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Prediction of severe neutropenia and diarrhoea in breast cancer patients treated with abemaciclib

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A B S T R A C T

Introduction: Neutropenia and diarrhoea are common and potentially serious adverse events associated with abemaciclib in advanced breast cancer (ABC), and the risk factors have been minimally explored. The study aimed to develop clinical prediction tools that allow personalized predictions of neutropenia and diarrhoea following abemaciclib initiation.

Materials and methods: Data was pooled from MONARCH 1, 2 and 3 trials investigating abemaciclib. Cox proportional hazard analysis was used to assess the association between pre-treatment clinicopathological data and grade ≥3 diarrhoea and neutropenia occurring within the first 365 days of abemaciclib use.

Results: Older age was associated with increased risk of grade ≥3 diarrhoea [HR [95%CI] for age > 70: 1.72 [1.14–2.58]; P = 0.009]. A clinical prediction tool for abemaciclib induced grade ≥3 neutropenia was optimally defined by race, ECOGPS and white blood cell count. Large discrimination between subgroups was observed; the highest risk subgroup had a 64% probability of grade ≥3 neutropenia within the first 365 days of abemaciclib (150 mg twice daily) + fulvestrant/NSAI, compared to 5% for the lowest risk subgroup.

Conclusion: The study identified advanced age as significantly associated with an increased risk of abemaciclib induced grade ≥ 3 diarrhoea. A clinical prediction tool, defined by race, ECOGPS and pre-treatment white blood cell count, was able to discriminate subgroups with significantly different risks of grade ≥3 neutropenia following abemaciclib initiation. The tool may enable improved interpretation of personalized risks and the risk-benefit ratio of abemaciclib.

1. Introduction

Hormone receptor-positive/human epidermal growth factor 2-negative (HR+/HER2-) BC represents nearly two-thirds of all breast cancer diagnosis [1,2]. Abemaciclib is a novel cyclin-dependent kinase (CDK) 4/6 reversible inhibitor that is used in the treatment of HR+/HER2-advanced BC (ABC) [3]. Current guidelines support the use of abemaciclib as a first-line therapy either in combination with a non-steroidal aromatase inhibitor (NSAI) or fulvestrant in patients with HR+/HER2- ABC [4,5]. Safety data emerging from the MONARCH 1, 2 and 3 clinical trials have identified diarrhoea and neutropenia (characterised by low neutrophil count) as key side effects associated with abemaciclib use [6,7]. Diarrhoea was experienced by the majority of the patients taking abemaciclib, either as a monotherapy (90%) [8], or in combination with fulvestrant (86%) [9] or NSAI (81%) [10]. Further, neutropenia was the most commonly reported severe (grade ≥ 3) adverse event in patients treated with abemaciclib, either as monotherapy (27%) [8], or in combination with fulvestrant (27%) [9] or NSAI (21%) [10].

The regulatory approval [11] and existing literature [12] present limited information about risk factors associated with developing diarrhoea and neutropenia in patients initiating abemaciclib. Development of clinical prediction models of diarrhoea and neutropenia using routinely collected clinicopathological data following abemaciclib therapy may assist clinicians in providing personalized toxicity risks. Valid prediction models can also enable clinicians to understand patients needing increased monitoring or

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preemptive strategies to manage toxicities – ultimately allowing patients to remain on beneficial treatments for longer [13,14].

The study aimed to develop clinical prediction models that allow personalized predictions of diarrhoea and neutropenia following abemaciclib initiation.

2. Materials and Methods

2.1. Patient population

Individual participant data (IPD) from Eli Lilly sponsored clinical trials MONARCH 1 [NCT02102490][8], MONARCH 2 [NCT02107703][7,9] and MONARCH 3 [NCT02246621][10,15] was utilized in this secondary analysis study. Data was accessed according to Eli Lilly policy and has been made available through Vivli, Inc (www.vivli.org). Secondary analysis of anonymized IPD was exempted from review by the Southern Adelaide Local Health Network, Office for Research and Ethics as it was classified as minimal risk research.

MONARCH 1 is a phase 2 single-arm clinical trial including patients with HR+/HER2- ABC enrolled to 200 mg of abemaciclib twice daily [8]. MONARCH 2 is a phase 3 clinical trial including patients with HR+/HER2- ABC randomized (1:2) to either placebo/abemaciclib (200 mg twice daily on initiation for some patients who then underwent mandatory dose reduction to 150 mg twice daily; all other patients dosed 150 mg twice daily) in combination with fulvestrant (500 mg on day 1 and 15 of cycle 1, and on day 1 of all subsequent 28-day cycles) [7,9]. MONARCH 3 is a phase 3 clinical trial including patients with HR+/HER2- ABC randomized (1:2) to either placebo/abemaciclib (150 mg twice daily) in combination with a nonsteroidal aromatase inhibitor (1 mg of anastrozole or 2.5 mg of letrozole once daily on every day of the 28-day cycle) [10,15].

Predictors and Outcomes.

Adverse events were reported in all trials using NCI CTCAE (Common Terminology Criteria for Adverse Events) version 4.0 [8,7,9,10,15]. Primary assessed outcomes were the development of abemaciclib induced (as reported by the study investigators) grade ≥ 3 diarrhoea and grade ≥ 3 neutropenia occurring within 365 days of therapy initiation.

Assessed pre-treatment variables were selected based on availability, prior evidence, and biological plausibility. Assessed pre-treatment variables included age (years), ECOG performance status (ECOGPS), race (Asian or Non-Asian), weight (kg), body mass index (BMI), liver metastasis, bilirubin count, alkaline phosphatase count, albumin count, white blood cell count, neutrophil count, aspartate aminotransferase count, prior neoadjuvant/adjuvant endocrine therapy or chemotherapy, and concomitant use of antidiarrhoeals or opioids.

2.2. Statistical analysis

Univariable Cox proportional hazard analysis was used to assess the association between pre-treatment variables and abemaciclib induced toxicities. Associations were reported as hazard ratios (HR) with 95% confidence intervals (CI). Statistical significance was set at a threshold of $P < 0.05$ and was determined via the likelihood ratio test. Continuous variables were categorized based on model fit, observed non-linearity, prior evidence, and clinically interpretable cut-points. All analyses were stratified by treatment arm and abemaciclib dose (150 mg and 200 mg). Prediction performances were assessed via the concordance statistic (*c*-statistic).

Multivariable prediction models were developed using a stepwise forward inclusion, backwards deletion process. On forward inclusion, variables were included based on statistical significance and the greatest improvement in the *c*-statistic at each step. On backwards deletion, variables were excluded if they did not increase the *c*-statistic by 0.01. The backwards elimination process was conducted with a focus on selecting the minimal number of predictors that maintained prediction performance. To facilitate clinical use, final multivariable prediction models were converted into a toxicity risk scoring tool with the variable coefficients scaled to a point score. The tool was internally validated using machine learning. Specifically, the potential for model overfitting and robustness of variable importance were assessed using a random forest with a 10 fold cross-validation, repeated 10 times, approach [16]. Kaplan-Meier analysis was used for plotting and estimating probabilities. All data analysis was conducted using R version 3.6.2.

3. Results

3.1. Patient population

Data was available from 900 patients. Pre-treatment patient characteristics are presented in Supplementary Table 1. Median follow-up was 21 months [95% CI: 20–22] in MONARCH 1, 18 months [18–19] in MONARCH 2, and 26 months [26–27] in MONARCH 3.

Of the 900 patients, 750 (82%) experienced diarrhoea from abemaciclib therapy, including 110 (12%) events of grade ≥ 3 (Supplementary Table 2). The median time to grade ≥3 diarrhoea was 21 days with 81% of grade ≥3 diarrhoea events occurring within the first 365 days of treatment initiation. Abemaciclib dose (200 mg vs 150 mg) was significantly associated with increased risk of grade ≥ 3 diarrhoea (P = 0.035, Supplementary Table 3). No significant association of grade ≥3 diarrhoea was identified between abemaciclib + fulvestrant versus abemaciclib + NSAI versus abemaciclib monotherapy (P = 0.648, Supplementary Table 4).

Of the 900 patients, 389 (43%) patients experienced neutropenia from abemaciclib therapy, including 223 (25%) events of grade ≥ 3 (Supplementary Table 2). The median time to grade ≥3 neutropenia was 29 days with 90% of grade ≥3 events occurred within the first 365 days of abemaciclib therapy. Abemaciclib dose (200 mg versus 150 mg) was significantly associated with an increase in the risk of grade ≥ 3 neutropenia (P = 0.037, Supplementary Table 5). No significant association of grade ≥3 neutropenia was identified between abemaciclib + fulvestrant versus abemaciclib + NSAI versus abemaciclib monotherapy (P = 0.237, Supplementary Table 6).

3.2. Prediction of grade ≥3 diarrhoea

On univariable analysis, advanced age (>70 years) was significantly associated with an increased risk of abemaciclib induced grade ≥ 3 diarrhoea (HR [95%CI]: 1.72 [1.14–2.58]; P = 0.009) – i.e. within the 23% of individuals greater than 70 years old, the risk of grade ≥3 diarrhoea was 1.72 times that of an individual aged 70 or below. No statistically significant association between grade ≥3 diarrhoea and ECOG PS, race, weight, body mass index, liver metastasis, bilirubin count, alkaline phosphatase count, albumin count, aspartate aminotransferase count, prior neoadjuvant/adjuvant endocrine therapy or chemotherapy, or concomitant use of antidiarrhoeals/opioids were identified (Supplementary Table 7), including on stepwise forward inclusion. The probability of grade ≥3 diarrhoea within the first 365 days of abemaciclib dosed at 150 mg twice daily in individuals greater than 70 years old was 13% [95% CI; 7%–18%], compared to 9% [6%–12%] for those aged 70 or below (Table 1). Supplementary Table 9 outlines the probability of grade ≥3 diarrhoea within the first 365 days of abemaciclib dosed at 200 mg twice daily. Further exploratory analysis also identified advanced age as significantly associated with an increased risk of abemaciclib induced grade ≥2 diarrhoea (HR [95%CI]: 1.56

Table 1
Probability of grade ≥3 diarrhoea by age group.

Time (days)	Abemaciclib 150 mg + Fulvestrant/NSAI	
	Age ≤ 70	Age > 70
	Median (%) [95% CI]	Median (%) [95% CI]
28	4 [2–6]	6 [2–10]
56	6 [3–8]	9 [4–13]
365	9 [6–12]	13 [7–18]

[1.24–1.95]; P < 0.001).

3.3. *Prediction of grade ≥3 neutropenia*

The univariable analysis identified Asian race, weight, BMI, neutrophil count, alkaline phosphatase, albumin, aspartate aminotransferase and white blood cell count as significantly associated with the development of abemaciclib induced grade ≥3 neutropenia (P < 0.05; Supplementary Table 8). On forward inclusion, Asian race, ECOGPS, alkaline phosphatase, albumin, liver metastasis, and white blood cell count were identified as the statistically significant predictors within a full multivariable model. The backwards elimination process resulted in a final clinical prediction model for grade ≥3 neutropenia optimally defined by race, ECOGPS and white blood cell count (WBC count < 4.0 vs 4.0–4.99 vs 5.0–6.5 vs ≥ 6.5 × 10 [9]/L) (Table 2). The discrimination performance (*c*-statistic) of the final multivariable model was 0.75 (Table 2). A risk scoring tool based on the final multivariable model was developed.

3.4. *Clinical prediction tool for grade ≥3 neutropenia*

The scores for the prediction tool were derived by scaling variable coefficients from the final multivariable model to a point score. Asian race equated to 1 risk point, ECOGPS of 1+ equated to 1 risk point, white blood cell count (WBC) (x10 [9]/L) of 5.0–6.49 equated to 1 risk point, WBC 4.0–4.99 to 2 risk points and WBC < 4.0 to 3 risk points (Fig. 1 and Supplementary Fig. 1). Patients were categorized into five subgroups according to their overall risk score (i.e. 0, 1, 2, 3, 4+). The risk scoring tool resulted in a *c*-statistic of 0.74 (Supplementary Table 10).

Table 3 and Fig. 1 present the risk score tools ability to calculate probabilities of grade ≥3 neutropenia within the first 365 days of abemaciclib (150 mg twice daily) + fulvestrant/NSAI. Of the 11% of individuals in the highest risk subgroup (i.e. risk score = 4+) the probability of developing grade ≥3 neutropenia within the first 365 days of abemaciclib (150 mg twice daily) + fulvestrant/NSAI therapy was 64% [48%–76%]. Comparatively, of the 12% of individuals in the lowest risk subgroup (i.e. risk score = 0) the probability of developing grade ≥3 neutropenia within the first 365 days of abemaciclib (150 mg twice daily) + fulvestrant/NSAI therapy was 5% [0%–10%]. Supplementary Table 11 and Supplementary Fig. 1 present the risk score tools ability to calculate probabilities of grade ≥3 neutropenia within the first 365 days of abemaciclib (200 mg twice daily) ± fulvestrant according to defined risk groups.

The random forest approach identified race, ECOGPS, neutrophil and white blood cell count as the most influential variables in predicting abemaciclib induced neutropenia; confirming the validity of the variables included in the prediction tool. The discrimination performance of the repeated cross-validated random forest model was 0.75 – indicating no problems with overfitting. Supplementary Fig. 2 presents Kaplan-Meier plots for grade ≥3 neutropenia according to the predicted risk scores by assessed abemaciclib dosing strategies.

Table 2
Final multivariable model of grade ≥ 3 neutropenia following abemaciclib initiation.

	HR	95% CI	P-value
ECOG PS			<0.001
0	1		
1+	1.64	1.23 to 2.18	
Race			<0.001
Non-Asian	1		
Asian	2.19	1.60 to 2.99	
White Blood Cell Count (x 10^9/L)			<0.001
≥ 6.5	1		
5.0–6.5	2.16	1.30 to 3.59	
4.0–4.99	4.42	2.72 to 7.17	
< 4.0	9.90	6.07 to 16.2	

CI = confidence interval, HR = hazard ratio, ECOG PS = Eastern cooperative oncology group performance status.

4. Discussion

This study used large pooled data to develop and present the first clinical prediction tool of abemaciclib induced grade ≥3 neutropenia in patients with HR+/HER2- ABC. The tool defined the risk of grade ≥3 neutropenia within the first 365 days of abemaciclib (150 mg twice daily) + fulvestrant/NSAI, which ranged from 5% to 64% according to patient race (Asian vs non-Asian), ECOGPS (1+ vs 0) and pre-treatment white blood cell count (<4.0 vs 4.0–4.99 vs 5.0–6.5 vs ≥ 6.5 × 10 [9]/L). The study also identified that advanced age (70 years) was associated with an increased risk of abemaciclib induced grade ≥ 3 diarrhoea.

Neutropenia is a common side effect associated with CDK 4/6 inhibitors due to their effects on the hematopoietic bone marrow. Whilst abemaciclib has a lower incidence of neutropenia when compared to other CDK 4/6 inhibitors, neutropenia was the most commonly reported severe (grade ≥ 3) side effect associated with its use [17]. Abemaciclib induced grade ≥3 neutropenia is commonly managed by drug suspension and dose reduction [17]. Therefore it is important to identify the cohort of patients at high risk of grade ≥3 neutropenia at baseline as it can progress to neutropenic sepsis [18]. Final multivariable analysis identified race, ECOGPS and pre-treatment white blood cell count as the most significant predictors associated with the development of abemaciclib induced grade ≥3 neutropenia. The findings of the final multivariable analysis are consistent with literature identifying race [19,20], ECOGPS [21,22] and pre-treatment white blood cell count [23] as prognostic factors associated with the development of neutropenia from anticancer therapies more generally. Whilst the final risk tool had a small decline in the discriminative performance (c = 0.74) compared to the final multivariable model (c = 0.75), clinical simplicity and user-friendliness was optimised.

Prior research indicates no statistical difference in abemaciclib pharmacokinetics according to race [24], suggesting the higher risk of developing abemaciclib induced grade ≥ 3 neutropenia in Asians is likely pharmacodynamically driven. Findings from a meta-analysis on other CDK4/6 inhibitors identified no differences in neutropenia and diarrhoea risk by ethnicity [25]. Addition of ECOGPS alongside race and white blood cell count provided synergistic enhancement of model discrimination – despite ECOGPS not being a significant variable on univariable analysis.

Future research should aim to validate the presented neutropenia prediction tool for other CDK 4/6 inhibitors. Nonetheless, the presented tool has significant potential to guide clinicians in identifying patients at an increased risk of abemaciclib induced neutropenia. For example, 21% of participants were identified to have a risk score of 3+, in which the risk of grade ≥3 neutropenia was >40% within the first 365 days of abemaciclib (150 mg twice

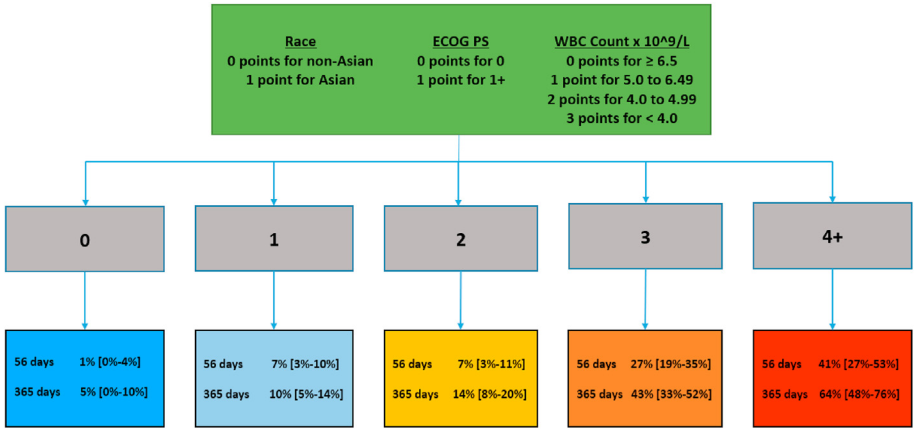

Fig. 1. Clinical prediction model of developing grade ≥ 3 neutropenia for Abemaciclib 150 mg + Fulvestrant/NSAI therapy at 56 and 365 days.

Table 3
Scoring metric for grade ≥ 3 neutropenia following Abemaciclib 150 mg + Fulvestrant/NSAI therapy initiation at 12 months.

Neutropenia Risk Factors	Points
Asian Race	1
ECOG Performance Score 1+	1
White Blood Cell Count [5.0 to 6.49 x 109/L]	1
White Blood Cell Count [4.0 to 4.99 x 109/L]	2
White Blood Cell Count [< 4.0 x 109/L]	3
Maximum Risk Score	**4+**

Abemaciclib 150 mg + Fulvestrant/NSAI therapy	
Risk Score	Predicted Neutropenia Incidence at 12 months
0	5%
1	10%
2	14%
3	43%
4+	64%

daily) + fulvestrant/NSAI therapy. Identifying these patients at a substantially increased risk of neutropenia enables clinicians to consider pre-emptive strategies (e.g. prophylactic granulocyte colony stimulating factors, abemaciclib dose reductions or more stringent monitoring of white blood cell counts) to facilitate effective and safe long term abemaciclib treatment without necessitating persistent clinician-initiated interventions in the form of abemaciclib withdrawal. Minimization of persistent clinician-initiated interventions for the management side effects can also contribute to lower levels of patient anxiety to treatment [26].

Diarrhoea is a common side effect with many anticancer drugs (including with CDK 4/6 inhibitors) [27]. Abemaciclib use is associated with a higher rate of grade ≥3 diarrhoea compared to other CDK 4/6 inhibitors [28]. Advanced age (>70 years) was identified as the only variable associated with an increased risk of grade ≥ 3 diarrhoea, consistent with prior literature indicating that the advanced age population is at higher risk of diarrhoea from active oncological treatment [29]. The absolute difference in risk of developing abemaciclib induced grade ≥3 diarrhoea between the advanced and young ages was small (13% vs 9% in the first 365 days, respectively), however, in relative terms the study was able to highlight that advanced age individuals were at 1.72 times greater risk of abemaciclib induced grade ≥ 3 diarrhoea. It is hypothesized that polypharmacy, pharmacokinetics, and pharmacodynamics changes in the advanced age subgroup, may contribute to the increased risk of abemaciclib induced grade ≥3 diarrhoea [30–32]. Future research should aim to elucidate the relationship between age and the risk of diarrhoea from other CDK 4/6 inhibitors and if the association is further established a stricter adherence to standardized management of diarrhoea in the form of antidiarrhoeal medications, dose reduction and drug suspension should be followed.

Randomized control trials (RCTs) are the backbone of evidence-based medicine, however, strict inclusion criteria within RCTs can limit the generalizability of results [33]. Contrasting this, RCTs provide rigorous, high quality collection of adverse event data, allowing for the development of well-defined prediction tools [34]. Additionally, this study pooled large ($n = 900$) data from three trials (MONARCH 1, 2 and 3) to increase study power and generalizability. Ultimately this allowed the development of a well-performing and highly discriminatory clinical prediction tool ($c = 0.74$) which has the potential to be used by patients and clinicians to better interpret the risk-benefit ratio of abemaciclib in ABC patients. Effective communication of personalized and well-validated predictions of an individual's expected adverse outcomes can improve shared decision making, empower patients, and enable patients and clinicians to make better decisions regarding strategies to mitigate adverse outcomes [35]. Nevertheless, with advances in large electronic health record platforms, future opportunities to externally validate the presented tool within observational datasets of patients using abemaciclib in routine clinical care should occur – in the future this may also include evaluating the tools appropriateness for abemaciclib's use as a neo-adjuvant treatment [36].

In conclusion, the study identified advanced age as being significantly associated with an increased risk of abemaciclib induced grade ≥3 diarrhoea. The study also developed a clinical prediction tool based upon race, ECOGPS and white blood cell count for predicting abemaciclib induced grade ≥3 neutropenia. The developed tool offered large and substantial discrimination between subgroups, exemplifying the ability of the developed tool to inform on clinically significant difference in neutropenia risk to clinicians and patients considering abemaciclib use.

Ethics

Secondary analysis of anonymized IPD was exempted from review by the Southern Adelaide Local Health Network, Office for Research and Ethics as it was classified as minimal risk research.

Data availability

This publication is based on research using de-identified individual participant data from data contributor Eli Lilly that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication.

Contributions

All authors were involved in the data analyses and writing of the manuscript.

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Declaration of competing interest

Associate Professor Rowland, Professor Sorich and Professor McKinnon report grants from Pfizer, outside the submitted work. The authors have no other conflicts of interest to disclose.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.04.003.

References

[1] Hosford SR, Miller TW. Clinical potential of novel therapeutic targets in breast cancer: CDK4/6, Src, JAK/STAT, PARP, HDAC, and PI3K/AKT/mTOR pathways. Pharmgenomics Pers Med 2014;7:203–15. https://doi.org/10.2147/PGPM.S52762.

[2] Zhang MH, Man HT, Zhao XD, Dong N, Ma SL. Estrogen receptor-positive breast cancer molecular signatures and therapeutic potentials (Review). Biomed Rep 2014;2:41–52. https://doi.org/10.3892/br.2013.187.

[3] Corona SP, Generali D. Abemaciclib: a CDK4/6 inhibitor for the treatment of HR+/HER2- advanced breast cancer. Drug Des Dev Ther 2018;12:321–30. https://doi.org/10.2147/dddt.S137783.

[4] Cardoso F, et al. ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol : Off J Eur Soc Med Oncol 2020;31:1623–49. https://doi.org/10.1016/j.annonc.2020.09.010.

[5] Nsw CI. Breast metastatic abemaciclib. https://www.eviq.org.au/medical-oncology/breast/metastatic/3625-breast-metastatic-abemaciclib; 2020.

[6] Ettl J. Management of adverse events due to cyclin-dependent kinase 4/6 inhibitors. Breast Care 2019;14:86–92. https://doi.org/10.1159/000499534.

[7] Sledge Jr GW, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor–positive, ERBB2-negative breast cancer that progressed on endocrine therapy—MONARCH 2: a randomized clinical trial. JAMA Oncol 2020;6:116–24. 10.1001/jamaoncol.2019.4782 %J JAMA Oncology.

[8] Dickler MN, et al. MONARCH 1, A phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR(+)/HER2(-) metastatic breast cancer. Clin Canc Res 2017;23:5218–24. https://doi.org/10.1158/1078-0432.CCR-17-0754.

[9] Sledge GW, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2− advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 2017;35:2875–84. https://doi.org/10.1200/JCO.2017.73.7585.

[10] Goetz MP, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 2017;35:3638–46. https://doi.org/10.1200/JCO.2017.75.6155.

[11] Company ELa. VERZENIO (abemaciclib) - highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208855s000lbl.pdf; 2018.

[12] Gebbia V, Valerio MR, Firenze A, Vigneri P. Abemaciclib: safety and effectiveness of a unique cyclin-dependent kinase inhibitor. Expet Opin Drug Saf 2020;19:945–54. https://doi.org/10.1080/14740338.2020.1781814.

[13] Vogenberg FR. Predictive and prognostic models: implications for healthcare decision-making in a modern recession. Am Health Drug Benefits 2009;2:218–22.

[14] Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. BMC Med 2015;13:1. https://doi.org/10.1186/s12916-014-0241-z.

[15] Johnston S, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. npj Breast Canc 2019;5:5. https://doi.org/10.1038/s41523-018-0097-z.

[16] Bischl B, et al. mlr: Mach Learn R. 2016;17:5938–42.

[17] Rugo HS, et al. Management of abemaciclib-associated adverse events in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: safety analysis of MONARCH 2 and MONARCH 3. Oncol 2021;26:e53–65. https://doi.org/10.1002/onco.13531.

[18] Clarke RT, Jenyon T, van Hamel Parsons V, King AJ. Neutropenic sepsis: management and complications. Clin Med 2013;13:185–7. https://doi.org/10.7861/clinmedicine.13-2-185.

[19] Laskey RA, et al. Predictors of severe and febrile neutropenia during primary chemotherapy for ovarian cancer. Gynecol Oncol 2012;125:625–30. https://doi.org/10.1016/j.ygyno.2012.03.015.

[20] Grann VR, et al. Ethnic neutropenia among women of European, African, and Caribbean backgrounds. J Clin Oncol 2007;25. https://doi.org/10.1200/jco.2007.25.18_suppl.6587. 6587-6587.

[21] Fontanella C, Bolzonello S, Lederer B, Aprile G. Management of breast cancer patients with chemotherapy-induced neutropenia or febrile neutropenia. Breast Care 2014;9:239–45. https://doi.org/10.1159/000366466.

[22] Keum J, et al. Single-center risk factor analysis for FOLFIRINOX associated febrile neutropenia in patients with pancreatic cancer. Canc Chemother Pharmacol 2020;85:651–9. https://doi.org/10.1007/s00280-020-04051-x.

[23] Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: a systematic review. Crit Rev Oncol Hematol 2014;90:190–9. https://doi.org/10.1016/j.critrevonc.2013.12.006.

[24] Chigutsa E, et al. Development and application of a mechanistic population modeling approach to describe abemaciclib pharmacokinetics. CPT Pharmacometrics Syst Pharmacol 2020;9:523–33. https://doi.org/10.1002/psp4.12544.

[25] Lee KWC, et al. The impact of ethnicity on efficacy and toxicity of cyclin D kinase 4/6 inhibitors in advanced breast cancer: a meta-analysis. Breast Canc Res Treat 2019;174:271–8. https://doi.org/10.1007/s10549-018-5054-x.

[26] Martin MY, et al. What do cancer patients worry about when making decisions about treatment? Variation across racial/ethnic groups. Support Care Canc 2014;22:233–44. https://doi.org/10.1007/s00520-013-1958-5.

[27] Shohdy KS, Lasheen S, Kassem L, Abdel-Rahman O. Gastrointestinal adverse effects of cyclin-dependent kinase 4 and 6 inhibitors in breast cancer patients: a systematic review and meta-analysis. Ther Adv Drug Saf 2017;8:337–47. https://doi.org/10.1177/2042098617722516.

[28] Thill M, Schmidt M. Management of adverse events during cyclin-dependent kinase 4/6 (CDK4/6) inhibitor-based treatment in breast cancer. Ther Adv Med Oncol 2018;10. https://doi.org/10.1177/1758835918793326. 1758835918793326-1758835918793326.

[29] Bossi P, et al. Diarrhoea in adult cancer patients: ESMO clinical practice guidelines. Ann Oncol : Off J Eur Soc Med Oncol 2018;29:iv126–42. https://doi.org/10.1093/annonc/mdy145.

[30] Tan JL, Eastment JG, Poudel A, Hubbard RE. Age-related changes in hepatic function: an update on implications for drug therapy. Drugs Aging 2015;32:999–1008. https://doi.org/10.1007/s40266-015-0318-1.

[31] Palumbo A, Lau G, Saraceni M. Abemaciclib: the newest CDK4/6 inhibitor for the treatment of breast cancer. Ann Pharmacother 2018;53:178–85. https://doi.org/10.1177/1060028018795146.
[32] Hubbard RE, et al. Polypharmacy among inpatients aged 70 years or older in Australia. Med J Aust 2015;202:373–7. https://doi.org/10.5694/mja13.00172.
[33] Faraoni D, Schaefer ST. Randomized controlled trials vs. observational studies: why not just live together? BMC Anesthesiol 2016;16. https://doi.org/10.1186/s12871-016-0265-3. 102-102.
[34] Phillips R, Hazell L, Sauzet O, Cornelius V. Analysis and reporting of adverse events in randomised controlled trials: a review. BMJ Open 2019;9:e024537. https://doi.org/10.1136/bmjopen-2018-024537.
[35] Modi ND, et al. A literature review of treatment-specific clinical prediction models in patients with breast cancer. Crit Rev Oncol Hematol 2020;148: 102908. https://doi.org/10.1016/j.critrevonc.2020.102908.
[36] Hurvitz SA, et al. Potent cell-cycle inhibition and upregulation of immune response with abemaciclib and anastrozole in neoMONARCH, phase II neoadjuvant study in HR(+)/HER2(-) breast cancer. Clin Canc Res 2020;26: 566–80. https://doi.org/10.1158/1078-0432.CCR-19-1425.