



# Consensus Guidelines for the Use of Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors in the Management of Hormone Receptor Positive (HR+ve), Her2–ve Early Breast Cancer (EBC)

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### Abstract



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It is still not possible for all patients with early breast cancer to be cured. Even when they respond well to initial therapy, there exists a substantial risk for recurrence, sometimes after several years. With the availability of cyclin-dependent kinase (CDK) 4/6 inhibitors the role of adjuvant therapy has improved, and so has the chance of cure. These consensus guidelines will ensure that the community oncologist will be able to take the right decision for their patient. The expert committee shares their real-world experience as well as the consensus voting results. Patients eligible for adjuvant therapy with CDK4/6 inhibitors should start that treatment at the earliest. Based on current published data, abemaciclib is the preferred CDK4/6 inhibitor that should be used in eligible patients (unless contraindicated). To ensure optimal dose intensity and

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- ▶ targeted therapy
- ▶ IDFS
- ▶ high risk
- ▶ regulatory approval

adherence to treatment schedule, use of literature and patient information material can improve compliance. Treatment modification requires early reporting of adverse effects, a responsibility of the patient and caregiver (relatives).

**Introduction**

Breast cancer is a major public health challenge in India and the world.<sup>1</sup> The HR+ luminal-like subtypes (luminal A and B) form up to 70% of such cases. When treated with endocrine therapy (ET), development of ET resistance invariably occurs in due course of time. As a result, even in patients presenting in the early stage, up to 20% relapse within 10 years of initial diagnosis.<sup>2</sup> Aberrant activation of the cyclin-dependent kinase 4 and 6 (CDK4/6) pathway, independent of mitogenic signaling, is one pathway leading to uncontrolled proliferation. When activated by cyclin D, CDK4/6 phosphorylates the retinoblastoma protein (Rb), releasing the transcription factor E2F, which in turn, pushes the cells from the G1 phase to the S phase.<sup>3–5</sup>

CDK4/6 inhibitors (CDK4/6i) act by stopping the proliferation and normalizing the cell cycle. Their value in the metastatic setting is already established. At present, there are three CDK4/6i approved by the U.S. Food and Drug Administration (FDA) (palbociclib by Pfizer; abemaciclib by Eli Lilly; and ribociclib by Novartis) plus one licensed by the Chinese FDA (darpiciclib by Herngri).<sup>6,7</sup> Results of the large adjuvant trials (MonarchE with 2 years of abemaciclib and 5-year updated follow-up; NATALEE, 3 years of ribociclib and 2-year follow-up data) demonstrate their value in early breast cancer (EBC) as well.<sup>8,9</sup>

**Methods**

We established a subject expert committee that included medical oncologists with proven experience in the management of breast cancer as well as academic background (all of them as coauthors).<sup>10,11</sup> We represent teaching institutions, corporate hospitals, and private practice from across India. After one-on-one discussion, and obtaining consent to join the expert guidelines committee, we made a formal group for online (email, WhatsApp, webinar, videoconference) and in-person discussions in a structured manner. The preliminary discussions led to the development of the draft questions for voting. We followed the Delphi method that we have used previously taking into consideration various modifications of the process and parameters used in the Delphi method (including Real-Time Delphi, Argumentative Delphi, Policy Delphi, Delphi Markets, and Group Delphi techniques).<sup>12–14</sup> Our process included several rounds of voting and discussions after each voting that led to modification, addition, and/or deletion of questions. The agreement percentage cutoff value we used for these consensus guidelines' recommendations was 75% (in the literature it has varied

from 20 to 100% agreement).<sup>14</sup> For questions where initial consensus was lacking, additional group discussions were undertaken where relevant updated published evidence was provided to the group. The final voting was then tabulated. Further discussions by the experts provided insights based on published literature, Indian data, and real-world situations. All the expert committee members/authors participated at each step, provided critical review, voted several times, and thus contributed to the crafting of these Consensus Guidelines for the use of CDK4/6i in the management of HR+ve Her2–ve EBC.

**Results**

The voting on the consensus guidelines statements are shown in **▶Table 1**. There are a total of 27 guideline statements. There was more than 75% consensus for all the statements. A total of 9 statements had 100% (18/18; unanimous consensus). Another 7 had 17/18 (94%) consensus.

We also documented real-world experiences in clinical practice of our experts. These are shown in **▶Table 2**. The majority (15/18) said that the percentage of HR+ve Her2–ve EBC in their practice was between 20 and 40%. Regarding impact on quality of life in their patients, 11/18 expressed that it was slightly affected. And 14/18 found that incidence of adverse events like diarrhea was less in Indian patients as compared with that reported in the western literature.

**Discussion**

CDK4/6i, such as abemaciclib, ribociclib, and palbociclib, have revolutionized the treatment landscape for HR+HER2– breast cancer by targeting key regulators of cell cycle progression.<sup>15</sup> The clinical efficacy of these agents has been demonstrated in several pivotal trials, including the MonarchE and NATALEE studies, providing robust data for their use in the adjuvant setting.<sup>16–19</sup>

To summarize, the phase III randomized MonarchE study evaluated adjuvant abemaciclib in 5,637 patients with high-risk HR+ve, HER2-negative EBC. Patients were randomized to either receive abemaciclib (150 mg orally twice a day for 2 years) in combination with ET or ET alone. At a median follow-up of 42 months, abemaciclib resulted in a significant improvement in invasive disease-free survival (IDFS; 4-year IDFS of 85.8% in the abemaciclib group compared with 79.4% in the ET alone group; absolute difference of 6.4%; hazard ratio [HR] 0.696 [95% confidence interval: 0.588–0.823], *p*-value < 0.0001).<sup>18,20</sup> Interestingly, older patients (i.e., > 65 years

**Table 1** Consensus voting by guidelines committee experts—guidelines for the use of cyclin-dependent kinase (CDK) 4/6 inhibitors in the management of hormone receptor positive (HR+ve), Her2–ve early breast cancer (EBC)

Question no.	Question	Yes	No	Abstain
1	HR+, HER2– EBC patients constitute a heterogeneous group with varying prognosis. A subset with high risk of recurrence require more than ET in adjuvant setting	18/18 (100%)	0	0
2	Factors indicating high risk of recurrence in node-positive patients include tumor size and grade, in addition to lymph node involvement	15/18 (83%)	2/18	1/18
3	Factors indicating high risk of recurrence in node-negative patients include tumor size, tumor grade, Ki67 > 20, and genomic profiling	17/18 (94%)	0	1/18
4	For node-negative HR+, HER2– EBC patients, having other high-risk features it is recommended to consider treatment with CDK4/6 inhibitors along with ET	14/18 (78%)	3/18	1/18
5	In real-world practice, many high-risk patients considered as EBC and commenced on adjuvant endocrine therapy plus additional drugs, may be found to be LN positive at surgery and would actually be LABC	15/18 (83%)	1/18	2/18
6	The criteria for usage of CDK4/6 inhibitors in node-positive HR+, HER2– EBC patients, as used in regulatory trials, are adequate to select subset of patient with high risk of recurrence. Such patients should receive/continue to receive CDK4/6 inhibitors	18/18 (100%)	0	0
7	Based on STEEP criteria, IDFS and DRFS are adequate endpoints to understand the efficacy of CDK4/6i in adjuvant setting for EBC	17/18 (94%)	1/18	0
8	Ki67 expression testing is optional when selecting patients requiring CDK4/6 inhibitors	17/18 (94%)	0	1/18
9	Use of CDK4/6 inhibitors plus ET for HR+, HER2– EBC patients is possible irrespective of menopausal status	18/18 (100%)	0	0
10	Use of CDK4/6 inhibitors plus ET for HR+, HER2– EBC patients is possible irrespective of NACT status	17/18 (94%)	1/18	0
11	Use of CDK4/6 inhibitors plus ET for HR+, HER2– EBC patients is possible irrespective of ACT status	15/18 (83%)	1/18	2/18
12	Use of CDK4/6 inhibitors plus ET for HR+, HER2– EBC patients is possible irrespective of PgR status	18/18 (100%)	0	0
13	Use of CDK4/6 inhibitors plus ET for HR+, HER2– EBC patients is possible irrespective of the ET used (AI or tamoxifen)	15/18 (83%)	3/10	0
14	When a patient is identified who is a candidate for CDK4/6 inhibitors, that treatment should be commenced as soon as possible	17/18 (94%)	1/18	0
15	Based on current available data, abemaciclib should be the preferred CDK4/6 inhibitor that should be used in eligible patients (unless contraindicated)	18/18 (100%)	0	0
16	If the patient of HR+ve Her2–ve early breast cancer requires treatment with a CDK4/6 inhibitor, palbociclib should not be used as a substitute for abemaciclib or ribociclib	18/18 (100%)	0	0
17	Selecting the right CDK4/6 inhibitor is also guided by safety profile, patient preferences, and unique individual patient characteristics	18/18 (100%)	0	0
18	In case of clinically significant adverse events with CDK4/6i, it is better to follow dose reduction strategy first. In that way premature discontinuations can be avoided	18/18 (100%)	0	0
19	Counseling (providing access to literature and information) can improve compliance (maintaining dose intensity) and early reporting of adverse effects	18/18 (100%)	0	0
20	The outcome with continuation of dose reduced CDK4/6 inhibitors are better than with discontinuation of the drug	16/18 (89%)	1/18	1/18
21	It is the combined responsibility of the patient and caregiver (relatives) to ensure that they promptly inform their doctors regarding any adverse effects and/or before discontinuation of their prescribed doses	17/18 (94%)	0	1/18

(Continued)

**Table 1** (Continued)

Question no.	Question	Yes	No	Abstain
22	Patient should promptly report to their doctors regarding any changes in their symptoms, quality of life, and adherence to prescribed treatment and /or change in their treatment preferences/goals	17/18 (94%)	0	1/18

Abbreviations: ACT, adjuvant chemotherapy; AI, aromatase inhibitor; DRFS, distant relapse-free survival; ET, endocrine therapy; IDFS, invasive disease-free survival; LABC, locally advanced breast cancer; LN, lymph node; NACT, neoadjuvant chemotherapy; PgR, progesterone receptor; STEEP, Standardized Definitions for Efficacy Endpoints.

**Table 2** Real-world experience of guidelines committee experts

Question no.	Question	Answer 1	Answer 2	Answer 3	Answer 4
1	In the real-world Indian context, proportions of HR+, HER2– EBC patients who are high risk and therefore require use of CDK4/6 inhibitors are:	20–40% of cases 15/18	> 40% of cases by 2/18	Abstain 1/18	
2	Impact on quality of life of CDK4/6 inhibitors plus ET (as compared with ET alone), in real-world HR+, HER2– EBC patients is:	Significantly more 2/18	Slightly more 11/18	Similar 4/18	Abstain 1/18
3	Real-world experience indicates that the adverse event of CDK4/6 inhibitors like diarrhea are less in Indian patients:	True 14/18	False 0/18	Abstain 4/18	

Abbreviations: CDK, cyclin-dependent kinase; EBC, early breast cancer; ET, endocrine therapy.

old) receiving abemaciclib demonstrated similar benefits in IDFS and distant relapse-free survival as their younger counterparts, reinforcing the robustness of these findings.<sup>21</sup>

The NATALEE trial was also a phase III randomized study, included ribociclib plus ET but in 5,101 patients with stage II to III HR+ve, HER2-negative breast cancer. Ribociclib (400 mg/day; 3 weeks on, 1 week off for 3 years) was given in combination with ET (letrozole 2.5 mg/day or anastrozole 1 mg/day with or without goserelin for at least 5 years) in the study arm and the control arm received ET alone. At a median follow-up of 34 months, ribociclib demonstrated 3-year IDFS of 90.4% compared with 87.1% in the control arm ( $p = 0.0014$ ). This benefit was observed across all subgroups.<sup>19,22</sup>

The updated 5-year results from the MonarchE trial show a continuous improvement in outcomes over time (more mature data, longer follow-up).<sup>20,23,24</sup> The trial design was

straightforward, with clearly defined patient groups, and demonstrated that abemaciclib can prevent relapse in approximately 15 to 20% of patients (equating to one in six patients). At the 3-year mark, IDFS favored abemaciclib over ribociclib. Notably, abemaciclib was administered for a shorter 2 years, while ribociclib was given for 3 years. And the follow-up available for abemaciclib extends to 5 years for abemaciclib as compared with 2 years for ribociclib.<sup>20,25,26</sup>

The underlying rationale for CDK4/6i is to induce permanent senescence in any cancer cells still present in the body. The natural history of breast cancer recurrence shows the highest risk is within the first 3 years, making this period critical for intervention.<sup>27,28</sup>

Despite approximately 20% of patients in both trials discontinuing treatment due to toxicity, the overall survival

**Table 3** Differences between adjuvant abemaciclib (MonarchE) and ribociclib (NATALEE)<sup>30–33</sup>

	Adjuvant abemaciclib	Adjuvant ribociclib
Regulatory approval	Approved by FDA and EMA	Not yet approved
Indications	Only node-positive HR+ /HER2– EBC: <ul style="list-style-type: none"> <li>• <math>\geq 4</math> lymph nodes, or</li> <li>• 1–3 lymph nodes with G3, or T <math>\geq 5</math> cm, or <math>K_{i-67} \geq 20\%</math></li> </ul>	<ul style="list-style-type: none"> <li>• Stage IIB–III HR+ /HER2– EBC</li> <li>• Stage IIA if either node-positive or G3, or G2 with <math>K_{i-67} \geq 20\%</math>, or high genomic risk</li> </ul>
Treatment duration	2 y	3 y
Safety profile	Mainly gastrointestinal toxicity	Mainly neutropenia, liver-related AEs and QT prolongation
Follow-up data published	5 y	2 y

Abbreviations: AEs, adverse events; EBC, early breast cancer; EMA, European Medicine Agency; FDA, Food and Drug Administration; HR+, hormone receptor-positive.

(OS) and IDFS show benefit.<sup>29</sup> For abemaciclib the delta has increased to more than 7 (at 5-year follow-up) with an impressive HR.<sup>20</sup> Similarly, the delta for ribociclib is 5.<sup>22</sup>

Abemaciclib and ribociclib, as demonstrated in their respective MonarchE and NATALEE trials, have some differences (► **Table 3**).<sup>30–33</sup> This relates to patient and disease heterogeneity, level of risk in their populations, correlation with study response rates with those in the real world, and toxicity.

The abemaciclib MonarchE trial was cleaner and had only node-positive high-risk patients. N1 disease patients were included only if they had large tumors. On the other hand, ribociclib NATALEE trial seems to be both confusing and overly ambitious. It seemed the trial aimed to answer too many questions simultaneously, diluting its focus. NATALEE included N0 (10%) and N1 (even if they had smaller T1 tumors) patients. Notably, the 30% of patients in the ribociclib trial with N0 disease were given neoadjuvant chemotherapy. Yet, only 10% of the intent-to-treat population was represented in the forest plot analysis. The inclusion of gonadotropin-releasing hormone (GNRH) analogs in the ribociclib arm also raised questions about potential over-treatment. Its explanation was that for high-risk patients this was necessary. It could have also contributed to better outcomes, raising the question of the contribution of GNRH analogs versus ribociclib to ultimate patient benefit.

The challenge, therefore, remains in determining the best approach for the small subset of high-risk N0 patients. While ribociclib is less toxic, fear of toxicity often drives its choice, yet in any node-positive (N+), abemaciclib is the preferred option. Toxicity differences can be understood by the mechanism of action of these two CDK4/6i.<sup>29,34–36</sup> Abemaciclib, for instance, has a stronger selectivity for CDK4 over CDK6, which contributes to its reduced bone marrow toxicity but increases gastrointestinal side effects. Ribociclib, in contrast, exhibits equal inhibition of CDK4 and CDK6 and is associated with risks of neutropenia, liver enzyme elevations, and QT interval prolongation.<sup>29,36</sup> Interestingly, some of our experts experiences lower incidence of diarrhea with abemaciclib in their practice, a benefit attributed to the high consumption of dahi (not yoghurt) in the Indian population.

We also need to keep in mind that in the real-world Indian context, few node-negative (N0) patients actually relapse. Additionally, ribociclib has not yet received U.S. FDA approval for this indication.

When making treatment decisions, it is crucial to consider the combined risk factors that an individual patient faces—risks exist on a continuum and cannot be easily compartmentalized. For example, a patient with N1 disease might have a lower overall risk than a patient with N0 disease when other factors are taken into account. This creates a gray area in decision-making. Earlier, the American Society of Clinical Oncology (ASCO) had stated that no specific recommendation can be made for node-negative patients due to the small number of such patients in trials, their lower risk, and the minimal differences observed with intervention.<sup>37</sup>

It is interesting that, although the U.S. FDA has not yet approved ribociclib in the adjuvant setting, in its subsequent

clinical guidelines of May 2024, ASCO has published rapid recommendation update in which they have simply repeated the inclusion criteria of the MonarchE and NATALEE trials as the recommendation for the use of adjuvant abemaciclib and ribociclib, respectively.<sup>38</sup> This is in contrast to the National Comprehensive Cancer Network guidelines, which do not include any drug that is not approved by the U.S. FDA.<sup>39</sup> We are left wondering whether American payors will reimburse for a drug that is not licensed by its drug regulators. This action is also exactly opposite to what happened with docetaxel and S1.<sup>39,40</sup> Docetaxel was standard of care in Europe for decades before U.S. finally acknowledged its value and robust data.<sup>39</sup> So also S1 is approved in Europe, Japan, and 27 other countries, but U.S. has to still “discover” its merit.<sup>40</sup>

Given the partially overlapping indications, differing durations of therapy, and varying toxicity profiles between these two positive studies, it became necessary to examine the finer points and develop consensus guidelines to assist the community oncologists in making informed treatment decisions for their individual patients.

## Real-World Challenges and Expert Consensus in the Indian Context

The adoption of CDK4/6i in India faces several real-world challenges. First, the patient population in India presents unique characteristics that may influence the efficacy and tolerability of these treatments. For instance, the consensus panel noted that adverse events, such as gastrointestinal toxicity, appear to be less severe in Indian patients, possibly due to dietary habits that include higher intake of natural probiotics.

In terms of clinical practice, the expert panel estimated that 20 to 40% of HR+ HER2– EBC patients in India are at high risk of recurrence and could benefit from CDK4/6i. However, the high cost of these therapies is a significant barrier, particularly in low- and middle-income countries like India. The panel stressed the importance of identifying biomarkers that can more accurately predict which patients will derive the most benefit from these treatments, thus enhancing cost-effectiveness.

The consensus guidelines developed through the Delphi process are designed to help oncologists navigate these challenges. They emphasize the need for personalized treatment plans that take into account not only clinical factors but also socioeconomic conditions. For example, while abemaciclib is currently the preferred CDK4/6i due to its robust efficacy data, the choice of the agent for a specific patient should take into consideration that patient's unique risk factors, preferences, comorbidities, polypharmacy, fitness, and the potential adverse events that need to be avoided.

## CDK4/6i Rechallenge

The possibility of rechallenging a patient with a second CDK4/6i after disease progression on a previous CDK4/6i is a pertinent question in current clinical practice. Several international guidelines endorse this approach. For instance, a retrospective study evaluated the use of abemaciclib after palbociclib failure, reporting a median progression-free survival (PFS) of 5.3

**Table 4** Summary of the main points of the consensus guidelines recommendations for the use of cyclin-dependent kinase (CDK) 4/6 inhibitors in the management of hormone receptor positive (HR+ve), Her2–ve early breast cancer (EBC)

No.	Main points of the consensus guideline recommendations
1	HR+, HER2– EBC patients constitute a heterogeneous group with varying prognosis. A subset with high risk of recurrence require more than ET in adjuvant setting
2	Factors indicating high risk of recurrence in node-positive patients include tumor size and grade, in addition to lymph node involvement
3	Factors indicating high risk of recurrence in node-negative patients include tumor size, tumor grade, Ki67 > 20, and genomic profiling
4	For node-negative HR+, HER2– EBC patients, having other high-risk features it is recommended to consider treatment with CDK4/6 inhibitors along with ET
5	In real-world practice, many high-risk patients considered as EBC and commenced on adjuvant endocrine therapy plus additional drugs, may be found to be LN positive at surgery and would actually be LABC
6	The criteria for usage of CDK4/6 inhibitors in node-positive HR+, HER2– EBC patients, as used in regulatory trials, are adequate to select subset of patient with high risk of recurrence. Such patients should receive/continue to receive CDK4/6 inhibitors
7	Based on STEEP criteria, IDFS and DRFS are adequate endpoints to understand the efficacy of CDK4/6i in adjuvant setting for EBC
8	Testing for Ki67 expression is optional when selecting patients requiring CDK4/6 inhibitors
9	Use of CDK4/6 inhibitors plus ET for HR+, HER2– EBC patients is possible irrespective of menopausal status, NACT status, ACT status, PgR status, and type of ET used (AI or tamoxifen)
10	When a patient is identified who is a candidate for CDK4/6 inhibitors, that treatment should be commenced as soon as possible
11	Based on current available data, abemaciclib should be the preferred CDK4/6 inhibitor that should be used in eligible patients (unless contraindicated)
12	If the patient of HR+ve Her2–ve early breast cancer requires treatment with a CDK4/6 inhibitor, palbociclib should not be used as a substitute for abemaciclib or ribociclib
13	Selecting the right CDK4/6 inhibitor is also guided by safety profile, patient preferences, and unique individual patient characteristics
14	In case of clinically significant adverse events with CDK4/6i, it is better to follow dose reduction strategy first. In that way premature discontinuations can be avoided
15	Counseling (providing access to literature and information) can improve compliance (maintaining dose intensity) and early reporting of adverse effects
16	The outcome with continuation of dose reduced CDK4/6 inhibitors are better than with discontinuation of the drug
17	It is the combined responsibility of the patient and caregiver (relatives) to ensure that they promptly inform their doctors regarding any adverse effects and/or before discontinuation of their prescribed doses
18	Patient should promptly report to their doctors regarding any changes in their symptoms, quality of life, and adherence to prescribed treatment and/or change in their treatment preferences/goals

Abbreviations: ACT, adjuvant chemotherapy; AI, aromatase inhibitor; DRFS, distant relapse-free survival; ET, endocrine therapy; IDFS, invasive disease-free survival; LABC, locally advanced breast cancer; LN, lymph node; NACT, neoadjuvant chemotherapy; PgR, progesterone receptor; STEEP, Standardized Definitions for Efficacy Endpoints.

months and an OS of 17.2 months in heavily pretreated patients.<sup>41</sup> Similarly, the MAINTAIN trial demonstrated a comparable benefit with ribociclib as a second-line CDK4/6i, with a median PFS of 5.29 months compared with 2.76 months in the placebo arm.<sup>42</sup> Since palbociclib is no longer approved for use in the adjuvant setting, we have to relook at the rechallenge strategy.<sup>43,44</sup> Currently, this question remains unanswered.

### Limitations of Current Evidence and Future Directions

Both the MonarchE and NATALEE trials experienced significant dropout rates in the control arms.<sup>45</sup> What was the cause is not clear. In these open-labeled trials, what did the patient

do after discontinuing trial medication? The impact of the coronavirus disease 2019 pandemic, particularly in the NATALEE study, introduces additional uncertainty. The pandemic led to interruptions in treatment and follow-up, which may have affected the OS outcomes.

Cost is another critical issue. The addition of CDK4/6i to the adjuvant treatment regimen significantly increases the cost by as much as 35%. Given that breast cancer has one of the highest incidences in India, this financial burden needs to be taken into consideration by all stake holders. Better predictive biomarkers that help identify real high-risk patients will prevent unnecessary treatment and cost in those that do not require additional interventions. As new data emerge from ongoing trials, it will be crucial to update

patient management algorithms to ensure that they continue to meet the needs of patients and oncologists in India.

## Guideline Recommendations

The summary of the main points of the consensus guidelines recommendation are shown in [Table 4](#).

## Conclusion

CDK4/6i increase the chance of cure (with acceptable toxicity) in HR+ve HER2–ve EBC.<sup>45</sup> At the current time, abemaciclib is the preferred choice because of its shorter duration of therapy, longer follow-up, more robust data with increasing statistical difference up to 5 years, and regulatory approval.<sup>20</sup> Differences in toxicities can guide the preferred choice in specific patients.<sup>29,36</sup> Ongoing trials with CDK4/6i in the EBC will help throw more light when their data are mature and available (e.g., NCT04565054, NCT04584853).<sup>46,47</sup>

## Disclaimer

Due diligence has been followed using modified Delphi process while developing these consensus guidelines. Medical knowledge is constantly evolving. After the guidelines document was finalized and approved by all the authors, new data and insights could be available on a dynamic basis. Hence, our document may not be considered as up-to-date, complete, or accurate at a different time or for a unique individual patient and their specific circumstances. These guidelines can only be interpreted by a qualified, experienced, and trained medical oncologist in their real-world application. As new evidence emerges, their applicability to individual patients will have to be reevaluated on a case-to-case basis. We have addressed the disease specifically mentioned in the title. Our recommendations are not to be used for any other diseases, stage, intervention, or other medical/nonmedical circumstances. Our guidelines do not substitute the opinion, insight, and decision of the treating medical oncologist, who alone is competent to arrive at the management plan for individual patients. Even when we have used words like should/should not, must/must not, likely/unlikely, advised/not advised are only used in general terms. The treating medical oncologist has the full latitude to select other courses of action as may be necessary. Use of our guidelines is voluntary. We do not endorse any particular drugs, devices, diagnostic consumables, or services that may or may not be used for patient diagnosis, treatment, or management in any form. Use of any brand or trade name is for identification purposes only and should not be interpreted as an endorsement. We make no warranty, express, or implied, regarding these guidelines. We also disclaim any warrant, merchantability, or fitness for any specific use or purpose. We cannot be held responsible for any or all injuries or damages to persons or property arising out of, directly or indirectly, any use of this information. This is also applicable to any or all errors or omissions.

## Conflict of Interest

None declared.

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