	NCT04191382 (AMEERA-4)	150 Participants, Interventional Randomized Parallel Assignment	Amcenestrant	Stage I-III HR+HER2- BC	Change in Ki67	2	Terminated
Tyrosine Kinase inhibitors	NCT02562118	40 Participants, Interventional, Single Group Assignment, Open Label	Lenvatinib	Stage II-III HR+HER2- BC	CRR	1/2	Recruiting
ROS inhibitors	NCT04551495 (ROSALINE)	45 Participants, Interventional, Single Group Assignment, Open Label	Entrectinib	Multifocal unilateral or bilateral breast HR+HER2- LABC	RCB	2	Recruiting
Histone deacetylase inhibitors	NCT04465097 NeoTEE	30 Participants, Interventional, Single Group Assignment, Open Label	Tucidinostat	Stage II-III HR+HER2- BC	ORR evaluated by MRI	2	Recruiting

Legend. CCR: Clinical Complete Response; CRR: Clinical response rate, CRR; HR: hormone receptors; + : positive; -: negative; LABC: Locally advanced breast cancer; BC: breast cancer; ORR: Objective Response Rate; RCB: Residual cancer burden; MRI: magnetic resonance imaging; ET: endocrine therapy; PEPI: preoperative endocrine prognostic index; SERD: selective estrogen receptor degraders.

genetic-molecular mechanisms in the development, characterization and treatment of tumors.

Author contributions

MS, FS and UDG conceived the study. MS, BC and AV performed the revision of the literature. MS, BC, AV, FS, MM and UDG wrote the first manuscript draft. All authors revised and approved the final submitted manuscript.

Declaration of Competing Interest

MP, received advisory board fees from Novartis. GB received honoraria or speaker's fee from Novartis, GSK, Eli-Lilly, Pfizer, Astra-Zeneca, Roche and Genetic Spa. UDG received honoraria for advisory boards or invited speaker fees from Pfizer, BMS, MSD, PharmaMar, Astellas, Bayer, Ipsen, Novartis, Roche, Clovis, AstraZeneca, institutional research grants from AstraZeneca, Sanofi and Roche. The other authors declare no conflict of interests.

Acknowledgements

FS received a European Society for Medical Oncology (ESMO) Fellowship – Translational and the 2021 BBVA Foundation/Hospital Clinic of Barcelona Joan Rodés - Jose Baselga Advanced Research Contract in Oncology. However, any views, opinions, findings, conclusions, or recommendations expressed in this material are those solely of the author(s) and do not necessarily reflect those of ESMO, BBVA Foundation/Hospital Clinic of Barcelona. Figure 1 realized with BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.

Author contributions

MS, FS and UDG conceived the study. MS, BC and AV performed the revision of the literature. MS, BC, AV, FS, MM and UDG wrote the first manuscript draft. All authors revised and approved the final submitted manuscript.

References

Abrial, C., Mouret-Reynier, M.A., Curé, H., Feillel, V., Leheurteur, M., Lemery, S., Le Bouëdec, G., Durando, X., Dauplat, J., Chollet, P., 2006. Neoadjuvant endocrine therapy in breast cancer. Breast (Edinb., Scotl.) 15, 9–19. https://doi.org/10.1016/J.BREAST.2005.07.009.

Allevi, G., Strina, C., Andreis, D., Zanoni, V., Bazzola, L., Bonardi, S., Foroni, C., Milani, M., Cappelletti, M.R., Gussago, F., Aguggini, S., Giardini, R., Martinotti, M., Fox, S.B., Harris, A.L., Bottini, A., Berruti, A., Generali, D., 2013. Increased pathological complete response rate after a long-term neoadjuvant letrozole treatment in postmenopausal oestrogen and/or progesterone receptor-positive breast cancer. Br. J. Cancer 108, 1587–1592. https://doi.org/10.1038/BJC.2013.151.

Arpino, G., Bianchini, G., Malorni, L., Zambelli, A., Puglisi, F., Del Mastro, L., Colleoni, M., Montemurro, F., Bianchi, G.V., Paris, I., Allegrini, G., Tamberi, S., Cazzaniga, M.E., Orditura, M., Zamagni, C., Grasso, D., Benelli, M., Callari, M., Benfante, A., De Laurentiis, M., 2022. Circulating tumor DNA (ctDNA) and serum thymidine kinase 1 activity (TKa) matched dynamics in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor 2–negative (HER2-) advanced breast cancer (ABC) treated in first-line (1L) with ribociclib (RIB) and letrozole (LET) in the BioItaLEE trial, 1012–1012 JCO 40. https://doi.org/10.1200/JCO.2022.40.16_suppl.1012.

Barker, A.D., Sigman, C.C., Kelloff, G.J., Hylton, N.M., Berry, D.A., Esserman, L.J., 2009. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin. Pharmacol. Ther. 86, 97–100. https://doi.org/10.1038/CLPT.2009.68.

Baselga, J., Semiglazov, V., Van Dam, P., Manikhas, A., Bellet, M., Mayordomo, J., Campone, M., Kubista, E., Greil, R., Bianchi, G., Steinseifer, J., Molloy, B., Tokaji, E.,

Gardner, H., Phillips, P., Stumm, M., Lane, H.A., Dixon, J.M., Jonat, W., Rugo, H.S., 2009. Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 27, 2630–2637. https://doi.org/10.1200/JCO.2008.18.8391.

Bear, H.D., 2010. Neoadjuvant chemotherapy for operable breast cancer: individualizing locoregional and systemic therapy. Surg. Oncol. Clin. North Am. 19, 607–626. https://doi.org/10.1016/J.SOC.2010.04.001.

Bear, H.D., Wan, W., Robidoux, A., Rubin, P., Limentani, S., White, R.L., Granfortuna, J., Hopkins, J.O., Oldham, D., Rodriguez, A., Sing, A.P., 2017. Using the 21-gene assay from core needle biopsies to choose neoadjuvant therapy for breast cancer: a multicenter trial. J. Surg. Oncol. 115, 917–923. https://doi.org/10.1002/JSO.24610.

Buono, G., Schettini, F., Perri, F., Arpino, G., Bianco, R., Criscitiello, C., De Placido, S., Giuliano, M., 2018. The impact of translational research in breast cancer care: can we improve the therapeutic scenario. Anti-Cancer Agents Med. Chem. 18, 832–836. https://doi.org/10.2174/1871520617666171103105247.

Burstein, H.J., Curigliano, G., Thürlimann, B., Weber, W.P., Poortmans, P., Regan, M.M., Senn, H.J., Winer, E.P., Gnant, M., Aebi, S., André, F., Barrios, C., Bergh, J., Bonnefoi, H., Bretel Morales, D., Brucker, S., Burstein, H., Cameron, D., Cardoso, F., Carey, L., Chua, B., Ciruelos, E., Colleoni, M., Curigliano, Giuseppe, Delaloge, S., Denkert, C., Dubsky, P., Ejlertsen, B., Fitzal, F., Francis, P., Galimberti, V., Gamal El Din Mohamed Mahmoud, H., Garber, J., Gnant, Michael, Gradishar, W., Gulluoglu, B., Harbeck, N., Huang, C.S., Huober, J., Ilbawi, A., Jiang, Z., Johnston, S., Lee, E.S., Loibl, S., Morrow, M., Partridge, A., Piccart, M., Poortmans, Philip, Prat, A., Regan, M., Rubio, I., Rugo, H., Rutgers, E., Sedlmayer, F., Semiglazov, V., Senn, Hans Joerg, Shao, Z., Spanic, T., Tesarova, P., Thürlimann, Beat, Tjulandin, S., Toi, M., Trudeau, M., Turner, N., Vaz Luis, I., Viale, G., Watanabe, T., Weber, Walter, Winer, P., Eric, P., Xu, B., 2021a. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann. Oncol.: Off. J. Eur. Soc. Med. Oncol. 32, 1216–1235. https://doi.org/10.1016/J.ANNONC.2021.06.023.

Burstein, H.J., Curigliano, G., Thürlimann, B., Weber, W.P., Poortmans, P., Regan, M.M., Senn, H.J., Winer, E.P., Gnant, M., Panelists of the St Gallen Consensus Conference, 2021b. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann. Oncol. 32, 1216–1235. https://doi.org/10.1016/j.annonc.2021.06.023.

Cailleux, F., Agostinetto, E., Lambertini, M., Rothé, F., Wu, H.-T., Balcioglu, M., Kalashnikova, E., Vincent, D., Viglietti, G., Gombos, A., Papagiannis, A., Veys, I., Awada, A., Sethi, H., Aleshin, A., Larsimont, D., Sotiriou, C., Venet, D., Ignatiadis, M., 2022. Circulating tumor DNA after neoadjuvant chemotherapy in breast cancer is associated with disease relapse. JCO Precis. Oncol., e2200148 https://doi.org/10.1200/PO.22.00148.

Cain, H., Macpherson, I.R., Beresford, M., Pinder, S.E., Pong, J., Dixon, J.M., 2017. Neoadjuvant therapy in early breast cancer: treatment considerations and common debates in practice. Clin. Oncol. 29, 642–652. https://doi.org/10.1016/J.CLON.2017.06.003.

Carbognin, L., Simbolo, M., Cali, A., Vicentini, C., Delfino, P., Sperduti, I., Fassan, M., Schettini, F., Dieci, M.V., Griguolo, G., Pilotto, S., Fiorio, E., Arpino, G., Guarneri, V., De Placido, S., Conte, P., Manfrin, E., Brunelli, M., Scambia, G., Scarpa, A., Tortora, G., Bria, E., 2020. Targeted next-generation sequencing identifies genomic abnormalities potentially driving the prognosis of early-stage invasive lobular breast carcinoma patients stratified according to a validated clinico-pathological model-NC-ND license. Breast (http://creativecommons.org/licenses/by-nc-nd/4.0/). The Breast. https://doi.org/10.1016/j.breast.2020.01.034.

Cardoso, F., Kyriakides, S., Ohno, S., Penault-Llorca, F., Poortmans, P., Rubio, I.T., Zackrisson, S., 2019. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up †. https://doi.org/10.1093/annonc/mdz173.

Cardoso, F., Kyriakides, S., Ohno, S., Penault-Llorca, F., Poortmans, P., Rubio, I.T., Zackrisson, S., Senkus, E., 2019a. Early breast cancer: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Oncol.: Off. J. Eur. Soc. Med. Oncol. 30, 1194–1220. https://doi.org/10.1093/ANNONC/MDZ173.

Cardoso, F., Kyriakides, S., Ohno, S., Penault-Llorca, F., Poortmans, P., Rubio, I.T., Zackrisson, S., Senkus, E., 2019b. Early breast cancer: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Oncol.: Off. J. Eur. Soc. Med. Oncol. 30, 1194–1220. https://doi.org/10.1093/ANNONC/MDZ173.

Cardoso, F., van't Veer, Bogaerts, L.J., Slaets, J., Viale, L., Delaloge, G., Pierga, S., Brain, J.-Y., Causeret, E., DeLorenzi, S., Glas, M., Golfinopoulos, A.M., Goulioti, V., Knox, T., Matos, S., Meulemans, E., Neijenhuis, B., Nitz, P.A., Passalacqua, U., Ravdin, R., Rubio, P., Saghatchian, I.T., Smilde, M., Sotiriou, T.J., Stork, C., Straehle, L., Thomas, C., Thompson, G., van der Hoeven, A.M., Vuylsteke, J.M., Bernards, P., Tryfonidis, R., Rutgers, K., Piccart, M, E., 2016a. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N. England J. Med. 717–729. https://doi.org/10.1056/NEJMOA1602253/SUPPL_FILE/NEJMOA1602253_DISCLOSURES.PDF.

Cardoso, F., van't Veer, Bogaerts, L.J., Slaets, J., Viale, L., Delaloge, G., Pierga, S., Brain, J.-Y., Causeret, E., DeLorenzi, S., Glas, M., Golfinopoulos, A.M., Goulioti, V., Knox, T., Matos, S., Meulemans, E., Neijenhuis, B., Nitz, P.A., Passalacqua, U., Ravdin, R., Rubio, P., Saghatchian, I.T., Smilde, M., Sotiriou, T.J., Stork, C., Straehle, L., Thomas, C., Thompson, G., van der Hoeven, A.M., Vuylsteke, J.M., Bernards, P., Tryfonidis, R., Rutgers, K., Piccart, M, E., 2016b. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N. England J. Med. 717–729. https://doi.org/10.1056/NEJMOA1602253/SUPPL_FILE/NEJMOA1602253_DISCLOSURES.PDF.

Cataliotti, L., Buzdar, A.U., Noguchi, S., Bines, J., Takatsuka, Y., Petrakova, K., Dube, P., De Oliveira, C.T., 2006. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer: the Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) trial. Cancer 106, 2095–2103. https://doi.org/10.1002/CNCR.21872.

Chow, L.W.C., Morita, S., Chow, C.Y.C., Ng, W.K., Toi, M., 2018. Neoadjuvant palbociclib on ER+ breast cancer (N007): clinical response and EndoPredict's value. Endocr. -Relat. Cancer 25, 123–130. https://doi.org/10.1530/ERC-17-0396.

Cortazar, P., Zhang, L., Untch, M., Mehta, K., Costantino, J.P., Wolmark, N., Bonnefoi, H., Cameron, D., Gianni, L., Valagussa, P., Swain, S.M., Prowell, T., Loibl, S., Wickerham, D.L., Bogaerts, J., Baselga, J., Perou, C., Blumenthal, G., Blohmer, J., Mamounas, E.P., Bergh, J., Semiglazov, V., Justice, R., Eidtmann, H., Paik, S., Piccart, M., Sridhara, R., Fasching, P.A., Slaets, L., Tang, S., Gerber, B., Geyer, C.E., Pazdur, R., Ditsch, N., Rastogi, P., Eiermann, W., von Minckwitz, G., 2014a. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 384, 164–172. https://doi.org/10.1016/S0140-6736(13)62422-8.

Cortazar, P., Zhang, L., Untch, M., Mehta, K., Costantino, J.P., Wolmark, N., Bonnefoi, H., Cameron, D., Gianni, L., Valagussa, P., Swain, S.M., Prowell, T., Loibl, S., Wickerham, D.L., Bogaerts, J., Baselga, J., Perou, C., Blumenthal, G., Blohmer, J., Mamounas, E.P., Bergh, J., Semiglazov, V., Justice, R., Eidtmann, H., Paik, S., Piccart, M., Sridhara, R., Fasching, P.A., Slaets, L., Tang, S., Gerber, B., Geyer, C.E., Pazdur, R., Ditsch, N., Rastogi, P., Eiermann, W., Von Minckwitz, G., 2014b. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet (Lond., Engl.) 384, 164–172. https://doi.org/10.1016/S0140-6736(13)62422-8.

Cottu, P., D'Hondt, V., Dureau, S., Lerebours, F., Desmoulins, I., Heudel, P.E., Duhoux, F. P., Levy, C., Mouret-Reynier, M.A., Dalenc, F., Frenel, J.S., Jouannaud, C., Venat-Bouvet, L., Nguyen, S., Ferrero, J.M., Canon, J.L., Grenier, J., Callens, C., Gentien, D., Lemonnier, J., Vincent-Salomon, A., Delaloge, S., 2018. Letrozole and palbociclib versus chemotherapy as neoadjuvant therapy of high-risk luminal breast cancer. Ann. Oncol.: Off. J. Eur. Soc. Med. Oncol. 29, 2334–2340. https://doi.org/10.1093/ANNONC/MDY448.

Curigliano, G., Omez Pardo, G., Meric-Bernstam, P., Conte, F., Lolkema, P., Beck, M.P., Bardia, J.T., Martínez García, A., Penault-Llorca, M., Dhuria, F., Tang, S., Solovieff, Z., Miller, N., Di Tomaso, M., Hurvitz, S.A, E., 2016. Ribociclib plus letrozole in early breast cancer: a presurgical, window-of-opportunity study. Breast 28, 191–198. https://doi.org/10.1016/j.breast.2016.06.008.

Dixon, J.M., Renshaw, L., Dixon, J., Thomas, J., 2011. Invasive lobular carcinoma: response to neoadjuvant letrozole therapy. Breast Cancer Res. Treat. 130, 871–877. https://doi.org/10.1007/S10549-011-1735-4/TABLES/2.

Dixon, J.M., Renshaw, L., MacAskill, E.J., Young, O., Murray, J., Cameron, D., Kerr, G.R., Evans, D.B., Miller, W.R., 2008. Increase in response rate by prolonged treatment with neoadjuvant letrozole. Breast Cancer Res. Treat. 145–151. https://doi.org/10.1007/S10549-008-9915-6.

Dowsett, M., 2022. Testing endocrine response for managing primary estrogen-receptor positive breast cancer. J. Clin. Oncol. Epub Print. https://doi.org/10. 1200/JCO.22.00214.

Dowsett, M., Nielsen, T.O., A'Hern, R., Bartlett, J., Coombes, R.C., Cuzick, J., Ellis, M., Henry, N.L., Hugh, J.C., Lively, T., McShane, L., Paik, S., Penault-Llorca, F., Prudkin, L., Regan, M., Salter, J., Sotiriou, C., Smith, I.E., Viale, G., Zujewski, J.A., Hayes, D.F., 2011. Assessment of Ki67 in breast cancer: recommendations from the international Ki67 in breast cancer working group. J. Natl. Cancer Inst. 103, 1656–1664. https://doi.org/10.1093/JNCI/DJR393.

Dowsett, M., Smith, I.E., Ebbs, S.R., Dixon, J.M., Skene, A., A'Hern, R., Salter, J., Detre, S., Hills, M., Walsh, G., 2007. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. J. Natl. Cancer Inst. 99, 167–170. https://doi.org/10.1093/JNCI/DJK020.

Dubsky, P., Brase, J.C., Jakesz, R., Rudas, M., Singer, C.F., Greil, R., Dietze, O., Luisser, I., Klug, E., Sedivy, R., Bachner, M., Mayr, D., Schmidt, M., Gehrmann, M.C., Petry, C., Weber, K.E., Fisch, K., Kronenwett, R., Gnant, M., Filipits, M., 2013a. The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. Br. J. Cancer 109, 2959–2964. https://doi.org/10.1038/BJC.2013.671.

Dubsky, P., Brase, J.C., Jakesz, R., Rudas, M., Singer, C.F., Greil, R., Dietze, O., Luisser, I., Klug, E., Sedivy, R., Bachner, M., Mayr, D., Schmidt, M., Gehrmann, M.C., Petry, C., Weber, K.E., Fisch, K., Kronenwett, R., Gnant, M., Filipits, M., 2013b. The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. Br. J. Cancer 109, 2959–2964. https://doi.org/10.1038/BJC.2013.671.

Eiermann, W., Paepke, S., Appfelstaedt, J., Llombart-Cussac, A., Eremin, J., Vinholes, J., Mauriac, L., Ellis, M., Lassus, M., Chaudri-Ross, H.A., Dugan, M., Borgs, M., Semiglazov, V., 2001. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. Ann. Oncol.: Off. J. Eur. Soc. Med. Oncol. 12, 1527–1532. https://doi.org/10.1023/A:1013128213451.

Ellis, M.J., Coop, A., Singh, B., Mauriac, L., Llombert-Cussac, A., Jänicke, F., Miller, W.R., Evans, D.B., Dugan, M., Brady, C., Quebe-Fehling, E., Borgs, M., 2001. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a phase III randomized trial. J. Clin. Oncol. 19, 3808–3816. https://doi.org/10.1200/JCO.2001.19.18.3808.

Ellis, M.J., Suman, V.J., Hoog, J., Goncalves, R., Sanati, S., Creighton, C.J., DeSchryver, K., Crouch, E., Brink, A., Watson, M., Luo, J., Tao, Y., Barnes, M., Dowsett, M., Budd, G.T., Winer, E., Silverman, P., Esserman, L., Carey, L., Ma, C.X., Unzeitig, G., Pluard, T., Whitworth, P., Babiera, G., Guenther, J.M., Dayao, Z.,

Ota, D., Leitch, M., Olson, J.A., Allred, D.C., Hunt, K., 2017. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: Results from the American college of surgeons oncology group Z1031 trial (alliance. J. Clin. Oncol. 35, 1061–1069. https://doi.org/10.1200/JCO.2016.69.4406.

Ellis, M.J., Tao, Y., Luo, J., A'Hern, R., Evans, D.B., Bhatnagar, A.S., Chaudri Ross, H.A., Von Kameke, A., Miller, W.R., Smith, I., Eiermann, W., Dowsett, M., 2008. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J. Natl. Cancer Inst. 100, 1380–1388. https://doi.org/10.1093/JNCI/DJN309.

Filipits, M., Dubsky, P., Rudas, M., Greil, R., Balic, M., Bago-Horvath, Z., Singer, C.F., Hlauschek, D., Brown, K., Bernhisel, R., Kronenwett, R., Lancaster, J.M., Fitzal, F., Gnant, M., 2019a. Prediction of distant recurrence using endopredict among women with ER+, HER2- node-positive and node-negative breast cancer treated with endocrine therapy only. Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 25, 3865–3872. https://doi.org/10.1158/1078-0432.CCR-19-0376.

Filipits, M., Dubsky, P., Rudas, M., Greil, R., Balic, M., Bago-Horvath, Z., Singer, C.F., Hlauschek, D., Brown, K., Bernhisel, R., Kronenwett, R., Lancaster, J.M., Fitzal, F., Gnant, M., 2019b. Prediction of distant recurrence using endopredict among women with ER+, HER2- node-positive and node-negative breast cancer treated with endocrine therapy only. Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 25, 3865–3872. https://doi.org/10.1158/1078-0432.CCR-19-0376.

Filipits, M., Nielsen, T.O., Rudas, M., Greil, R., Stoger, H., Jakesz, R., Bago-Horvath, Z., Dietze, O., Regitnig, P., Gruber-Rossipal, C., Muller-Holzner, E., Singer, C.F., Mlineritsch, B., Dubsky, P., Bauernhofer, T., Hubalek, M., Knauer, M., Trapl, H., Fesl, C., Schaper, C., Ferree, S., Liu, S., Cowens, J.W., Gnant, M., 2014. The PAM50 risk-of-recurrence score predicts risk for late distant recurrence after endocrine therapy in postmenopausal women with endocrine-responsive early breast cancer. Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 20, 1298–1305. https://doi.org/10.1158/1078-0432.CCR-13-1845.

Fisher, B., Brown, A., Mamounas, E., Wieand, S., Robidoux, A., Margolese, R.G., Cruz, A. B., Fisher, E.R., Wickerham, D.L., Wolmark, N., DeCillis, A., Hoehn, J.L., Lees, A.W., Dimitrov, N.V., 1997. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from national surgical adjuvant breast and bowel project B-18. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 15, 2483–2493. https://doi.org/10.1200/JCO.1997.15.7.2483.

Garcia-Fructuoso, I., Gomez-Bravo, R., Schettini, F., 2022. Integrating new oral selective oestrogen receptor degraders in the breast cancer treatment. Curr. Opin. Oncol. 34, 635–642. https://doi.org/10.1097/CCO.0000000000000892.

Garcia-Murillas, I., Schiavon, G., Weigelt, B., Ng, C., Hrebien, S., Cutts, R.J., Cheang, M., Osin, P., Nerurkar, A., Kozarewa, I., Garrido, J.A., Dowsett, M., Reis-Filho, J.S., Smith, I.E., Turner, N.C., 2015. Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer. Sci. Transl. Med. 7 https://doi.org/10.1126/scitranslmed.aab0021.

Gianni, L., Pienkowski, T., Im, Y.-H., Roman, L., Tseng, L.-M., Liu, M.-C., Lluch, A., Staroslawska, E., de la Haba-Rodriguez, J., Im, S.-A., Pedrini, J.L., Poirier, B., Morandi, P., Semiglazov, V., Srimuninnimit, V., Bianchi, G., Szado, T., Ratnayake, J., Ross, G., Valagussa, P., 2012. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 13, 25–32. https://doi.org/10.1016/S1470-2045(11)70336-9.

Giuliano, M., Schettini, F., Rognoni, C., Milani, M., Jerusalem, G., Bachelot, T., De Laurentiis, M., Thomas, G., De Placido, P., Arpino, G., De Placido, S., Cristofanilli, M., Giordano, A., Puglisi, F., Pistilli, B., Prat, A., Del Mastro, L., Venturini, S., Generali, D., 2019. Endocrine treatment versus chemotherapy in postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer: a systematic review and network meta-analysis. Lancet Oncol. 20, 1360–1369. https://doi.org/10.1016/S1470-2045(19)30420-6.

Gnant, M., Filipits, M., Greil, R., Stoeger, H., Rudas, M., Bago-Horvath, Z., Mlineritsch, B., Kwasny, W., Knauer, M., Singer, C., Jakesz, R., Dubsky, P., Fitzal, F., Bartsch, R., Steger, G., Balic, M., Ressler, S., Cowens, J.W., Storhoff, J., Ferree, S., Schaper, C., Liu, S., Fesl, C., Nielsen, T.O., 2014. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. Ann. Oncol.: Off. J. Eur. Soc. Med. Oncol. 25, 339–345. https://doi.org/10.1093/ANNONC/MDT494.

Hammond, M.E.H., Hayes, D.F., Dowsett, M., Allred, D.C., Hagerty, K.L., Badve, S., Fitzgibbons, P.L., Francis, G., Goldstein, N.S., Hayes, M., Hicks, D.G., Lester, S., Love, R., Mangu, P.B., McShane, L., Miller, K., Osborne, C.K., Paik, S., Perlmutter, J., Rhodes, A., Sasano, H., Schwartz, J.N., Sweep, F.C.G., Taube, S., Torlakovic, E.E., Valenstein, P., Viale, G., Visscher, D., Wheeler, T., Williams, R.B., Wittliff, J.L., Wolff, A.C., 2010. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 28, 2784–2795. https://doi.org/10.1200/JCO.2009.25.6529.

Harris, L., Fritsche, H., Mennel, R., Norton, L., Ravdin, P., Taube, S., Somerfield, M.R., Hayes, D.F., Bast, R.C., 2007. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 25, 5287–5312. https://doi.org/10.1200/JCO.2007.14.2364.

Hurvitz, S.A., Martin, M., Press, M.F., Chan, D., Fernandez-Abad, M., Petru, E., Rostorfer, R., Guarneri, V., Huang, C.-S., Barriga, S., Wijayawardana, S., Brahmachary, M., Ebert, P.J., Hossain, A., Liu, J., Abel, A., Aggarwal, A., Jansen, V. M., Slamon, D.J., 2020. Potent cell-cycle inhibition and upregulation of immune response with abemaciclib and anastrozole in neoMONARCH, Phase II neoadjuvant study in HR þ /HER2 à breast cancer. Clin. Cancer Res. https://doi.org/10.1158/1078-0432.CCR-19-1425.

Ignatiadis, M., Sledge, G.W., Jeffrey, S.S., 2021. Liquid biopsy enters the clinic - implementation issues and future challenges. Nat. Rev. Clin. Oncol. 18, 297–312. https://doi.org/10.1038/s41571-020-00457-x.

Jiang, Z., Li, W., Hu, X., Zhang, Q., Sun, T., Cui, S., Wang, Shusen, Ouyang, Q., Yin, Y., Geng, C., Tong, Z., Cheng, Y., Pan, Y., Sun, Y., Wang, H., Ouyang, T., Gu, K., Feng, J., Wang, X., Wang, Shubin, Liu, T., Gao, J., Cristofanilli, M., Ning, Z., Lu, X., 2019. Tucidinostat plus exemestane for postmenopausal patients with advanced, hormone receptor-positive breast cancer (ACE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 20, 806–815. https://doi.org/10.1016/S1470-2045(19)30164-0.

Johnston, S., Puhalla, S., Wheatley, D., Ring, A., Barry, P., Holcombe, C., Boileau, J.F., Provencher, L., Robidoux, A., Rimawi, M., McIntosh, S.A., Shalaby, I., Stein, R.C., Thirlwell, M., Dolling, D., Morden, J., Snowdon, C., Perry, S., Cornman, C., Batten, L. M., Jeffs, L.K., Dodson, A., Martins, V., Modi, A., Kent Osborne, C., Pogue-Geile, K.L., Cheang, M.C.U., Wolmark, N., Julian, T.B., Fisher, K., MacKenzie, M., Wilcox, M., Bartlett, C.H., Koehler, M., Dowsett, M., Bliss, J.M., Jacobs, S.A., 2019. Randomized Phase II study evaluating palbociclib in addition to letrozole as neoadjuvant therapy in estrogen receptor-positive early breast cancer: PALLET trial. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 37, 178–189. https://doi.org/10.1200/JCO.18.01624.

Khan, Q.J., O'Dea, A., Bardia, A., Kalinsky, K., Wisinski, K.B., O'Regan, R., Yuan, Y., Ma, C.X., Jahanzeb, M., Trivedi, M.S., Spring, L., Makhoul, I., Wagner, J.L., Winblad, O., Amin, A.L., Blau, S., Crane, G.J., Elia, M., Hard, M., Sharma, P., 2020. Letrozole + ribociclib versus letrozole + placebo as neoadjuvant therapy for ER+ breast cancer (FELINE trial). https://doi.org/10.1200/JCO.2020.38.15_suppl.505 38, 505–505. https://doi.org/10.1200/JCO.2020.38.15_SUPPL.505.

Korde, L.A., Somerfield, M.R., Carey, L.A., Crews, J.R., Denduluri, N., Hwang, E.S., Khan, S.A., Loibl, S., Morris, E.A., Perez, A., Regan, M.M., Spears, P.A., Sudheendra, P.K., Symmans, W.F., Yung, R.L., Harvey, B.E., Hershman, D.L., 2021a. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 39, 1485–1505. https://doi.org/10.1200/JCO.20.03399.

Korde, L.A., Somerfield, M.R., Carey, L.A., Crews, J.R., Denduluri, N., Hwang, E.S., Khan, S.A., Loibl, S., Morris, E.A., Perez, A., Regan, M.M., Spears, P.A., Sudheendra, P.K., Symmans, W.F., Yung, R.L., Harvey, B.E., Hershman, D.L., 2021b. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. J. Clin. Oncol. 39, 1485–1505. https://doi.org/10.1200/JCO.20.03399.

Lænkholm, A.V., Jensen, M.B., Eriksen, J.O., Rasmussen, B.B., Knoop, A.S., Buckingham, W., Ferree, S., Schaper, C., Nielsen, T.O., Haffner, T., Kibøl, T., Talman, M.L.M., Jylling, A.M.B., Tabor, T.P., Ejlertsen, B., 2018. PAM50 risk of recurrence score predicts 10-year distant recurrence in a comprehensive danish cohort of postmenopausal women allocated to 5 years of endocrine therapy for hormone receptor-positive early breast cancer. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 36, 735–740. https://doi.org/10.1200/JCO.2017.74.6586.

Lena, E.Di, Hopkins, B., Wong, S.M., Meterissian, S., 2021. Delays in operative management of early-stage, estrogen receptorepositive breast cancer during the COVID-19 pandemic: a multi-institutional matched historical cohort study. Surgery. https://doi.org/10.1016/j.surg.2021.10.033.

Lerebours, F., Rivera, S., Mouret-Reynier, M.A., Alran, S., Venat-Bouvet, L., Kerbrat, P., Salmon, R., Becette, V., Bourgier, C., Cherel, P., Boussion, V., Balleyguier, C., Thibault, F., Lavau-Denes, S., Nabholz, J.M., Sigal, B., Trassard, M., Mathieu, M.C., Martin, A.L., Lemonnier, J., Mouret-Fourme, E., 2016. Randomized phase 2 neoadjuvant trial evaluating anastrozole and fulvestrant efficacy for postmenopausal, estrogen receptor–positive, human epidermal growth factor receptor 2–negative breast cancer patients: results of the UNICANCER CARMINA 02 French trial (UCBG 0609). Cancer 122, 3032–3040. https://doi.org/10.1002/CNCR.30143.

Ma, C.X., Gao, F., Luo, J., Northfelt, D.W., Goetz, M., Forero, A., Hoog, J., Naughton, M., Ademuyiwa, F., Suresh, R., Anderson, K.S., Margenthaler, J., Aft, R., Hobday, T., Moynihan, T., Gillanders, W., Cyr, A., Eberlein, T.J., Hieken, T., Krontiras, H., Guo, Z., Lee, M.V., Spies, N.C., Skidmore, Z.L., Griffith, O.L., Griffith, M., Thomas, S., Bumb, C., Vij, K., Huang Bartlett, C., Koehler, M., Al-Kateb, H., Sanati, S., Ellis, M.J., 2017. NeoPalAna: Neoadjuvant Palbociclib, a cyclin-dependent kinase 4/6 inhibitor, and anastrozole for clinical stage 2 or 3 estrogen receptor-positive breast cancer. Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 23, 4055–4065. https://doi.org/10.1158/1078-0432.CCR-16-3206.

Magbanua, M.J.M., Swigart, L.B., Wu, H.-T., Hirst, G.L., Yau, C., Wolf, D.M., Tin, A., Salari, R., Shchegrova, S., Pawar, H., Delson, A.L., DeMichele, A., Liu, M.C., Chien, A.J., Tripathy, D., Asare, S., Lin, C.-H.J., Billings, P., Aleshin, A., Sethi, H., Louie, M., Zimmermann, B., Esserman, L.J., van 't Veer, L.J., 2021. Circulating tumor DNA in neoadjuvant-treated breast cancer reflects response and survival. Ann. Oncol. 32, 229–239. https://doi.org/10.1016/j.annonc.2020.11.007.

Marczyk, M., Mrukwa, A., Yau, C., Wolf, D., Chen, Y.-Y., Balassanian, R., Nanda, R., Parker, B.A., Krings, G., Sattar, H., Zeck, J.C., Albain, K.S., Boughey, J.C., Liu, M.C., Elias, A.D., Clark, A.S., Venters, S.J., Shad, S., Basu, A., Asare, S.M., Buxton, M., Asare, A.L., Rugo, H.S., Perlmutter, J., DeMichele, A.M., Yee, D., Berry, D.A., Veer, L. V., Symmans, W.F., Esserman, L., Pusztai, L., Consortium, I.-S.P.Y., 2022. Treatment Efficacy Score-continuous residual cancer burden-based metric to compare neoadjuvant chemotherapy efficacy between randomized trial arms in breast cancer trials. Ann. Oncol. 33, 814–823. https://doi.org/10.1016/j.annonc.2022.04.072.

Martínez-Sáez, O., Pascual, T., Brasó-Maristany, F., Chic, N., González-Farré, B., Sanfeliu, E., Rodríguez, A., Martínez, D., Galván, P., Rodríguez, A.B., Schettini, F., Conte, B., Vidal, M., Adamo, B., Martínez, A., Muñoz, M., Moreno, R., Villagrasa, P., Salvador, F., Ciruelos, E.M., Faull, I., Odegaard, J.I., Prat, A., 2021. Circulating

tumor DNA dynamics in advanced breast cancer treated with CDK4/6 inhibition and endocrine therapy. NPJ Breast Cancer 7, 8. https://doi.org/10.1038/s41523-021-00218-8.

Masuda, N., Sagara, Y., Kinoshita, T., Iwata, H., Nakamura, S., Yanagita, Y., Nishimura, R., Iwase, H., Kamigaki, S., Takei, H., Noguchi, S., 2012. Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. Lancet Oncol. 13, 345–352. https://doi.org/10.1016/S1470-2045(11)70373-4.

Mayer, I.A., Prat, A., Egle, D., Blau, S., Alejandro Perez Fidalgo, J., Gnant, M., Fasching, P.A., Colleoni, M., Wolff, A.C., Winer, E.P., Singer, C.F., Hurvitz, S., Estevez, L.G., Van Dam, P.A., Kummel, S., Mundhenke, C., Holmes, F., Babbar, N., Charbonnier, L., Diaz-Padilla, I., Vogl, F.D., Sellami, D., Arteaga, C.L., 2019. A phase II randomized study of neoadjuvant letrozole plus alpelisib for hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer (NeoORB. Clin. Cancer Res. 25, 2975–2987. https://doi.org/10.1158/1078-0432.CCR-18-3160.

McDonald, B.R., Contente-Cuomo, T., Sammut, S.-J., Odenheimer-Bergman, A., Ernst, B., Perdigones, N., Chin, S.-F., Farooq, M., Mejia, R., Cronin, P.A., Anderson, K.S., Kosiorek, H.E., Northfelt, D.W., McCullough, A.E., Patel, B.K., Weitzel, J.N., Slavin, T.P., Caldas, C., Pockaj, B.A., Murtaza, M., 2019. Personalized circulating tumor DNA analysis to detect residual disease after neoadjuvant therapy in breast cancer. Sci. Transl. Med. 11, eaax7392. https://doi.org/10.1126/scitranslmed.aax7392.

Nitz, U.A., Gluz, O., Kümmel, S., Christgen, M., Braun, M., Aktas, B., Lüdtke-Heckenkamp, K., Forstbauer, H., Grischke, E.-M., Schumacher, C., Darsow, M., Krauss, K., Nuding, B., Thill, M., Potenberg, J., Uleer, C., Warm, M., Fischer, H.H., Malter, W., Hauptmann, M., Kates, R.E., Gräser, M., Würstlein, R., Shak, S., Baehner, F., Kreipe, H.H., Harbeck, N., 2022. Endocrine therapy response and 21-gene expression assay for therapy guidance in HR+/HER2– early breast cancer. J. Clin. Oncol. 21, 02759. https://doi.org/10.1200/JCO.21.02759.

Papakonstantinou, A., Gonzalez, N.S., Pimentel, I., Suñol, A., Zamora, E., Ortiz, C., Espinosa-Bravo, M., Peg, V., Vivancos, A., Saura, C., Villacampa, G., Oliveira, M., 2022. Prognostic value of ctDNA detection in patients with early breast cancer undergoing neoadjuvant therapy: a systematic review and meta-analysis. Cancer Treat. Rev. 104, 102362 https://doi.org/10.1016/j.ctrv.2022.102362.

Pennisi, A., Kieber-Emmons, T., Makhoul, I., Hutchins, L., 2016. Relevance of pathological complete response after neoadjuvant therapy for breast cancer. Breast Cancer.: Basic Clin. Res. 10, 103. https://doi.org/10.4137/BCBCR.S33163.

Prat, A., Lluch, A., Turnbull, A.K., Dunbier, A.K., Calvo, L., Albanell, J., De La Haba-Rodríguez, J., Arcusa, A., Chacón, J.I., Sánchez-Rovira, P., Plazaola, A., Muñoz, M., Paré, L., Parker, J.S., Ribelles, N., Jimenez, B., Bin Aiderus, A.A., Caballero, R., Adamo, B., Dowsett, M., Carrasco, E., Martín, M., Dixon, J.M., Perou, C.M., Alba, E., 2017. A PAM50-based chemoendocrine score for hormone receptor-positive breast cancer with an intermediate risk of relapse. Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 23, 3035–3044. https://doi.org/10.1158/1078-0432.CCR-16-2092.

Prat, A., Saura, C., Pascual, T., Hernando, C., Muñoz, M., Paré, L., González Farré, B., Fernández, P.L., Galván, P., Chic, N., González Farré, X., Oliveira, M., Gil-Gil, M., Arumi, M., Ferrer, N., Montaño, A., Izarzugaza, Y., Llombart-Cussac, A., Bratos, R., González Santiago, S., Martínez, E., Hoyos, S., Rojas, B., Virizuela, J.A., Ortega, V., López, R., Céliz, P., Ciruelos, E., Villagrasa, P., Gavilá, J., 2020. Ribociclib plus letrozole versus chemotherapy for postmenopausal women with hormone receptor-positive, HER2-negative, luminal B breast cancer (CORALLEEN): an open-label, multicentre, randomised, phase 2 trial. Lancet Oncol. 21, 33–43. https://doi.org/10.1016/S1470-2045(19)30786-7.

Quenel-Tueux, N., Debled, M., Rudewicz, J., MacGrogan, G., Pulido, M., Mauriac, L., Dalenc, F., Bachelot, T., Lortal, B., Breton-Callu, C., Madranges, N., De Lara, C.T., Fournier, M., Bonnefoi, H., Soueidan, H., Nikolski, M., Gros, A., Daly, C., Wood, H., Rabbitts, P., Iggo, R., 2015. Clinical and genomic analysis of a randomised phase II study evaluating anastrozole and fulvestrant in postmenopausal patients treated for large operable or locally advanced hormone-receptor-positive breast cancer. Br. J. Cancer 113, 585–594. https://doi.org/10.1038/BJC.2015.247.

Saura, C., Hlauschek, D., Oliveira, M., Zardavas, D., Jallitsch-Halper, A., de la Peña, L., Nuciforo, P., Ballestrero, A., Dubsky, P., Lombard, J.M., Vuylsteke, P., Castaneda, C. A., Colleoni, M., Santos Borges, G., Ciruelos, E., Fornier, M., Boer, K., Bardia, A., Wilson, T.R., Stout, T.J., Hsu, J.Y., Shi, Y., Piccart, M., Gnant, M., Baselga, J., de Azambuja, E., 2019. Neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with oestrogen receptor-positive, HER2-negative, early-stage breast cancer (LORELEI): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 20, 1226–1238. https://doi.org/10.1016/S1470-2045(19)30334-1.

Schettini, F., Brasó-Maristany, F., Kuderer, N.M., Prat, A., 2022. A perspective on the development and lack of interchangeability of the breast cancer intrinsic subtypes. NPJ Breast Cancer 8, 85. https://doi.org/10.1038/s41523-022-00451-9.

Schettini, F., Giudici, F., Giuliano, M., Cristofanilli, M., Arpino, G., Del Mastro, L., Puglisi, F., De Placido, S., Paris, I., De Placido, P., Venturini, S., De Laurentis, M., Conte, P., Juric, D., Llombart-Cussac, A., Pusztai, L., Prat, A., Jerusalem, G., Di Leo, A., Generali, D., 2020. Overall survival of CDK4/6-inhibitor-based treatments in clinically relevant subgroups of metastatic breast cancer: systematic review and meta-analysis. J. Natl. Cancer Inst. 112, 1089–1097. https://doi.org/10.1093/JNCI/DJAA071.

Schettini, F., Giuliano, M., Giudici, F., Conte, B., De Placido, P., Venturini, S., Rognoni, C., Leo, A., et al., 2021. Endocrine-based treatments in clinically-relevant subgroups of hormone receptor-positive/HER2-negative metastatic breast cancer: systematic review and meta-analysis. Cancers (Basel) 5, 20. https://doi.org/10.3390/cancers.

Schneeweiss, A., Chia, S., Hickish, T., Harvey, V., Eniu, A., Hegg, R., Tausch, C., Seo, J. H., Tsai, Y.-F., Ratnayake, J., McNally, V., Ross, G., Cortés, J., 2013. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA. Ann. Oncol. 24, 2278–2284. https://doi.org/10.1093/annonc/mdt182.

Semiglazov, V.F., Semiglazov, V.V., Dashyan, G.A., Ziltsova, E.K., Ivanov, V.G., Bozhok, A.A., Melnikova, O.A., Paltuev, R.M., Kletzel, A., Berstein, L.M., 2007. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer 110, 244–254. https://doi.org/10.1002/CNCR.22789.

Sestak, I., Cuzick, J., Dowsett, M., Lopez-Knowles, E., Filipits, M., Dubsky, P., Cowens, J. W., Ferree, S., Schaper, C., Fesl, C., Gnant, M., 2015. Prediction of late distant recurrence after 5 years of endocrine treatment: a combined analysis of patients from the Austrian breast and colorectal cancer study group 8 and arimidex, tamoxifen alone or in combination randomized trials using the PAM50 risk of recurrence score. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 33, 916–922. https://doi.org/10.1200/JCO.2014.55.6894.

Sestak, I., Martín, M., Dubsky, P., Kronenwett, R., Rojo, F., Cuzick, J., Filipits, M., Ruiz, A., Gradishar, W., Soliman, H., Schwartzberg, L., Buus, R., Hlauschek, D., Rodríguez-Lescure, A., Gnant, M., 2019a. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. Breast Cancer Res. Treat. 176, 377–386. https://doi.org/10.1007/S10549-019-05226-8.

Sestak, I., Martín, M., Dubsky, P., Kronenwett, R., Rojo, F., Cuzick, J., Filipits, M., Ruiz, A., Gradishar, W., Soliman, H., Schwartzberg, L., Buus, R., Hlauschek, D., Rodríguez-Lescure, A., Gnant, M., 2019b. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. Breast Cancer Res. Treat. 176, 377–386. https://doi.org/10.1007/S10549-019-05226-8.

Smith, I., Robertson, J., Kilburn, L., Wilcox, M., Evans, A., Holcombe, C., Horgan, K., Kirwan, C., Mallon, E., Sibbering, M., Skene, A., Vidya, R., Cheang, M., Banerji, J., Morden, J., Sidhu, K., Dodson, A., Bliss, J.M., Dowsett, M., 2020. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. Lancet Oncol. 21, 1443–1454. https://doi.org/10.1016/S1470-2045(20)30458-7.

Smith, I.E., Dowsett, M., Ebbs, S.R., Dixon, J.M., Skene, A., Blohmer, J.U., Ashley, S.E., Francis, S., Boeddinghaus, I., Walsh, G., 2005. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the immediate preoperative anastrozole, tamoxifen, or combined with tamoxifen (IMPACT) multicenter double-blind randomized trial. J. Clin. Oncol. 23, 5108–5116. https://doi.org/10.1200/JCO.2005.04.005.

Spanheimer, P.M., Park, J.M., Askeland, R.W., Kulak, M.V., Woodfield, G.W., De Andrade, J.P., Cyr, A.R., Sugg, S.L., Thomas, A., Weigel, R.J., 2014. Inhibition of RET increases the efficacy of antiestrogen and is a novel treatment strategy for luminal breast cancer. Clin. Cancer Res. 20, 2115–2125. https://doi.org/10.1158/1078-0432.CCR-13-2221.

Sparano, J.A., Gray, R.J., Makower, D.F., Pritchard, K.I., Albain, K.S., Hayes, D.F., Geyer, C.E., Dees, E.C., Goetz, M.P., Olson, J.A., Lively, T., Badve, S.S., Saphner, T.J., Wagner, L.I., Whelan, T.J., Ellis, M.J., Paik, S., Wood, W.C., Ravdin, P.M., Keane, M. M., Gomez Moreno, H.L., Reddy, P.S., Goggins, T.F., Mayer, I.A., Brufsky, A.M., Toppmeyer, D.L., Kaklamani, V.G., Berenberg, J.L., Abrams, J., Sledge, G.W., 2018. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N. Engl. J. Med. 379, 111–121. https://doi.org/10.1056/NEJMOA1804710/SUPPL_FILE/NEJMOA1804710_DISCLOSURES.PDF.

Spring, L.M., Gupta, A., Reynolds, K.L., Gadd, M.A., Ellisen, L.W., Isakoff, S.J., Moy, B., Bardia, A., 2016a. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. JAMA Oncol. 2, 1477–1486. https://doi.org/10.1001/JAMAONCOL.2016.1897.

Spring, L.M., Gupta, A., Reynolds, K.L., Gadd, M.A., Ellisen, L.W., Isakoff, S.J., Moy, B., Bardia, A., 2016b. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. JAMA Oncol. 2, 1477–1486. https://doi.org/10.1001/JAMAONCOL.2016.1897.

Suman, V.J., Ellis, M.J., Ma, C.X., 2015. The ALTERNATE trial: assessing a biomarker driven strategy for the treatment of post-menopausal women with ER+/Her2-invasive breast cancer. Chin. Clin. Oncol. 4. https://doi.org/10.3978/J.ISSN.2304-3865.2015.09.01.

Symmans, W.F., Peintinger, F., Hatzis, C., Rajan, R., Kuerer, H., Valero, V., Assad, L., Poniecka, A., Hennessy, B., Green, M., Buzdar, A.U., Singletary, S.E., Hortobagyi, G. N., Pusztai, L., 2007a. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J. Clin. Oncol. 25, 4414–4422. https://doi.org/10.1200/JCO.2007.10.6823.

Symmans, W.F., Peintinger, F., Hatzis, C., Rajan, R., Kuerer, H., Valero, V., Assad, L., Poniecka, A., Hennessy, B., Green, M., Buzdar, A.U., Singletary, S.E., Hortobagyi, G. N., Pusztai, L., 2007b. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 25, 4414–4422. https://doi.org/10.1200/JCO.2007.10.6823.

Symmans, W.F., Wei, C., Gould, R., Yu, X., Zhang, Y., Liu, M., Walls, A., Bousamra, A., Ramineni, M., Sinn, B., Hunt, K., Buchholz, T.A., Valero, V., Buzdar, A.U., Yang, W., Brewster, A.M., Moulder, S., Pusztai, L., Hatzis, C., Hortobagyi, G.N., 2017. Long-term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype. J. Clin. Oncol. 35, 1049–1060. https://doi.org/10.1200/JCO.2015.63.1010.

Thomssen, C., Balic, M., Harbeck, N., Gnant, M., 2021. St. Gallen/Vienna 2021: a brief summary of the consensus discussion on customizing therapies for women with early breast cancer. review article. Breast Care 16, 135–143. https://doi.org/10.1159/000516114.

Ueno, T., Saji, S., Masuda, N., Iwata, H., Kuroi, K., Sato, N., Takei, H., Yamamoto, Y., Ohno, S., Yamashita, H., Hisamatsu, K., Aogi, K., Sasano, H., Toi, M., 2019. Changes in recurrence score by neoadjuvant endocrine therapy of breast cancer and their prognostic implication. ESMO Open 4, 476. https://doi.org/10.1136/ESMOOPEN-2018-000476.

Wolf, D.M., Yau, C., Wulfkuhle, J., Brown-Swigart, L., Gallagher, R.I., Lee, P.R.E., Zhu, Z., Magbanua, M.J., Sayaman, R., O'Grady, N., Basu, A., Delson, A., Coppé, J.P., Lu, R., Braun, J., Investigators, I.-S.P.Y.2, Asare, S.M., Sit, L., Matthews, J.B., Perlmutter, J., Hylton, N., Liu, M.C., Pohlmann, P., Symmans, W.F., Rugo, H.S., Isaacs, C., DeMichele, A.M., Yee, D., Berry, D.A., Pusztai, L., Petricoin, E.F., Hirst, G. L., Esserman, L.J., van 't Veer, L.J., 2022. Redefining breast cancer subtypes to guide treatment prioritization and maximize response: predictive biomarkers across 10 cancer therapies. Cancer Cell 40 (609–623), e6. https://doi.org/10.1016/j.ccell.2022.05.005.

Yau, C., Osdoit, M., van der Noordaa, M., Shad, S., Wei, J., de Croze, D., Hamy, A.-S., Laé, M., Reyal, F., Sonke, G.S., Steenbruggen, T.G., van Seijen, M., Wesseling, J., Martín, M., Del Monte-Millán, M., López-Tarruella, S., Trial Consortium, I.-S.P.Y. 2, Boughey, J.C., Goetz, M.P., Hoskin, T., Gould, R., Valero, V., Edge, S.B., Abraham, J. E., Bartlett, J.M.S., Caldas, C., Dunn, J., Earl, H., Hayward, L., Hiller, L., Provenzano, E., Sammut, S.-J., Thomas, J.S., Cameron, D., Graham, A., Hall, P., Mackintosh, L., Fan, F., Godwin, A.K., Schwensen, K., Sharma, P., DeMichele, A.M., Cole, K., Pusztai, L., Kim, M.-O., van 't Veer, Esserman, L.J., Symmans, W.F, L.J., 2022. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. In: Lancet Oncol., 23, pp. 149–160. https://doi.org/10.1016/S1470-2045(21)00589-1.

Marianna Sirico: MD and Medical Oncologist Specialist currently working at the IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori" (Meldola, Italy). She is involved in patient care and clinical research, with main focus on breast cancer.

Alessandra Virga: biologist, PhD student and researcher involved in preclinical and translational research on uro-gynecological cancers at the IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori" (Meldola, Italy).

Benedetta Conte: MD, Medical Oncologist Specialist and PhD student within the European Union program Marie Curie Action. She is involved in clinical and translational research at the Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS) (Barcelona, Spain) under the supervision of Dr. Aleix Prat. Her main research focus is on breast cancer and the discovery and development of early prognostic and predictive biomarkers.

Milena Urbini: biologist and researcher with 10 year-experience on high-throughput molecular analysis of solid tumors. She has worked on the molecular characterization of rare sarcomas and now her research field includes the identification of diagnostic, predictive and prognostic markers for genitourinary, thoracic and gastric tumors. She is specialized in the use of next-generation sequencing (NGS) for genome, whole-exome, whole-transcriptome analysis on both tissue and liquid biopsy specimens.

Paola Ulivi: is a senior researcher at the Biosciences Laboratory of the IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori" (Meldola, Italy) with a long-standing experience in the areas of molecular biology, translational research and molecular diagnostics for different types of solid tumors. Her main field of research is that of translational research on lung cancer and tumors of gastrointestinal and uro-gynecological tract. Her main expertise regards the study of diagnostic, prognostic and predictive biomarkers in tissue and biological fluids. In particular, in the last years, her researches have been principally related to the discovery of primary and secondary resistance mechanisms to targeted therapy and immunotherapy in solid tumors.

Caterina Gianni: MD, and Medical Oncologist in training, currently attending the second year of Specialization School in Medical Oncology at the IRCSS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori" (Meldola, Italy).

Filippo Merloni: MD and Medical Oncologist Specialist, currently working at the Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" (Meldola, Italy). He is actively involved in clinical and research activities concerning breast cancer, systemic therapies (chemotherapy, immunotherapy, target therapy) administration in Day Hospital and clinical trials management.

Michela Palleschi: MD and Medical Oncologist Specialist at the Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" (Meldola, Italy). Her major clinical and research interests include breast cancer and phase I trials. She is currently performing a PhD program in Oncology, Hematology and Pathology at University of Bologna. Her research focus is based on the identification of predictive biomarkers of treatment response and the study of tumor microenvironment. She has published original several papers in peer-reviewed journals, and is an active member of many medical societies.

Marco Gasperoni: MD and breast surgeon, he is currently working at the Breast Surgical Unit of the Morgagni-Pierantoni Hospital, AUSL Romagna (Forlì-Ravenna, Italy). He has a second level university Master's Degree in Oncoplastic Surgery and is fully dedicated to the surgical treatment of breast cancer patient.

Annalisa Curcio: MD and breast surgeon, Chief of the Breast Surgical Unit of the Morgagni-Pierantoni Hospital, AUSL Romagna (Forlì-Ravenna, Italy). She is a board member of the "Associazione Nazionale Italiana Senologi Chirughi – ANISC".

Debjani Saha: Researcher with experience in various fields of Bioscience, including Molecular Biology, Cell Biology, Microbiology and Immunology. She is currently involved in a PhD program at the Imperial College London under the supervision of Professor Luca Magnani.

Giuseppe Buono: MD and Medical Oncologist Specialist. He is currently working at the Department of Breast and Thoracic Oncology of the National Cancer Institute, Fondazione G. Pascale (Naples, Italy). He is an active member of the Italian Cooperative Research Group on Breast Cancer (GIM) and his prominent research interests is represented by the relation between early breast cancer outcomes, obesity and metabolism. His clinical and research activities are mostly focused on breast cancer.

Montserrat Muñoz: MD, PhD and Medical Oncologist Specialist. Since 1992 she has been working in the Breast Unit of the Hospital Clinic de Barcelona (Spain), which she leads since several years. Moreover she has been appointed as head *ad interim* of the Medical Oncology Department of the same hospital during the last year. Dr. Muñoz carries out an important clinical research work. Her current fields of interest are those related to biological markers of response to treatment and new therapies in breast cancer.

Ugo de Giorgi: MD, PhD and Medical Oncologist Specialist at the Department of Medical Oncology of the IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori" (Meldola, Italy). He is the current head of the Uro-Gynecologic, Breast and Oncologic High Dose Innovative Treatments Units. Winner of numerous research awards and scholarships, which allowed him to experience in the Netherlands and the United States, he is the author of over 350 international publications, has the qualification as Full Professor of Oncology in Italy, and is a lecturer at several Specialization Schools of the University of Ferrara. He holds positions of responsibility in oncological scientific societies including AIOM, IGG, Meet-uro, where he was recently appointed as President.

Francesco Schettini: MD, PhD in Newest Biomedical and Surgical Treatments and Medical Oncologist Specialist at the Medical Oncology Department of the Hospital Clinic of Barcelona (Spain), with a position of clinical scientist. He is currently working within the Translational Genomics and Targeted Therapies in Solid Tumors research group led by Aleix Prat at the IDIBAPS (Barcelona, Spain) as post-doc researcher, with focus on breast cancer, especially hormone receptor-positive disease, intrinsic subtypes, HER2-low breast tumors and biomarker discovery for the prediction of immunotherapy benefit in solid tumors. He is adjunct professor at the University of Barcelona (Spain) and has published more than 40 international research articles in prestigious peer reviewed Journals.