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ORIGINAL ARTICLE

Current treatment landscape of HR+/HER2− advanced breast cancer in the Nordics: a modified Delphi study

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ABSTRACT

Background: This Delphi study aimed to assess current perspectives on hormone receptor-positive/human epidermal growth factor receptor 2-negative(HR+/HER2−) advanced breast cancer (aBC) treatment strategies across the Nordics, and to establish where consensus exists across the Nordics on HR+/HER2− aBC treatment.

Material and methods: A modified, three-round Delphi method was followed. A steering committee was appointed for study coordination, panellist selection, and questionnaire development. The questionnaires covered relevant topics on HR+/HER2− aBC treatment: treatment patterns in different lines of therapy (first [1L], second [2L], and third [3L]), oligometastatic disease, *de novo* aBC, brain metastases, age as influential factor, visceral crisis, radiotherapy, diagnostics, and clinical guidelines. Both open and closed-ended questions were included. Consensus was defined as at least 70% agreement.

Results: In total, 28 experienced BC oncologists participated in the study from all five Nordic countries. Overall, topics reaching consensus included: preferred treatment approach in 1L and 2L therapy, treatment of oligometastatic disease, visceral crisis, brain metastases, and age-related treatment considerations. No consensus was reached for 3L therapy and local treatment for primary tumour in *de novo* aBC. Endocrine therapy (ET) combined with a cyclin-dependent kinase (CDK)4/6 inhibitor was the treatment of choice for 1L and 2L therapy. Treatment patterns in clinical practice did not always follow recommendations in current Nordic guidelines, as seen in the case of recently approved treatments.

Discussion: ET in combination with a CDK4/6 inhibitor is the preferred frontline treatment for HR+/HER2− aBC in the Nordics. The observed discrepancy between current guidelines and clinical practice could be due to differences in the reimbursement of novel treatments in the Nordics. Collaborative research efforts are warranted for topics that lack consensus.

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KEYWORDS
HR+/HER2− advanced breast cancer; Delphi panel; HR+/HER2− aBC treatment strategies; Nordic countries

Background

In the Nordic region, Sweden, Norway, Denmark, Finland, and Iceland, breast cancer (BC) represented approximately 25% of all cancers and 14% of all cancer-related deaths between 2015 and 2019 [1]. Hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) BC is the most common subtype, comprising approximately 70% of all BC cancers [2–4]. This subtype is generally associated with a good prognosis, however, recurrences still occur (20–30%) [5,6].

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The treatment landscape of advanced BC (aBC) is rapidly evolving with the development of novel treatments [7]. Systemic treatment options for HR+/HER2− aBC include the use of single-agent endocrine therapy (ET), ET in combination with targeted therapies, as well as single-agent or combination chemotherapy (CT) alone or in combination with other agents [8–11]. Although the treatment strategies for patients with HR+/HER2− aBC proposed in national and international guidelines share similar principles [8–11]; the treatment in clinical settings may differ from guidelines and vary between countries [12,13]. These differences may relate to accessibility and the national reimbursement of novel treatments between the countries (e.g., alpelisib and palbociclib were not recommended in Denmark at the time of the study) [14]. Treatment strategies might also reflect different treatment practices, and differences in areas with low levels of evidence [13].

This study aimed to assess the current thoughts on HR+/HER2− aBC treatment among Nordic BC oncologists and to establish where consensus exists across the Nordics on HR+/HER2− aBC treatment.

Material and methods

The study followed a modified, three-round Delphi method and took place between January and December 2021 [15,16]. The Delphi method is a valid and used method in the research field of oncology [17–21]. It was chosen over other methods due to its advantages, namely anonymity, iteration, and flexibility [15,22,23]. The first two rounds were conducted virtually, while round 3 was held as a hybrid meeting. A steering committee (SC) was appointed to coordinate the Delphi panel discussions. The SC comprised four BC experts each from a Nordic country (Sweden, Norway, Denmark, and Finland). The composition of the SC is available in Supplementary Table S1. The SC was responsible for the final selection of topics and expert panellists, as well as the development of questionnaires, interpretation of the results, and content of this article. Panellist selection was completed through snowball sampling, to represent a group of experienced oncologists that have a direct influence on patient care [24]. For this reason, the inclusion of views from other stakeholders was considered not relevant in the present study. This sampling technique was chosen due to its convenience, i.e., it reduces the challenge of participant selection and is practical to implement [25]. The study was coordinated and sponsored by Novartis Sverige AB. Coordination of the study included administrative tasks, including liaison with medical writers and distribution of the links to the online questionnaires and other administrative tasks.

Data collection, analysis of results, and interpretation

Hosting and processing of the questionnaires from rounds 1 and 2 were handled through the online tool Alchemer™ [26]. Round 3 was handled via the web-based polling system Pigeonhole Live™ [27]. This software ensured that collected answers were directly anonymised. Panellists were asked to complete all questionnaires in English for anonymity to be maintained. The questionnaires followed a multiple-choice format, with an option to provide comments for certain questions. Consensus was defined as at least 70% agreement on individual statements, which was considered appropriate based on previous Delphi studies [28,29]. Following each round, a controlled feedback meeting was held with the SC where the collated results were analysed. Topics for which no consensus was reached were used to inform the development of subsequent questionnaires.

Round 1

The aim of round 1 was to expose areas of similarities and differences among HR+/HER2− aBC treatment patterns in the Nordic region. The questionnaire was distributed to all panellists, along with a letter of invitation describing the main objectives of the study and specific instructions. A total of 55 questions were included. The topics covered panellists' clinical and research experience, treatment patterns on different lines of therapy, clinical trial enrolment issues, treatment strategies in specific patient subgroups (oligometastatic disease, *de novo* aBC) as well as in patients with brain metastases.

Round 2

Round 2 aimed to establish consensus on topics for which none was reached previously. A total of 112 questions were included. Some topics were presented through three case vignettes whereas additional questions were included to cover topics related to 1L therapy, oligometastatic disease, special HR+/HER2− aBC treatment considerations (age, visceral crisis, ET evaluation), diagnostics, and clinical guidelines.

Round 3

The aim of round 3 was to establish consensus on topics for which none was reached previously (13 questions). There were 14 panellists attending the hybrid meeting in person and 12 attending virtually. Two panellists completed the third questionnaire later and were included in the results. Contrary to rounds 1 and 2, round 3 was not conducted anonymously to allow for panellists to discuss in-depth the topics for which consensus had not been reached. In round 3, the SC presented a summary of the results from previous rounds and mediated the live voting for the non-consensus reaching topics from previous rounds. The topics covered concerned the three case vignettes from round 2 as well as topics related to factors associated with choice of treatment, oligometastatic disease, and radiotherapy during cyclin-dependent kinase (CDK)4/6 inhibitors.

Patient cases

As part of rounds 2 and 3, three case vignettes describing patients (Patients A–C) were presented and different clinical scenarios and treatment choices were discussed. Table 1

Table 1. Description of the three patient cases.

Patient	Patient case A	Patient case B	Patient case C
Description	An 85-year-old woman with aBC, no comorbidities, and ECOG 0. ER+, PgR+ >10%/HER2− (IHC score 0) early BC in 2010. Adjuvant endocrine treatment was stopped after 2 years due to side effects. In 2019, bone metastases originating from BC (ER+/HER2−).	A 65-year-old woman with a history of hypertension (treated with candesartan). Right unilateral mastectomy and axillary dissection 3 years ago (35 mm tumor of ductal type, grade III, ER 40%, PgR 5%, Ki-67 35%, HER2−, 1/12 lymph nodes positive for cancer). Adjuvant treatment included CT. Initially treated with letrozole, with subsequent switch to tamoxifen after 13 months due to joint pain. Three years after initial BC diagnosis, bone metastases (computerized tomography scan showed virtually all bones affected). Additionally, multiple liver metastases (alanine transaminase twice the ULN, bilirubin close to ULN, cancer antigen 15-3 1253). A re-biopsy IHC revealed a similar phenotype as the primary tumor. The patient was ECOG 1 and received a moderate opioid dose.	A 38-year-old woman without comorbidities. Diagnosed with BRCA wild-type BC. Breast-conserving surgery and axillary dissection 4 years ago (grade II, 22 mm invasive ductal carcinoma, ER 25%, PgR 10%, Ki-67 40%, HER2−). The axillary status was 4/16 lymph nodes with extracapsular extension. Adjuvant treatment comprised CT, radiotherapy (breast and lymph node areas), and endocrine treatment. Four years later, diagnosed with lytic bone metastases in the spinal iliac (l.sin., ThVII, and ThVIII). She received oxycodone depot 10 mg twice daily for pain relief.

Abbreviations: aBC: advanced breast cancer; BC: breast cancer; BRCA1: breast cancer gene 1; CT: chemotherapy; ECOG: Eastern Cooperative Oncology Group performance status; ER: oestrogen receptor; IHC: immunohistochemistry; HER2−: human epidermal growth factor receptor 2 negative; PgR: progesterone receptor; ULN: upper limit of normal.

presents a description of the three patient cases used in this study.

Results

Panel participants

In total, 28 panellists participated in the study. Of these, nine practiced in Sweden, seven in Norway, six in Denmark, five in Finland, and one in Iceland. The majority (74%) had at least 10 years of clinical experience treating BC (30% reported more than 20 years) and two-thirds of the panellists currently practiced at a university hospital. Most panellists reported attendance at two to five BC-related international scientific conferences per year and 74% had the highest level of experience in clinical trials (principal investigator). The level of experience with co-authoring BC-related publications varied among the panel. Detailed information on the panellists is available in Supplementary Table S2.

Outcomes

A total of 180 questions were posed during the Delphi panel. In round 1, 55 questions were posed, with 31 being consensus-seeking questions, out of which 14 reached consensus (45%). In round 2, 112 questions were posed, with 55 being consensus-seeking questions, out of which 21 reached consensus (38%). In round 3, 13 questions were posed (all were consensus-seeking), out of which 10 reached consensus (77%).

Different lines of therapy

The main consensus statements and respective consensus levels of the different lines of therapy for HR+/HER2− aBC are presented in Supplementary Table S3.

Topic 1: First-line therapy

ET in combination with a CDK4/6 inhibitor was the preferred 1L treatment for both endocrine-resistant or endocrine-sensitive HR+/HER2− aBC patients (>90%), with CT being the preferred option in specific clinical situations, such as in patients with low HR expression (70%). Additionally, panellists listed overall survival (OS) as the most important clinical outcome for choosing a treatment for HR+/HER2− aBC patients when interpreting clinical studies (81%), followed by progression-free survival (PFS) and quality of life (QoL).

Topic 2: Second-line therapy

Overall, consensus regarding the selection of 2L therapy was partly reached. Continuing ET with/without targeted therapy was the preferred treatment choice in 2L (100%). Furthermore, panellists agreed on the use of ET in combination with a CDK4/6 inhibitor in 2L, following ET monotherapy (aromatase inhibitor or fulvestrant) in 1L (93% and 100%, respectively). The use of 2L CT, instead of ET, was suggested in patients with good performance status in specific clinical scenarios such as visceral crisis, endocrine resistance, or rapid progressive disease.

Topic 3: Third-line therapy

Consensus was not reached for questions on 3L treatment. Most panellists reported that they would not rechallenge with the same ET used in previous treatment lines (59%).

Specific HR+/HER2− aBC patient subgroups

The main consensus statements and respective consensus levels for specific HR+/HER2− aBC patient subgroups are presented in Supplementary Table S4.

Topic 4: Oligometastatic disease

Consensus was not reached regarding the definition of oligometastatic disease and the use of local treatment as a part of first-line therapy. Most panellists defined oligometastatic disease as the presence of up to three metastases (67%). However, consensus was reached on the use of systemic maintenance treatment for oligometastatic disease, following completion of local treatment (100%).

Topic 5: De novo aBC

No consensus was reached on the use of local treatment for primary tumours in *de novo* aBC.

Topic 6: Brain metastases

Consensus was reached on the use of radiotherapy/radiosurgery and ET in combination with a CDK4/6 inhibitor for the treatment of newly diagnosed brain metastases, in patients with both symptomatic and asymptomatic disease.

Special HR+/HER2− aBC treatment considerations

The main consensus statements and respective consensus levels for special HR+/HER2− aBC treatment considerations are presented in Supplementary Table S5.

Topic 7: Age-related treatment considerations

Panellists agreed that for first-line treatments, there is no age limit for the use of ET monotherapy and ET in combination with a CDK4/6 inhibitor (70% and 88% agreement, respectively). Lowering the starting dose of CDK4/6 inhibitors based on age was considered by 56% of the panellists but no consensus on this statement was reached.

Topic 8: Visceral crisis

The majority of panellists defined visceral crisis as the presence of dyspnoea at rest that cannot be relieved by pleural drainage (93%), as well as bilirubin levels higher than 1.5 times the upper limit of normal (78%). Biliary tract obstruction, >70% of the liver is occupied by metastases (liver enzymes are substantially altered but bilirubin is normal), and the presence of metastases in the central nervous system was not considered as visceral crisis by the majority of the panellists.

Topic 9: Evaluation of response to ET

Consensus was reached that evaluation of ET treatment should occur every 12 weeks (93%).

Topic 10: CDK4/6 inhibitor use during radiotherapy

The majority of panellists agreed that treatment with a CDK4/6 inhibitor should not be discontinued during single-fraction palliative radiotherapy (82%), rather it should be discontinued during fractioned palliative radiotherapy (5–10 fractions; 79%).

Other topics

Topic 11: Patient cases. In addition to the generic questions, panellists answered specific questions on three case vignettes. The answers were concordant with the results from the generic questions. Findings from the case vignettes are presented as decision trees (Figures 1–3).

Topic 12: Diagnostics. The majority of panellists agreed that for a patient to be eligible for ET, oestrogen receptor-positive (ER+) tumour cell expression should be >10%, independent of the line of therapy (85%). Most panellists considered that a biopsy would be ordered at diagnosis of aBC. Finally, most panellists reported the use of next-generation sequencing or other analytics for precision medicine in their daily clinical practice.

Topic 13: Guidelines. The majority of panellists adhered to international guidelines (85%), with the European Society for Medical Oncology (ESMO)/5th European School of Oncology–ESMO international consensus guidelines for advanced breast cancer (ABC5) guidelines reported as the most followed (83%). The reasons for lack of adherence to international guidelines included adherence firstly to national guidelines (mostly similar to international guidelines), as well as the lack of access to treatments listed in international guidelines in their respective country. Additionally, almost all panellists stated that their clinic recommended adhering to national guidelines (93%). All panellists reported the possibility to go outside recommended guidelines for specific cases (100%).

Topic 14: Current evidence versus clinical practice. Panellists were asked to describe their treatment choice according to current evidence and daily practice for different clinical scenarios relating to patient case vignettes B and C.

The following scenarios relate to patient B. Consensus was reached on the use of CT as the patient has had a short response to a CDK4/6 inhibitor, both according to current evidence and daily practice (85% for both). Consensus was also reached on the use of ET in combination with a CDK4/6 inhibitor when a patient has had a long response to CT,

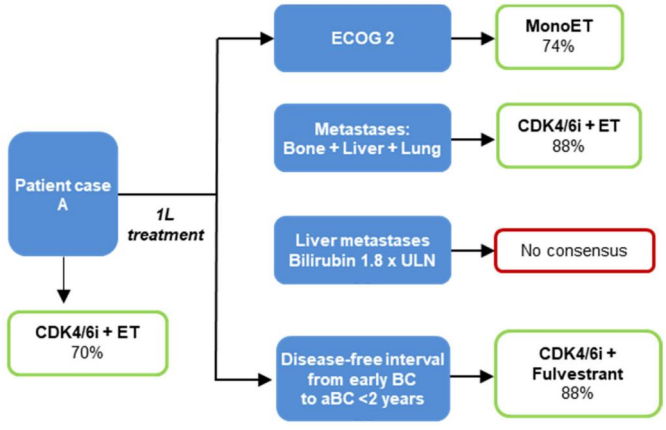

Figure 1. Patient case A.
Abbreviations: 1L: first-line; aBC: advanced breast cancer; BC: breast cancer; CDK4/6: cyclin-dependent kinase 4/6; ECOG: Eastern Cooperative Oncology Group; ET: endocrine therapy; MonoET: endocrine therapy in monotherapy; ULN: upper limit of normal.

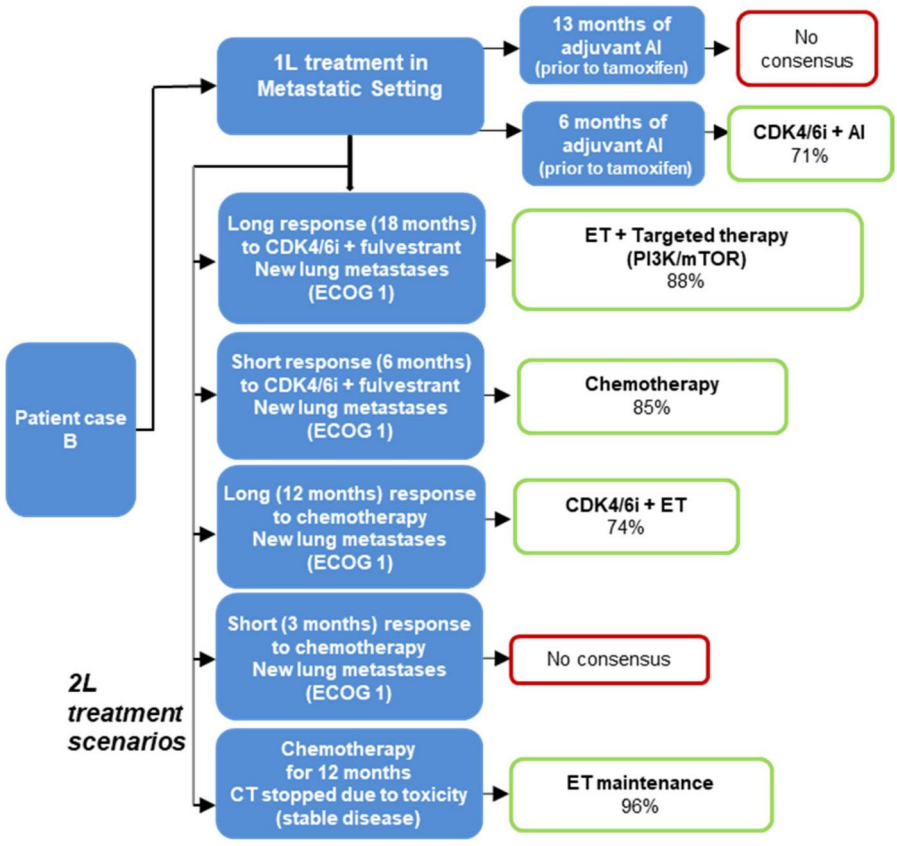

Figure 2. Patient case B.
Abbreviations: 1L: first-line; 2L: second-line; AI: aromatase inhibitor; CDK4/6: cyclin-dependent kinase 4/6; CT: chemotherapy; ECOG: Eastern Cooperative Oncology Group; ET: endocrine therapy; mTOR: mammalian target of rapamycin; PI3K: phosphatidylinositol 3-kinase.

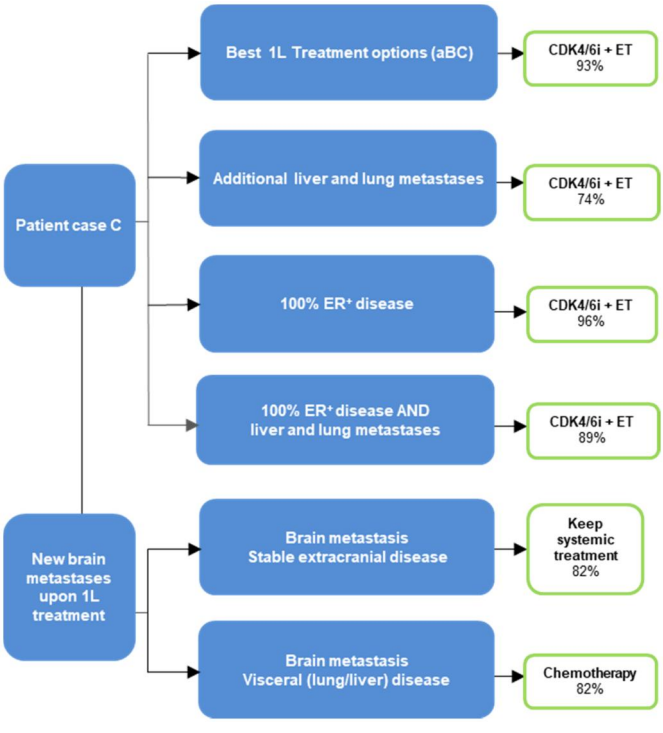

Figure 3. Patient case C.
Abbreviations: 1L: first-line; aBC: advanced breast cancer; CDK4/6: cyclin-dependent kinase 4/6; ER+: oestrogen receptor-positive; ET: endocrine therapy.

according to current evidence (74%). No consensus was reached on the treatment choice according to daily practice for this scenario. Regarding the use of ET in combination with alpelisib, consensus was reached when considering current evidence (88%), but not when considering daily practice.

Regarding patient C, consensus was reached on the use of ET in combination with a CDK4/6 inhibitor according to current evidence and daily practice for the following scenarios: best 1L treatment option for aBC (93% and 88.9%, respectively), 100% ER disease (96% and 96%, respectively) and 100% ER disease with liver and lung metastases (89% and 89%, respectively). Consensus was also reached on the use of ET in combination with a CDK4/6 inhibitor as the best 1L treatment for liver and lung metastases, according to current evidence (74%). No consensus was reached on treatment choice according to daily practice for the scenario.

Discussion

The treatment landscape of HR+/HER2− aBC is rapidly evolving with the development of new therapies [7,30]. This rapid development, together with the continuous update of the treatment guidelines, may pose a challenge in terms of therapeutic decision-making [7]; therefore, these findings have interest beyond the actual point in time and the actual treatments discussed. The aim of this Delphi study was to assess

perspectives on HR+/HER2− aBC treatment across the Nordics.

Consensus was reached on the topics of treatment approach in 1L and 2L therapy, brain metastases, visceral crisis, and CDK4/6 inhibitor use during radiotherapy. Regarding 1L and 2L therapy, the results of this study were, overall, in accordance with the national treatment guidelines for HR+/HER2− aBC in the Nordics [8–11]. Furthermore, these results were consistent with the guidelines from the ESMO/ABC5 and National Comprehensive Cancer Network [31–33]. Notably, in this study, consensus was not reached on rechallenging with ET or CDK4/6 inhibitor after disease progression.

The findings on treatment strategy in patients with brain metastases where radiotherapy as local treatment together with systemic therapy are the preferred options with continuation with current systemic treatments if the extracranial disease is stable are consistent with published literature and treatment guidelines [8–11,31,34,35].

Concerning visceral crisis, the findings on its definition and treatment are also concordant with the treatment guidelines (except for the Finnish guidelines that do not recommend a specific treatment) [9–11,31,32,36]. Additionally, the ABC5 guidelines define visceral crisis similarly to the findings of this study [32].

There was also consensus on OS remaining the gold standard when assessing clinical studies of new oncological products, as well as on its use to guide treatment choice for HR+/HER2− aBC patients [37].

Overall, these results suggest HR+/HER2− aBC treatment in these topics is similar across the Nordics. Choice of 1L and 2L therapy is well researched, with several phase 3 studies to support one's decisions. This could explain why consensus was reached as panellists would have more evidence to support their therapeutic decision making.

Consensus was not reached for 3L therapy, the definition of oligometastatic disease, and the local treatment of primary tumour in patients with *de novo* aBC. The lack of consensus may be explained by the different 3L therapies recommended in the national treatment guidelines in the Nordics at the time of the study. Similarly, there were also heterogeneous recommendations for third or later lines of therapy in the international guidelines [31,32,36]. This highlights the lack of pivotal randomised studies in this area. Additionally, the results of this study highlighted the heterogeneity in the definition of oligometastatic disease [38]. This heterogeneity could also have contributed to the lack of consensus observed in this topic. In the then-current ESMO/ABC5 guidelines, oligometastatic disease is defined as a 'limited number and size of metastatic lesions (up to 5 and not necessarily in the same organ)' [31,32]. Nevertheless, there was no specific definition of oligometastatic disease in the Nordic treatment guidelines [8–11]; even though recommendations for its treatment were found in the Swedish and Norwegian guidelines [9,10]. Initial randomised trials on the use of local treatment as a part of first-line therapy in oligometastatic disease have shown conflicting results which might also be an explanation for the lack of consensus [39,40].

Concerning the potential impact of surgical removal of primary tumour in *de novo* aBC, the available evidence is contradictory which could have contributed to the lack of consensus [31,32]. Further research is warranted on the topics that did not reach consensus to support oncologists and patients in the shared decision-making process.

The findings of this study indicate that ET in combination with a CDK4/6 inhibitor dominates the Nordic treatment landscape for HR+/HER2− aBC. ET remains the frontline treatment choice for this patient population [41]. Notably, 1L and 2L ET combinations with targeted therapies dominated as the preferred treatment choice [8–11,31–33,42]; with ET monotherapy reported in a few clinical situations (e.g., patients with poorer performance status). Among the targeted therapies, CDK4/6 inhibitors were consistently reported as the most used in combination with ET. Previous research has shown a statistically significant improvement of PFS and OS, as well as maintenance or improvement of QoL, in randomized clinical trials (RCTs) when adding a CDK4/6 inhibitor to ET, compared to ET monotherapy, in HR+/HER2− metastatic BC [30,43,44]. Furthermore, a statistically significant improvement in PFS has been demonstrated both in 1L and 2L use of a CDK4/6 inhibitor in combination with ET, compared to ET alone [45]. A systematic literature review demonstrated the PFS benefit in real-world evidence studies of CDK4/6 inhibitors in combination with ET compared to ET monotherapy [46]. These results are in line with a similar three-round Delphi method study conducted in Belgium [47], as well as the proceedings from a 2021 BC expert meeting group [48]. Although ET combined with targeted therapy was the preferred treatment option in general, CT still remained a relevant option in specific clinical situations (e.g., visceral crisis) [9–11,31,32,36].

This study also found that the patient's age is not a limiting factor when using a CDK4/6 inhibitor. This is in line with available research which has proved similar efficacy of a CDK4/6 inhibitor in older women, compared to younger women [49,50]. Furthermore, there was no consensus that a lower dose of CDK4/6 inhibitors should be considered in older patients, even though this strategy is quite common in clinical practice in older cancer patients.

Concerning the use of CDK4/6 inhibitors during radiotherapy, a recent literature review concluded that this use might have a synergistic radio-sensitising effect, even though further studies are needed to establish its safe use [51]. This is supported by the findings of this study, i.e., panellists considered that CDK4/6 inhibitors should be discontinued during fractioned palliative radiotherapy.

An interesting finding of this study was the observed discrepancy between current evidence and clinical practice. This discrepancy was evident in clinical situations where newer targeted therapies were in focus indicating that the uptake of targeted therapies differs across the Nordics. This could be explained by the differences in the reimbursement of novel BC treatments in the Nordics [14].

The strengths of this study include the use of the Delphi method ensuring the anonymity of panel questionnaires and voting [15,22,23]; and the inclusion of a panel with a high

level of expertise in the disease area, that is representative of the Nordics (inclusion of participants from all Nordic countries). In contrast, the main limitations of this study correspond to the limitations of the Delphi method [15,16]. These include, among others, a lengthy study time, risk of specious consensus (i.e., panellists conform to the dominant idea), sensitivity of the method to the questionnaire design (e.g., clarity of the questions), and panel composition (e.g., different groups will provide different answers). Further limitations of this study include the fact that all questions considered CDK4/6 inhibitors as a class rather than as three different substances as well as the fact that questions included in the Delphi reflect the treatment landscape of HR+/HER2− negative aBC at the time where they were constructed thus missing potential newer treatment options.

This was a multi-round modified Delphi study on the current treatment strategies of HR+/HER2− aBC, as well as its respective uptake and implementation in current clinical practice, across the Nordic countries. Overall, consensus was reached on topics where the certainty of available evidence is high, and the current international and national guidelines are in line. Conversely, the lack of consensus in some topics could be due to the paucity of evidence. ET in combination with a CDK4/6 inhibitor remains the frontline treatment choice for HR+/HER2− aBC in the Nordics. The uptake of targeted therapies differs across the Nordic countries and certain treatments are not part of the standard clinical practice. As the treatment landscape of HR+/HER2− aBC is evolving rapidly, the consensus obtained in this study is expected to change in the near future. As such, future Delphi studies are warranted to keep up-to-date with the HR+/HER2− aBC treatment landscape.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author (P.K.). The data are not publicly available due to restrictions, e.g., their containing information that could compromise the privacy of research participants.

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