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Accelerating progress to innovation for patients: Trial design and risk stratification☆

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ABSTRACT

In early breast cancer, we integrate risk stratification and trial design, together with subtype, to focus on clinical questions in specific patient populations. In the past, trials enrolled an "all-comers," broadly-defined population. More recently, trials enroll low-to intermediate-risk populations for whom testing strategies to de-escalate therapy are appropriate, or intermediate-to high-risk populations for whom testing additional and novel therapeutic strategies are needed. For example, in patients who have triple-negative breast cancer, the presence of residual disease after neoadjuvant therapy has become an approach to risk stratification for defining a trial population testing approaches to adjuvant therapy. In patients with hormone receptor positive, HER2-negative breast cancer, trials testing the addition of adjuvant CDK4/6 inhibitors to standard endocrine therapy have enrolled intermediate-to high-risk populations using various definitions and with heterogeneous results. Results of the recent generation of clinical trials testing systemic therapy for early breast cancer provide an opportunity to learn and improve future trial designs and accelerate progress to innovation for patients.
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1. Introduction

In early breast cancer, we integrate risk stratification and trial design, according to breast cancer subtype, to answer questions about the care of specific patient populations. Recent trials are generally designed to enroll low-risk populations for whom testing strategies to de-escalate systemic therapy are appropriate; or intermediate-to high-risk populations for whom additional and novel therapeutic strategies are needed. For patients diagnosed with early-stage triple-negative breast cancer (TNBC), the addition of immune checkpoint inhibitors (ICI) to neoadjuvant chemotherapy regimens have shown early favorable results [1,2]. For patients diagnosed with hormone receptor-positive (HR+), HER2-negative early breast cancer, several trials have added-on adjuvant CDK4/6 inhibitors to standard endocrine therapy, using various criteria to define an intermediate-to-high risk trial population, with mixed results [3–5]. The early results of these trials raise questions to consider for future trial design and risk stratification.

2. Trials in populations who receive neoadjuvant therapy

For patients who have early HER2+ or TNBC, the response to neoadjuvant systemic therapy, as measured by absence or presence of residual invasive disease in the breast and lymph nodes (i.e., pathologic complete response (pCR)), has become an approach to risk stratification for defining a trial population for testing adjuvant therapy regimens. The meta-analysis of Cortazar et al. [6] and other research have demonstrated the prognostic role of pCR vs. residual disease after neoadjuvant systemic therapy for risk stratification, based upon chemotherapeutic regimens (with HER2-directed therapy in the HER2+ population). Might the addition of ICIs to neoadjuvant regimens for TNBC affect this strategy?

One approach to trial design enrolls patients after neoadjuvant therapy is complete and post-treatment surgical specimens are assessed for pCR or residual disease. This response to neoadjuvant therapy is used as eligibility for clinical trials testing questions about either escalation of adjuvant therapy for patients with residual disease, or perhaps de-escalation of adjuvant therapy for patients who have pCR. In such trials, post-surgery invasive disease-free survival (iDFS) is frequently used as the primary endpoint. The clinical utility of this design for adjuvant therapy escalation was demonstrated in the TNBC cohort of the Create-X trial [7] and the KATHERINE trial for HER2+ breast cancer [8].

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Both trials enrolled patients with residual disease, and meaningful absolute improvements in 3-year iDFS relative to the control treatment groups were observed with escalation of therapy (83% vs 74% 3-year iDFS in Create-X; 88.3% vs 77.0% 3-year iDFS in KATHERINE).

A second approach to trial design enrolls previously-untreated patients, who are randomly allocated to experimental or control neoadjuvant therapies, which may or may not continue after surgery as adjuvant therapy [9]. The post-treatment surgical specimens are assessed for pCR or presence of residual disease, which is frequently used as the primary – or a co-primary –endpoint of the trial; it has not however had a risk stratification role in the trial design, with respect to post-surgery survival endpoints such as iDFS. Three ongoing randomized, double-blind placebo-controlled phase 3 trials use this approach to investigate the efficacy of ICI with chemotherapy in the treatment of stage II/III TNBC [1,2,10]. All three trials extend the ICI (or placebo) administration into the adjuvant setting to complete approximately 1 year of ICI therapy.

The smaller (n = 333) IMpassion031 has the more frequent approach to this design, with pCR as primary endpoint, but the trial design was not statistically powered for the secondary survival endpoints [1]. The larger Keynote-522 and GeparDouze trials (n = 1174 and 1520, respectively) both designed the trials using co-primary endpoints of pCR and event-free survival (EFS; 2,10). At the first interim analysis of the Keynote-522 trial, an absolute 13.6% increase in pCR rate was reported among the first 602 randomized patients (64.8% vs. 51.2% pCR among chemotherapy + pembrolizumab vs chemotherapy + placebo groups, respectively) [2]. At the second interim analysis, when 104 EFS events had been reported after 15.5 months median follow-up (327 events expected for final analysis of EFS), an improvement in 18-month EFS was reported (91.3% vs 85.3% 18-mo EFS) [2]. According to a February 2021 briefing for a US FDA Oncologic Drugs Advisory Committee (ODAC) meeting, at the third interim analysis the results may attenuate with longer follow-up [11], but these early results raise optimism of a potential role for ICIs in high-risk early TNBC.

Regardless of what the mature EFS results of Keynote-522 and other trials will show, these trials testing the addition of ICI to neoadjuvant chemotherapy, followed by adjuvant ICI to compete 1 year of ICI therapy, raise questions about what the introduction of ICIs might mean for risk stratification and trial design for early-stage TNBC. In future trials, if ICI-based chemo-immunotherapy were to become a standard neoadjuvant regimen, would the presence of residual disease after neoadjuvant chemo-immunotherapy still have clinical utility for risk stratification and trial eligibility? Do we need a trial designed to provide reliable estimation of the treatment effects upon post-surgery iDFS within subgroups who have pCR or residual disease, taking into account that the subgroups would be defined by the post-randomization pCR outcome? How will we design the next trials, given that the three ongoing trials have adjuvant ICI administration but we do not know if the adjuvant therapy was needed? Should trials that include an adjuvant component of therapy be designed to also determine whether or not the additional adjuvant administration is beneficial? We do not know yet whether ICIs will be approved in this setting of high-risk TNBC, but these first trials give us a lot to think about for future risk stratification and trial design.

3. Trials testing escalation of adjuvant therapy for HR+/HER2-negative breast cancer

For the large population of patients who have HR+/HER2-negative early breast cancer, survival outcomes with current endocrine therapy approaches are very heterogeneous and risk stratification relies on anatomic staging. With recent clinical trials in this population, including those testing CDK4/6 inhibitors, the questions are raised of how we should define the higher-risk patient population that should be enrolled in trials testing escalation of adjuvant endocrine therapy, and what pattern of outcomes we expect to observe with standard adjuvant ET?

In this population of patients with HR+/HER2-negative early breast cancer, disease outcomes after chemo-endocrine or endocrine therapy vary widely according to AJCC anatomic staging [12] or other measures of recurrence risk [13,14]. We recognize also that the patterns of the timing of recurrence events – in other words the hazard functions for disease-free survival endpoint events – vary by risk. For example, those patients with stage III cancers have highest hazard in the first years after diagnosis; in contrast, those patients with stage IIA cancers have slowly but steadily increasing hazard functions over time [15]. The hazard functions for post-menopausal women persist more over time, as non-breast cancer disease-free survival events start to contribute more than for pre-menopausal patients.

The ongoing trials testing the addition of CDK4/6 inhibitors to adjuvant endocrine therapy have targeted patients at intermediate- to high-risk of recurrence. Across four trials [3–5,16], the specific eligibility criteria to define this population have varied, and the enrolled patients referred to these trials have varied (Table 1). The trials all included pre- and postmenopausal women and men, which is different from the population of the past generation of clinical trials testing aromatase inhibitor vs. tamoxifen or extended adjuvant endocrine therapy. The PALLAS and NATALEE trials have taken the approach to include patients with lower-risk stage IIA disease, and thus included lymph node-negative disease and smaller tumors when 1 to 3 positive lymph nodes. In both trials, there was a limit to the number of patients with stage IIA disease. The PENELOPE-B trial was a different approach to defining the population, enrolling patients who had residual disease after receiving neoadjuvant chemotherapy. As a practical feature of trial entry, all the trials allowed patients to have started adjuvant endocrine therapy prior to enrollment, for varied duration according to the eligibility criterion for entry after definitive surgery or completion of adjuvant chemotherapy and/or radiotherapy. Unexpectedly, despite substantial differences between PALLAS and MonarchE eligibility, the statistical designs had similar estimates of 5-year iDFS for the standard-of-care endocrine therapy control arms (83.5% and 82.5%, respectively) and a lower estimate (approximately 75%) in NATALEE. Unsurprisingly, the PENELOPE-B trial had the lowest estimate, of 77% 3-year iDFS (64.7% 5-year iDFS) with endocrine therapy alone.

The three trials with results reported to date [3–5] enrolled patients with a median age of approximately 50 years old (Table 1). The distribution of anatomic stage and positive lymph nodes reflected expected differences based upon the eligibility criteria. The PENELOPE-B cohort had highest-risk features; and the MonarchE cohort had higher-risk features than the cohort enrolled in PALLAS. I commend the PALLAS study team for creating a *post-hoc* clinical low/high-risk subgroup variable, in which high-risk approximates the MonarchE eligibility criteria, and therefore helps to align the two endocrine therapy control arms for interpreting these two trials (PALLAS reported 59% of patients having clinical high-risk). In their execution, each of the four trials increased enrollment, 3 of 4 with unplanned substantial sample size increases of approximately 1000 patients – including an increase in MonarchE in order to decrease trial duration. Across PALLAS, MonarchE and NATALEE, the statistical designs planned a primary analysis after approximately 400 iDFS events (approximately 7.5-8.5% of patients); notably the smaller PENELOPE-B trial planned the primary analysis after 23% of patients had experienced iDFS events, which implies longer follow-

Table 1
HR+/HER2-negative adjuvant ET + CDK4/6 inhibitor trials: eligible and enrolled populations, statistical designs, and numbers of iDFS events and control group iDFS observed at time of primary report.

Trial:	PALLAS	MonarchE	NATALEE	PENELOPE-B
Eligible				
Population	Premenopausal, postmenopausal, male	Premenopausal, postmenopausal, male	Premenopausal, postmenopausal, male	Premenopausal, postmenopausal
Stage	IIA*, IIB, III (*limit 20%)	N+, high-risk	IIA, IIB, III (limit ~40% II)	No pCR after NACT; CPS-EG≥3; or CPS-EG 2 & ypN+
LN negative (N0)	N0 & T2 (IIA*) N0 & T3/4	n/a	N0 & T2 & G3 N0 & T2 & G2 & (Ki67 ≥ 20% or high MGA) N0 & T3/4	ypN0 & cIIB/IIIA, ypT1-4 & G3; or cIIIB/C, ypT1-4 & G3; or cIIIB/C, ypT2-4 & G1/2
LN positive	N1 & T0/1 (IIA*) N1 & T2/3/4 N2/N3	N1 & (T3/4 or G3 or Ki67 ≥ 20%); N2/N3	N1 & T0/1/2 (II*) N1 & T3/4 N2/N3	ypN1; ypN2/3 (exc. cI/IIA, ypN1/2 & G1/2)
Entry	Post CT/RT; ≤12 m from diagnosis; ≤6 m adjuvant ET	Post CT/RT; ≤16 m from surgery; ≤3 m adjuvant ET	Post CT/RT; ≤18 m from diagnosis; ≤12 m from start ET	Post-NACT; <16 weeks from surgery; <16 weeks adjuvant ET
ET control group iDFS expected[a]	5yr 83.5% (3yr 89.9%)	5yr 82.5% (2yr 92.6%)	5yr ~75%	(5yr 64.7%) 3yr 77%
Enrolled				
Age, median	52 yrs	51 yrs	(not yet reported)	49 yrs
Stage IIA/IIB/III	18/33/49% [b]	12/14/74%		–
N[b] **(N2/N3)**	87% (37%)	100% (60%)		? (50% ypN2 or ypN3)
Grade 3	28%	38%		47%
Mo. prior ET;	?	?		89.4% started
Mo. from surgery;	?	?		?
Prior CT/RT	82.5%/89%	95% (37% NACT)/95%		100% NACT/?
Statistical Design				
Plan/actual number of patients;	5600/5760 Increase from 4600	4580/5637 Increase from 3580 (to decrease duration)	5000/? Increase from 4000	1250/1250 Increase from 1100 (adaptive design)
Change				
iDFS events (% of # plan), 85% power	469 (8.4%)	390 (8.5%)	375 (7.5%)	290 (23%)
Anticipated HaR	0.75	0.73	0.73	0.685
At analysis				
iDFS events	351 @ 24 m MFU	323 @ 15.5 m MFU 395 @ 19.1 m MFU	–	308 @ 52 m MFU
ET control group iDFS observed	2yr 93.2% 3yr 88.5% (83.6% clin high-risk)	2yr 89% [c]		2yr 84.0% 3yr 77.7% 4yr 72.4%

Abbreviations: LN = lymph node; Nx = nodal status and Tx = tumor size per AJCC staging; pCR = pathologic complete response; NACT = neoadjuvant chemotherapy; Gx = grade x; CT = chemotherapy; RT = radiotherapy; ET = endocrine therapy; m = months; yr = year; iDFS = invasive disease-free survival; HaR = hazard ratio. MGA = multigene assay. MFU = median follow-up.

[a] Estimates at different timepoints assume exponential distribution of iDFS.

[b] PALLAS reported 59% clinical high-risk, which approximates MonarchE eligibility.

[c] MonarchE, observed iDFS at 2yrs reported as 88.7% after 15.5 m MFU and 89.3% after 19.1 m MFU.

up until reporting.

The PALLAS and MonarchE trials reported early, based upon interim analysis results after 24 and 15.5 months median follow-up, respectively [3,4], with a subsequent update of MonarchE results presented at the 2020 SABCS based upon the targeted number of iDFS events after 19.1 months median follow-up ([17]; Table 1). In the PALLAS control group, the estimated 3-year iDFS of 88.5% was slightly lower than the expected 89.9%; whereas in MonarchE, the estimated 2-year iDFS of approximately 89% in the control ET arm was much lower than the expected 92.6% 2-year iDFS. It contradicts our conventional wisdom to see that clinical trial patients fared *worse* than anticipated. However, based upon eligibility criteria and enrollment characteristics, it was likely the *expected* iDFS rate in the MonarchE statistical design that was too high. Finally, it is instructive to note that the clinical high-risk subgroup of PALLAS was reported to have 3-year iDFS of 83.6%, which is probably a good estimate of what will be observed in MonarchE at 3 years, suggesting comparable outcomes amongst the two ET control arms.

Where do we go from here with planning adjuvant ET trials? First, we must recognize that adjuvant trials testing the addition of CDK4/6 inhibitor to standard ET differ from our last generations of adjuvant ET trials. The trials had a mix of premenopausal and postmenopausal women and men having a median age of approximately 50 years, and were limited to a majority of high-risk, HER2-negative breast cancers. This necessitates updating our expectation about disease outcomes over time. It may be that we need also to update our approach to trial design, as the contributions of the dual objectives of treatment—reducing very early recurrence, i.e., high hazard in years 0–3, and reducing recurrence over lifetime, i.e., lower persistent hazard years 5–10 beyond—are different when enrolling a majority high-risk population than when enrolling an all-comers HR+/HER-negative population. We have previously focused on the long-term, persistent hazard of recurrence and later separation of Kaplan-Meier curves estimating the distributions of iDFS over time; the very early events and potential early treatment effects play a more critical role. The PENELOPE-B results should give us pause [5] to learn from this generation of trials. Further examination of the patterns of recurrence (i.e., iDFS hazard functions) of the ET control arms in these trials would provide valuable insight to resetting our expectations and planning future trials. Going forward, review of the targeted patient cohort for these trials, whether we can change our hypothesis testing strategy, and whether we can improve upon anatomic risk for risk stratification, is warranted for adjuvant ET trials.

4. Conclusions

The recent results of trials testing the addition of neoadjuvant + adjuvant ICIs to neoadjuvant chemotherapy for TNBC and of trials testing the addition of CDK4/6 inhibitor to standard adjuvant ET, have not—or maybe not yet—changed standards of care. We can learn from this generation of trials to improve future trial designs and accelerate progress to innovation for patients.

Declaration of competing interest

Dr Regan reports grants and non-financial support for IBCSG clinical trials from Novartis, Pfizer, Ipsen, TerSera, Merck, Ferring, Pierre Fabre, Roche, AstraZeneca, Bristol Myers Squibb; research grants (to institution) from Bayer and Bristol Myers Squibb; personal fees and non-financial support from Bristol Myers Squibb; personal fees from Tolmar Pharmaceuticals, all outside the submitted work.

References

[1] Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, Koehler A, Sohn J, Iwata H, Telli ML, Ferrario C, Punie K, Penault-Llorca F, Patel S, Duc AN, Liste-Hermoso M, Maiya V, Molinero L, Chui SY, Harbeck N. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet 2020;396(10257):1090–100. https://doi.org/10.1016/S0140-6736(20)31953-X. Epub 2020 Sep 20. PMID: 32966830.

[2] Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R, O'Shaughnessy J. KEYNOTE-522 investigators. Pembrolizumab for early triple-negative breast cancer. N Engl J Med 2020;382(9):810–21. https://doi.org/10.1056/NEJMoa1910549. PMID: 32101663.

[3] Mayer EL, Dueck AC, Martin M, Rubovszky G, Burstein HJ, Bellet-Ezquerra M, Miller KD, Zdenkowski N, Winer EP, Pfeiler G, Goetz M, Ruiz-Borrego M, Anderson D, Nowecki Z, Loibl S, Moulder S, Ring A, Fitzal F, Traina T, Chan A, Rugo HS, Lemieux J, Henao F, Lyss A, Antolin Novoa S, Wolff AC, Vetter M, Egle D, Morris PG, Mamounas EP, Gil-Gil MJ, Prat A, Fohler H, Metzger Filho O, Schwarz M, DuFrane C, Fumagalli D, Theall KP, Lu DR, Bartlett CH, Koehler M, Fesl C, DeMichele A, Gnant M. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2021;22(2):212–22. https://doi.org/10.1016/S1470-2045(20)30642-2. Epub 2021 Jan 15. PMID: 33460574.

[4] Johnston SRD, Harbeck N, Hegg R, Toi M, Martin M, Shao ZM, Zhang QY, Martinez Rodriguez JL, Campone M, Hamilton E, Sohn J, Guarneri V, Okada M, Boyle F, Neven P, Cortés J, Huober J, Wardley A, Tolaney SM, Cicin I, Smith IC, Frenzel M, Headley D, Wei R, San Antonio B, Hulstijn M, Cox J, O'Shaughnessy J, Rastogi P, , monarchE Committee Members, Investigators. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE). J Clin Oncol 2020;38(34):3987–98. https://doi.org/10.1200/JCO.20.02514. Epub 2020 Sep 20. PMID: 32954927; PMCID: PMC7768339.

[5] Loibl S, Marmé F, Martin M, Untch M, Bonnefoi H, Kim SB, Bear H, McCarthy N, Melé Olivé M, Gelmon K, García-Sáenz J, Kelly CM, Reimer T, Toi M, Rugo HS, Denkert C, Gnant M, Makris A, Koehler M, Huang-Bartelett C, Lechuga Frean MJ, Colleoni M, Werutsky G, Seiler S, Burchardi N, Nekljudova V, von Minckwitz G. Palbociclib for residual high-risk invasive HR-positive and HER2-negative early breast cancer-the penelope-B trial. J Clin Oncol 2021: JCO2003639. https://doi.org/10.1200/JCO.20.03639. Epub ahead of print. PMID: 33793299.

[6] Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P, Swain SM, Prowell T, Loibl S, Wickerham DL, Bogaerts J, Baselga J, Perou C, Blumenthal G, Blohmer J, Mamounas EP, Bergh J, Semiglazov V, Justice R, Eidtmann H, Paik S, Piccart M, Sridhara R, Fasching PA, Slaets L, Tang S, Gerber B, Geyer Jr CE, Pazdur R, Ditsch N, Rastogi P, Eiermann W, von Minckwitz G. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384(9938):164–72. https://doi.org/10.1016/S0140-6736(13)62422-8. Epub 2014 Feb 14. Erratum in: Lancet. 2019 Mar 9;393(10175):986. PMID: 24529560.

[7] Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, Kuroi K, Im SA, Park BW, Kim SB, Yanagita Y, Ohno S, Takao S, Aogi K, Iwata H, Jeong J, Kim A, Park KH, Sasano H, Ohashi Y, Toi M. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 2017;376(22):2147–59. https://doi.org/10.1056/NEJMoa1612645. PMID: 28564564.

[8] von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, Wolmark N, Rastogi P, Schneeweiss A, Redondo A, Fischer HH, Jacot W, Conlin AK, Arce-Salinas C, Wapnir IL, Jackisch C, DiGiovanna MP, Fasching PA, Crown JP, Wülfing P, Shao Z, Rota Caremoli E, Wu H, Lam LH, Tesarowski D, Smitt M, Douthwaite H, Singel SM, Geyer Jr CE. KATHERINE investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019;380(7):617–28. https://doi.org/10.1056/NEJMoa1814017. Epub 2018 Dec 5. PMID: 30516102.

[9] Pathological complete response in neoadjuvant treatment of high-risk early stage breast cancer: use as an endpoint to support accelerated approval. ReVision 2020;1. April 2021, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pathological-complete-response-neoadjuvant-treatment-high-risk-early-stage-breast-cancer-use.

[10] Geyer Jr CE, Loibl S, Rastogi P, Seiler S, Costantino JP, Nekljudova V, Cortazar P, Lucas PC, Denkert C, Mamounas EP, Jackish C, Wolmark N. A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy (NAC) with atezolizumab or placebo in patients (pts) with triple negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo: NSABP B-59/GBG 96-GeparDouze. Cancer Res 2020;80(4 suppl). https://doi.org/10.1158/1538-7445.SABCS19-OT2-04-08. Abstract OT-2-04-08.

[11] Oncologic Drugs Advisory Committee (ODAC). Combined FDA and applicant ODAC briefing document. https://www.fda.gov/media/145654/download; 2021.

[12] Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, et al., editors. AJCC cancer staging manual. eighth ed. Springer International Publishing: American Joint Commission on Cancer; 2017 April 2021 https://cancerstaging.org/references-tools/deskreferences/Pages/Breast-Cancer-Staging.aspx.

[13] Viale G, Regan MM, Dell'Orto P, Mastropasqua MG, Maiorano E, Rasmussen BB, MacGrogan G, Forbes JF, Paridaens RJ, Colleoni M, Láng I, Thürlimann B, Mouridsen H, Mauriac L, Gelber RD, Price KN, Goldhirsch A, Gusterson BA, Coates AS. BIG 1-98 Collaborative and International Breast Cancer Study Groups. Which patients benefit most from adjuvant aromatase inhibitors? Results using a composite measure of prognostic risk in the BIG 1-98 randomized trial. Ann Oncol 2011;22(10):2201–7. https://doi.org/10.1093/annonc/mdq738. Epub 2011 Feb 18. PMID: 21335417; PMCID: PMC3179413.

[14] Regan MM, Francis PA, Pagani O, Fleming GF, Walley BA, Viale G, Colleoni M, Láng I, Gómez HL, Tondini C, Pinotti G, Price KN, Coates AS, Goldhirsch A, Gelber RD. Absolute benefit of adjuvant endocrine therapies for premenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative early breast cancer: TEXT and SOFT trials. J Clin Oncol 2016;34(19):2221–31. https://doi.org/10.1200/JCO.2015.64.3171. Epub 2016 Apr 4. PMID: 27044936; PMCID: PMC4962708.

[15] Colleoni M, Sun Z, Price KN, Karlsson P, Forbes JF, Thürlimann B, Gianni L, Castiglione M, Gelber RD, Coates AS, Goldhirsch A. Annual hazard rates of recurrence for breast cancer during 24 Years of follow-up: results from the international breast cancer study group trials I to V. J Clin Oncol 2016;34(9):927–35. https://doi.org/10.1200/JCO.2015.62.3504. Epub 2016 Jan 19. PMID: 26786933; PMCID: PMC4933127.

[16] Slamon DJ, Fasching PA, Patel R, Verma S, Hurvitz SA, Chia SKL, Crown J, Martin M, Barrios CL, Spera G, Lopez C, Hor I, Pelov D, Hughes G, Nawinne M, Hortobagyi GN. NATALEE: phase III study of ribociclib (RIBO) + endocrine therapy (ET) as adjuvant treatment in hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) early breast cancer (EBC). J Clin Oncol 2019;37(15_suppl):TPS597.

[17] O'Shaughnessy JA, Johnston S, Harbeck N, Toi M, Im Y-H, Reinsch M, Shao Z, Lehtinen PL, Huang C-S, Tryakin A, Goetz M, Rugo HS, Senkus E, Testa L, Andersson M, Tamura K, Steger GG, Del Mastro L, Cox J, Forrester T, Sherwood S, Li X, Wei R, Martin M, Rastogi P. Primary outcome analysis of invasive disease-free survival for monarchE: abemaciclib combined with adjuvant endocrine therapy for high risk early breast cancer. In: San antonio breast cancer symposium; 2020. Abstract GS1-01.