Purpose
To report the treatment utilization patterns for hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2−) breast cancer in urban mainland China (CancerMPact®).

Methods
The results presented are from an online survey conducted in September 2019 with 45 physicians treating breast cancer patients from 11 cities in mainland China.

Results
Surveyed physicians reported that Stage I HR+/HER2(−) breast cancer patients are often treated with surgery alone (42%), whereas the use of surgery in combination with systemic therapy with or without radiotherapy increases in later stages (Stage II 67%, Stage III 77%). Doxorubicin–cyclophosphamide (AC)-based regimens were the most common in both the neoadjuvant and adjuvant settings in HR+/HER2(−) breast cancer patients, across all stages. In metastatic patients, use of surgery and radiotherapy decreases in favor of utilization of systemic therapy alone. Pre- and post-menopausal metastatic patients were frequently treated with hormone therapy or AC-based regimens in first line. Regardless of the first-line therapy administered, capecitabine-based regimens were commonly used in second line. In third line, chemotherapy regimens containing capecitabine or gemcitabine were given to nearly 40% of HR+/HER2(−) breast cancer patients. There were no standard of care regimens established for fourth or greater lines of treatment. In metastatic HR+/HER2(−) breast cancer, physicians reported 50% objective response rates in first-line settings with a progression-free survival of 16 months.

Conclusion
HR+/HER2(−) breast cancer patients in urban mainland China were prescribed chemotherapy regimens more frequently than CDK4/6 inhibitors. Treatment practices varied, with physicians reporting the use of multiple modalities and treatment regimens for their patients.

Keywords
Breast cancer · Chemotherapy · Treatment patterns · Cancer treatment · China

Introduction
Breast cancer is the leading cause of cancer-related deaths in women worldwide [1]. The incidence of breast cancer has been decreasing in the United States (USA) and Western Europe (EU5), while in Asian countries, including China, breast cancer incidence and mortality have been rising over the past several years [2]. In China, it is estimated that 307,184 people were diagnosed with breast cancer in 2019 [3]. Lifestyle changes, obesity, and lack of...
access to reliable diagnostics and effective therapies have contributed to this rise in breast cancer mortality in China and other developing countries [4].

Aberrations in hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) pathways are frequently observed in breast cancer patients [5]. Based on molecular biomarkers, breast cancer can be classified into at least four different subtypes, with different treatments and prognoses: HR-negative and HER2-enriched, HR-positive and HER2-negative luminal A, HR-positive and HER2-positive luminal B and triple negative/basal-like, which is a subtype that is negative for both HR and HER2. In 2019, approximately 54% of breast cancer cases in China were diagnosed with HR+/HER2(−), 17% with HR+/HER2+, 12% with HR(−)/HER2+, and 17% with triple negative subtypes [3]. The HR+/HER2(−) subtype is likely to remain the most commonly diagnosed type of breast cancer, and its annual incidence is predicted to increase by 2% over the next 3 years [3, 6–8].

Currently available treatment options for breast cancer include surgery, radiation, and systemic therapies, including chemotherapy, hormone therapy, immunotherapies, and targeted therapies. Choice of modality is highly complex and is based on the stage at diagnosis, biomarker status, subtype, patient age, comorbidities, and menopausal status [9]. Over the last few decades, treatment options for metastatic HR+/HER2(−) breast cancer patients have evolved with the approval of targeted agents. Hormone therapy is still widely used as a standard of care either as single agent or in combination with other systemic drugs such as chemotherapy and CDK4/6 inhibitors [10, 11]. Most of the studies that determined the effectiveness of these treatments were performed in western countries and some Asian institutions have questioned the generalizability of these data to Eastern women, underlining the need to better understand how these patients are treated in Asia, particularly in China [12].

The current patterns of care of breast cancer patients in Asia, and in China specifically, are largely unknown [12]. A better understanding of treatment practices could highlight the existing strengths and knowledge gaps and accordingly inform clinical trial design and resource allocations in the local healthcare systems.

Previously, we reported real-world evidence (RWE)-based data collected from various registries and primary physician surveys that identified how physicians treat non-small-cell lung cancer and melanoma in the USA and EU5 countries and provided a better understanding of the treatment dynamics in various markets [13, 14]. Here, we aim to report the results of a survey of physicians treating HR+/HER2(−) breast cancer patients in urban mainland China.

Materials and methods

CancerMPact® (CMP) is a proprietary database from Cerner Enviza (formerly known as Kantar Health), which contains oncology epidemiology and cancer treatment data [3]. Cerner Enviza conducts annual surveys with physician specialists, including oncologists, treating cancer patients across various tumor types in the USA, EU5, Japan, and China. In 2019, this CMP study surveyed 4859 physicians from these geographic regions about the treatment of 31 different tumors.

The survey performed in China for breast cancer in 2019 recruited 45 physicians from 11 cities in mainland China using an online format. To be eligible for the survey, physicians must have been a board-certified practitioner of one of the following specialties: medical oncology, surgical oncology, or surgery; be in practice for a minimum of 5 years; and must have treated a minimum of 23 breast cancer patients per month.

The survey questionnaire was developed by an internal Oncology team, who reviewed current treatment algorithms recommended by international guidelines, such as those from the Chinese Society of Clinical Oncology (CSCO) [15], as well as new drug approvals by China’s national agency for regulating drugs and medical devices, The National Medical Products Administration (NMPA). This was supplemented with English and Chinese language literature reviews of registrational clinical trial data from medical journals and oncology conferences to identify the practice behavior and potential changes in the treatment of breast cancer in China.

The 2019 breast cancer survey asked physicians about their oncology practice experience, their patient characteristics (e.g., patient volume, the stages of patients seen and patient biomarker status) and to consider patients that they had treated in the last 6 months. Detailed questions covered aspects of treatment by stage and subtype, and physicians were asked to report the proportion of their patients treated by each modality type and the percentage of patients treated with each systemic therapy regimen, the duration of the treatment, and their results. Chemotherapy agents, subtype-specific targeted agents, and hormonal agents at each line of therapy were also reported. Physicians were asked to report treatment outcomes (percentage of recurrence and patient prognosis) at each line of therapy up to fifth line, if applicable. The survey explicitly communicated to physicians that they should answer questions on their utilization of Western treatment modalities and Western medicines and to not include Traditional Chinese Medicine (TCM) in their responses. In addition, definitions of relapse and refractory patients, and endpoints, including overall response rate (ORR) or progression-free survival.
(PFS), were not provided in the survey and were based on
the physicians’ own clinical practice and experience.

The online physician questionnaire was programmed,
fielded, and hosted by an online-survey company and the
anonymized raw data were securely transferred to Cerner
Enviza, where data analysis was completed. Data from the
survey are reported as unweighted averages of all responses
and no formal statistical treatment was applied to the results.

The survey was fielded in September 2019. The CMP
data source used for this research does not collect or use
patient-level data, or any data involving people, medical
records, or human samples. The researchers did not review
patient charts, survey patients, or interact with patients in
any way. All information is retrieved from online physician
surveys regarding information around overall treatment pat-
terns. Therefore, no Institutional Review Board approval was
necessary.

Results

On average, the 45 Chinese physicians included in this sur-
vey had 16.3 years of medical experience post-residency
training and treated 41 breast cancer patients per month.
More than half of them were medical oncologists from Level
III hospitals and together they treated 1848 breast cancer
patients per month (Table 1). Over half of the respondents
(60.0%) were located in Beijing, Shanghai, or Guangzhou/
Shenzhen.

Treatment modalities and regimens in early-stage
HR+/HER2(−) breast cancer

According to the physician respondents, 42% of their stage
I patients received surgery only, while almost half received
a combination of surgery with radiation and/or systemic
therapy. As the disease progresses, the triple combination
of surgery, radiation, and systemic therapy is increasingly
utilized due to the higher tumor burden associated with more
advanced disease (Table 2).

In both the neoadjuvant (Table 3) and adjuvant (Table 4)
settings, and across stages I–III, physicians reported using
doxorubicin in combination with cyclophosphamide (AC)
with or without a taxane in more than 40% of their HR+/HER2(−)
breast cancer patients. Regimens with an epiru-
bicin and cyclophosphamide (EC) backbone are also quite
commonly used in early-stage patients in the perioperative
setting (Tables 3, 4).

According to the physicians, approximately half of the stage
I patients remained in remission for at least a decade (Table 5).
As disease progresses, the proportion of patients in remission
starts to drop with only 17% of stage III patients not experi-
encing relapse within 10 years of initial therapy. Across stages

| Table 1 Characteristics of physicians surveyed, China, 2019 |
|---------------------------------------------------------|
| Characteristics of physician respondents | N% |
| Number of physicians surveyed | 45 |
| Average number of years of practice after residency (range) | 16.3 (5–30) |
| Average number of breast cancer patients treated by each physician monthly (range) | 41.1 (23–100) |
| Board-certified specialty | |
| Medical oncology (%) | 57.8% |
| Surgical oncology (%) | 22.2% |
| Surgery (%) | 20.0% |
| Hospital levels | |
| Level III (%) | 91.1% |
| Level II (%) | 4.4% |
| Cancer specialty (%) | 4.4% |
| Practice locations | |
| Beijing (%) | 22.2% |
| Shanghai (%) | 22.2% |
| Guangzhou/Shenzhen (%) | 15.6% |
| Xi’an (%) | 6.7% |
| Chengdu (%) | 6.7% |
| Tianjin (%) | 6.7% |
| Othera (%) | 20.0% |

aLocations not individually reported if less than 5%

| Table 2 Initial treatment modalities for HR+/HER2(−) breast cancer patients, Stages I–III, China, 2019 |
|-------------------------------------------------|
| Modality | Stage I (%) | Stage II (%) | Stage III (%) |
| Surgery only | 41.9 | 14.1 | 4.5 |
| Surgery, systemic therapy | 26.5 | 35.4 | 36.4 |
| Surgery, RT, systemic therapy | 16.1 | 31.9 | 41.0 |
| Surgery, RT | 4.9 | 3.5 | 2.2 |
| Systemic therapy only | 4.4 | 4.6 | 6.4 |
| No therapy/observationa | 2.6 | 1.8 | 3.3 |
| RT, systemic therapy | 2.4 | 7.6 | 5.5 |
| RT only | 1.2 | 1.1 | 1.7 |

Systemic therapy includes chemotherapy, biologic therapy as well
as HER2 targeted and other targeted agents. Survey of 45 physicians
who treat a total of 1,848 breast cancer patients monthly, conducted
in September 2019; 36 physicians completed data for stage I, 43 phy-
sicians completed data for stage II, and 45 physicians completed data
for stage III. Survey of 45 physicians who treat a total of 1,848 breast
cancer patients monthly, conducted in September 2019

RT radiation therapy

aIn the survey, supportive care and/or traditional Chinese medicine
are included within no therapy/observation

I–III, approximately 20% of the patients remained disease-
free between 6 and 10 years following therapy. The proportion
Table 3 Utilization of neoadjuvant systemic therapy regimens in HR+/HER2− breast cancer patients, Stages I–III, China, 2019

| Regimen              | Stage I (%) | Average number of months (range) | Stage II (%) | Average number of months (range) | Stage III (%) | Average number of months (range) |
|----------------------|-------------|---------------------------------|--------------|----------------------------------|--------------|----------------------------------|
| AC, docetaxel        | 19.0        | 5.0 (3–7)                       | 22.2%        | 4.5 (2–8)                        | 22.7%        | 4.7 (2–8)                        |
| AC, paclitaxel       | 14.1        | 5.7 (3–8)                       | 6.4%         | 4.8 (3–6)                        | 9.1%         | 4.2 (3–6)                        |
| EC                   | 11.6        | 5.3 (2–8)                       | a            | –                                | a            | –                                |
| Other                | 11.8        | 6.0                             | 11.2%        | 5.1                              | 13.2%        | 5.6                              |
| Other AC-based       | 12.2        | 6.0                             | 17.0%        | 4.4                              | 20.7%        | 4.6                              |
| Other docetaxel-based| 6.8         | 9.0                             | 14.4%        | 5.6                              | 11.5%        | 5.7                              |
| Other EC-based       | 9.9         | 9.0                             | 11.2%        | 5.8                              | 13.0%        | 5.6                              |
| Other epirubicin-based| 14.5      | 7.6                             | 13.3%        | 5.2                              | 6.7%         | 5.9                              |

Seventeen physicians completed data for stage I, 37 physicians completed data for stage II, and 44 physicians completed data for stage III. “Other” category includes various therapies used in <5% of patients each.

AC doxorubicin, cyclophosphamide, EC epirubicin, cyclophosphamide

*Less than 5%

Table 4 Utilization of adjuvant systemic therapy regimens in HR+/HER2− breast cancer patients, Stages I–III, China, 2019

| Regimen            | Stage I (%) | Average number of months (range) | Stage II (%) | Average number of months (range) | Stage III (%) | Average number of months (range) |
|--------------------|-------------|---------------------------------|--------------|----------------------------------|--------------|----------------------------------|
| AC                 | 13.8%       | 4.3 (1–6)                       | 10.1         | 5.4 (3–8)                        | 9.8          | 5.5 (4–6)                        |
| AC, docetaxel      | 14.6%       | 5.7 (3–8)                       | 12.9         | 5.5 (3–8)                        | 19.3         | 5.5 (3–8)                        |
| EC, docetaxel      | 9.6%        | 5.4 (4–6)                       | 11.2         | 5.4 (3–8)                        | 8.5          | 5.8 (4–8)                        |
| Other doxorubicin-based | a        | –                               | 5.5          | 4.8 (2–6)                        | 5.3          | 6.4 (5–13)                       |
| Other AC-based     | 21.1%       | 5.0                             | 28.7         | 5.8                              | 26.2         | 5.5                              |
| Other EC-based     | 17.7%       | 10.5                            | 15.2         | 5.4                              | 15.1         | 5.5                              |
| Other              | 19.1%       | 9.4                             | 16.4         | 6.1                              | 15.8         | 5.7                              |

Twenty-eight physicians completed data for Stage I, 38 physicians completed data for Stage II, and 43 physicians completed data for Stage III. “Other” category includes various therapies used in <5% of patients each.

AC doxorubicin, cyclophosphamide, EC epirubicin, cyclophosphamide

*Less than 5%

Table 5 Recurrence patterns in stage I–III HR+/HER2− breast cancer patients in China after receiving initial treatment, China, 2019

| Regimen                                | Stage I (%) | Stage II (%) | Stage III (%) |
|----------------------------------------|-------------|--------------|---------------|
| Patients who do not respond to therapy (refractory) | 3.4         | 5.8          | 11.5          |
| Patients who respond but relapse within 1 year of therapy | 8.9         | 13.2         | 20.4          |
| Patients who respond but relapse between 1 and 5 years of therapy | 17.9        | 25.1         | 30.5          |
| Patients who respond but relapse between 6 and 10 years of therapy | 22.0        | 22.9         | 20.2          |
| Patients who do not relapse within 10 years of therapy | 47.8        | 32.9         | 17.2          |

Survey of 45 physicians who treat a total of 1,848 breast cancer patients monthly, conducted in September 2019; 36 physicians completed data for Stage I, 43 physicians completed data for Stage II, and 45 physicians completed data for Stage III.
of patients with refractory tumors or disease relapse within a year, varied from 12% for stage I to 32% for stage III (Table 5).

In nearly 60% of the patients with stage I breast cancer with local recurrence, surgery, either alone or in combination with systemic therapy, was the modality of choice for managing local recurrence (Table 6). Systemic therapy alone was used in 9% to 12% of stage I–III breast cancer patients with local recurrence (Table 6). The proportion of patients with local recurrence requiring a combination of surgery, radiation, and systemic therapy increased from 18% in stage I to 34% in stage III breast cancer (Table 6).

### Treatment regimens used in advanced HR+/HER2(−) breast cancer

In stage IV HR+/HER2(−) breast cancer, systemic therapy is the mainstay of treatment. Physicians reported that over 80% of patients receive systemic therapy in their first-line treatment, either alone or in combination with other modalities (Table 7). About 40% of metastatic patients also receive surgery as part of a multimodal treatment approach, often in combination with systemic therapy and/or radiation. Although surgery is not associated with improvement in survival in metastatic patients [16, 17], clinical guidelines recognize that it may still be suitable in some patients to achieve local control of the primary tumor [18]. In pre-menopausal stage IV patients, AC-based regimens or hormone therapies were frequently used, with each group having about 25% utilization share (Table 8). Docetaxel was the most frequently prescribed taxane in these advanced HR+/HER2(−) breast cancer patients. Palbociclib, the only CDK4/6-targeted agent approved in China at the time the survey, was conducted and was prescribed in 5% of metastatic patients, regardless of menopausal status (Table 8).

The general treatment pattern of post-menopausal patients is similar to that of pre-menopausal patients, with AC-based regimens and hormone-alone therapies getting highest utilization. Aromatase inhibitors were most frequently prescribed in post-menopausal patients, with AC-based regimens and hormone-alone therapies getting highest utilization. Aromatase inhibitors were most frequently prescribed in post-menopausal patients, with AC-based regimens and hormone-alone therapies getting highest utilization. Aromatase inhibitors were most frequently prescribed in post-menopausal patients, with AC-based regimens and hormone-alone therapies getting highest utilization. Aromatase inhibitors were most frequently prescribed in post-menopausal patients, with AC-based regimens and hormone-alone therapies getting highest utilization. Aromatase inhibitors were most frequently prescribed in post-menopausal patients, with AC-based regimens and hormone-alone therapies getting highest utilization. Aromatase inhibitors were most frequently prescribed in post-menopausal patients, with AC-based regimens and hormone-alone therapies getting highest utilization. Aromatase inhibitors were most frequently prescribed in post-menopausal patients, with AC-based regimens and hormone-alone therapies getting highest utilization. Aromatase inhibitors were most frequently prescribed in post-menopausal patients, with AC-based regimens and hormone-alone therapies getting highest utilization. Aromatase inhibitors were most frequently prescribed in post-menopausal patients, with AC-based regimens and hormone-alone therapies getting highest utilization. Aromatase inhibitors were most frequently prescribed in post-menopausal patients, with AC-based regimens and hormone-alone therapies getting highest utilization. Aromatase inhibitors were most frequently prescribed in post-menopausal patients, with AC-based regimens and hormone-alone therapies getting highest utilization. Aromatase inhibitors were most frequently prescribed in post-menopausal patients, with AC-based regimens and hormone-alone therapies getting highest utilization.

Second-line treatment choice is often influenced by exposure to prior therapy. Combination regimens containing bevacizumab were used in about 20% of HR+/HER2(−) breast cancer patients who had previously received everolimus with anti-hormonal therapy, while about 8% received palbociclib hormonal therapy and 20% continued with everolimus-based hormonal therapy (Table 9). Patients who progressed on single-agent non-steroidal hormonal therapy in front-line settings were frequently prescribed hormonal therapy-based combinations (15%) or hormone therapy as single agent (23%) (Table 9). Chemotherapy combination regimens with capecitabine or gemcitabine were commonly used in second line following progression after single-agent aromatase inhibitors (Table 9). Palbociclib was used in less than 5% of the patients in second line if they progressed on a single-agent aromatase inhibitor (Table 9). Once the disease progressed, about 25% of the patients who received palbociclib with a hormonal agent in first line continued to receive palbociclib-based regimens in second line, but most other patients receive chemotherapy-based regimens (Table 9). Capecitabine-based treatments were reported in about 34% of the patients after progressing on first-line palbociclib hormonal therapy combination (Table 9).
In the third-line setting, chemotherapy containing capecitabine (25%) or gemcitabine (17%) was most commonly used to treat metastatic HR+/HER2(−) breast cancer patients (Table 10). Nearly one-third of the patients were treated with hormone therapy, either as a single agent (13%) or in combination with everolimus (13%) or palbociclib (5%; Table 10).

In both fourth and fifth lines, the most commonly used therapy was anti-endocrine. More than 30% of fourth-line patients and over 40% of fifth-line patients received an anti-endocrine therapy either alone or in combination with either palbociclib or everolimus (Table 11). Capecitabine-based regimens were prescribed in over 20% of fourth-line cases (Table 11). As available treatment options diminish in later lines, reliance on clinical trials increases. About 6% of fourth-line patients were participants in clinical trials while 13% enrolled in clinical trial studies in fifth-line settings.

Table 8  Utilization of first-line systemic regimens in pre-menopausal and post-menopausal patients with HR+/HER2− breast cancer, China, 2019

| Regimen                          | Pre-menopausal |       |       | Post-menopausal |       |       |
|----------------------------------|----------------|-------|-------|-----------------|-------|-------|
|                                  | Utilization    | Average number of months (range) |       | Utilization     | Average number of months (range) |       |
| Bevacizumab-based                | 7.2%           | 6.3 (3–12) |       | 7.6%           | 6.1 (3–12) |       |
| Carboplatin-based                | 5.6%           | 5.2 (3–6)  |       |                 |        |       |
| AC                               | 8.2%           | 4.6 (3–6)  |       | 7.3%           | 4.7 (1–6) |       |
| AC, docetaxel                    | 8.0%           | 5.7 (3–12) |       | 7.4%           | 5.8 (3–12) |       |
| Docetaxel, capecitabine          | 6.2%           | 5.8 (4–8)  |       |                 |        |       |
| Everolimus-based                 | 13.6%          | 5.7 (1–60) |       | 9.6%           | 8.5 (3–60) |       |
| Tamoxifen                        | 4.8%           | 6.1 (1–60) |       | 16.7%          | 12.0 (1–36) |       |
| Palbociclib, hormone therapy     | 6.1%           | 5.7 (1–14) |       | 16.2%          | 5.2 (3–12) |       |
| Fulvestrant                      | 6.3%           | 9.6 (1–60) |       | 17.3%          | 12.1 (3–60) |       |
| Aromatase inhibitor              |                |          |       |                |        |       |
| Other                            | 18.3%          | 6.8 (3–14) |       | 16.2%          | 5.2 (3–12) |       |
| Other capcitabine-based          | 4.8%           | 6.2 (4–8)  |       | 9.6%           | 7.1 (3–12) |       |
| Other AC-based                   | 6.1%           | 8.5 (3–12) |       | 8.3%           | 6.1 (3–12) |       |

Forty-two physicians completed data for pre- and post-menopausal patients. “Other” category includes various therapies used in ≤5% of patients each

AC doxorubicin, cyclophosphamide

aLess than 5% utilization

Table 9  Second-line utilization by systemic regimen according to first-line regimen received in metastatic HR+/HER2− breast cancer, China, 2019

| Regimen                          | Received Everolimus plus hormone agent 1st line (%) | Received non-steroidal aromatase inhibitor alone 1st line (%) | Received palbociclib plus hormone agent 1st line (%) |
|----------------------------------|----------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------|
| Hormone therapy                  | 9                                                  | 23                                                          | 1                                                        |
| Bevacizumab-based                | 19                                                 | 11                                                          | 5                                                        |
| Everolimus, hormone therapy      | 20                                                 | 12                                                          | 12                                                       |
| Palbociclib, hormone therapy      | 8                                                  | 3                                                           | 25                                                       |
| Nab-paclitaxel                   | 2                                                  | 5                                                           | 5                                                        |
| Chemo therapy, hormone therapy   | 5                                                  | 0                                                           | 2                                                        |
| Gemcitabine-based                | 9                                                  | 8                                                           | 5                                                        |
| Capecitabine-based               | 17                                                 | 21                                                          | 34                                                       |
| Doxorubicin/cyclophosphamide-based| 8                                                  | 14                                                          | 9                                                        |
| Other                            | 4                                                  | 3                                                           | 3                                                        |

Survey of 45 physicians who treat a total of 1,848 breast cancer patients monthly, conducted in September 2019; 17 physicians completed data for Everolimus plus hormone, 24 physicians completed data for non-steroidal aromatase inhibitor alone, and 11 physicians completed data for palbociclib plus hormone. “Other” category includes various therapies used in ≤5% of patients each.
Treatment outcomes in advanced breast cancer

Nearly 60% of pre- and post-menopausal HR+/HER2(−) breast cancer patients experience disease progression following first-line therapy. Of these, about 40% of patients will receive therapy in second line, and rates of subsequent therapy decrease for later lines, with less than 15% of patients receiving sixth line upon progression (Table 12). About 20% of first-line patients do achieve remission; however, remission rates significantly decrease, to less than 10% in fourth line and beyond (Table 12).

Table 10  Third-line utilization by systemic regimen received in HR+/HER2− breast cancer, China, 2019

| Modality               | Third line | Average number of months (range) |
|------------------------|------------|----------------------------------|
| Gemcitabine-based      | 16.9       | 5.7 (2–12)                       |
| Capecitabine-based     | 14.6       | 4.8 (2–12)                       |
| Everolimus, hormone therapy | 13.5 | 7.3 (3–12)                       |
| Hormone therapy        | 12.8       | 5.9 (3–12)                       |
| Bevacizumab-based      | 10.7       | 5.9 (2–12)                       |
| Capecitabine           | 9.1        | 5.6 (3–12)                       |
| Palbociclib, hormone therapy | 5.3 | 8.4 (5–12)                       |
| AC-based               | 5.2        | 5.8 (4–12)                       |
| Other                  | 12.0       | 4.8                              |

Survey of 45 physicians who treat a total of 1848 breast cancer patients monthly, conducted in September 2019; 32 physicians completed data for this question. Other category includes various therapies used in <5% of patients each

AC doxorubicin, cyclophosphamide

Based on their clinical experience and practice, physicians estimated just over 50% disease regression in first line, with patients not progressing to second line for about 16 months; but clinical benefit from treatment decreased with each line of therapy (Table 13). Regardless of line of therapy, over 20% of the patients exhibited stable disease with the respective administered systemic therapy (Table 13).

Discussion

Despite recent advances achieved in early diagnosis and targeted therapies, breast cancer continues to be the leading cause of cancer-related deaths worldwide. These cancer patients respond well to hormonal therapies; however, many will have disease progression after just over a year on hormonal monotherapy [9, 10].

In early stages of breast cancer, surgery is commonly used along with an adjuvant therapy involving systemic agents or radiation. HR+ breast cancer patients respond well to hormonal therapy, which can be either aromatase inhibitors or estrogen receptor binders/degraders. CSCO guidelines emphasize the importance of hormonal therapy, but also state that some patients, such as those with large (> 2 cm) tumors or nodal involvement, may be suitable for treatment with adjuvant chemotherapy. In such cases, hormonal therapy is often administered sequentially after adjuvant chemotherapy [15].

Our research revealed a similar utilization pattern of systemic therapies in both neoadjuvant and adjuvant settings in urban mainland China and elsewhere globally for treating HR+/HER2(−) breast cancer patients [3]. However, the choice of chemotherapy treatment regimen may differ

Table 11  Utilization of fourth-line and fifth-line systemic regimens in HR+/HER2− breast cancer, China, 2019

| Regimen                        | Fourth line | Fifth line |
|--------------------------------|-------------|------------|
|                                | Utilization (%) | Average number of months (range) | Utilization (%) | Average number of months (range) |
| Hormone therapy alone          | 15.6        | 5.1 (2–12) | 24.0        | 5.1 (2–12) |
| Everolimus, hormone therapy    | 10.0        | 7.2 (3–12) | 11.6        | 6.7 (3–12) |
| Palbociclib, hormone therapy   | 10.2        | 6.9 (3–12) | 6.1         | 7.1 (3–12) |
| Nab-paclitaxel                 | 6.9         | 4.0 (3–6)  | 6.1         | 4.1 (3–6)  |
| Capecitabine                   | 5.7         | 3.8 (3–6)  | 7.8         | 4.0 (2–6)  |
| Bevacizumab-based              | 8.6         | 4.9 (3–6)  | 3.2         | 7.8 (4–12) |
| Gemcitabine-based              | 5.5         | 5.1 (3–12) | 7.8         | 6.0 (3–12) |
| Investigational drug (clinical trial) | 6.1 | –          | 13.3        | –          |
| Other capecitabine-based       | 16.7        | 4.6        | 7.7         | 5.8        |
| Other                          | 14.7        | 4.1        | 12.4        | 3.7        |

Survey of 45 physicians who treat a total of 1,848 breast cancer patients monthly, conducted in September 2019; 22 physicians completed data for fourth line and 18 physicians completed data for fifth line. “Other” category includes various therapies used in <5% of patients each
slightly across various markets. In urban mainland China, physicians did show a preference for AC plus taxane regimens, over docetaxel plus cyclophosphamide, which are more commonly used in the US, whereas EC-based regimens are dominant among EU5 physicians for treating stage I HR+/HER2(−) breast cancer patients.

International guidelines for the treatment of metastatic HR+/HER2(−) breast cancer recommend chemotherapy or hormone therapy as the first therapeutic choice for most patients, either as a single agent or in combination with a CDK4/6 inhibitor [9, 10]. The optimal sequence for using hormonal therapy alone or in combination with targeted therapy in front-line settings in metastatic patients is not strictly defined and is often based on patient characteristics. We noted in our survey that, in urban mainland China, physicians most commonly treat pre-menopausal stage IV patients with front-line chemotherapy combination regimens.

Palbociclib was approved in China in July 2018 and launched on September 2018 [19]. At the time that this survey was conducted (September 2019), palbociclib was the only CDK4/6 inhibitor approved by NMPA and its usage in front line was about 5%, which is at a much lower proportion than in the USA, where CDK4/6 plus aromatase inhibitors have become the standard of care for treating HR+/HER2(−) metastatic patients regardless of menopausal phase [3]. In clinical studies, palbociclib with letrozole was shown to provide significant progression-free survival over letrozole alone in HR+/HER2(−) metastatic breast cancer patients [20]. Since the time of survey fielding, there has been a flurry of development in this space, including the approval of two CDK4/6 inhibitors. Abemaciclib was first approved in December 2020 for the treatment of metastatic patients [21], and most recently, in January 2022, it also received approval for use in the adjuvant setting [22]. In addition, in December 2021, a domestically developed CDK4/6 inhibitor, dalpiclrib, was approved by the NMPA [23]. Around the end of 2020, the first generic palbociclib, also got approved, but is not set to launch until the branded agent’s patent expiration in January 2023. A fourth CDK4/6 inhibitor, ribociclib, was reported to provide significant improvements in overall survival when combined with fulvestrant relative to fulvestrant plus placebo in HR+/HER2(−) metastatic breast cancer patients [24]. However, ribociclib is not yet on the market in China; an NDA is under regulatory review by the NMPA and the approval may not be too far in future.

Table 12 Physician-reported outcomes of metastatic breast cancer patients who received later lines of systemic therapy in HR+/HER2− breast cancer, China, 2019

| Outcomes                                                                 | First line to second line | Second line to third line (%) | Third line to fourth line (%) | Fourth line to fifth line (%) | Fifth line to sixth line (%) |
|------------------------------------------------------------------------|---------------------------|-------------------------------|------------------------------|-----------------------------|-------------------------------|
| Pre-menopausal (%)                                                     | 20.4                      | 18.8                          | 10.5                         | 9.3                         | 8.5                           |
| Post-menopausal (%)                                                    | 22.0                      | 25.9                          | 43.2                         | 48.2                        | 49.6                          |

Forty-two physicians completed data for first to second line (pre-menopausal), 42 physicians completed data for first to second line (post-menopausal), 41 physicians completed data for second to third line, 33 physicians completed data for third to fourth line, 24 physicians completed data for fourth to fifth line, 19 physicians completed data for fifth to sixth line

Table 13 Physician-reported outcomes of various lines of systemic therapies in HR+/HER2− breast cancer patients, China, 2019

| Modality      | CR (%) | PR (%) | SD (%) | Average PFS (mos) |
|---------------|--------|--------|--------|-------------------|
| First line    | 20.8   | 29.6   | 27.2   | 16.3              |
| Second line   | 13.6   | 27.7   | 25.9   | 11.1              |
| Third line    | 5.2    | 20.1   | 27.8   | 7.0               |
| Fourth line   | 3.8    | 15.4   | 26.7   | 5.2               |
| Fifth line    | 2.9    | 11.2   | 22.0   | 4.3               |

Survey of 45 physicians who treat a total of 1,848 breast cancer patients monthly, conducted in September 2019; For response rates, 42 physicians completed data for first line, 41 physicians completed data for second line, 33 physicians completed data for third line, 24 physicians completed data for fourth line, and 19 physicians completed data for fifth line; For PFS: 40 physicians completed data for first line, 39 physicians completed data for second line, 32 physicians completed data for third line, 23 physicians completed data for fourth line, and 18 physicians completed data for fifth line.

CR, complete response rate; PR, partial response rate; SD, stable disease; PFS, progression-free survival
Overall, this influx of several CDK4/6 inhibitor options could push adoption in favor of this class of agent in first-line patients. However, the significantly higher cost of these targeted agents, compared to chemotherapy and hormone therapies, has the potential to impact uptake by physicians. In China, approvals may not translate to clinical use unless the drug is made affordable to patients by inclusion in the National Reimbursement Drug List (NRDL), which provides up to 80% reimbursement of drug cost to patients. Nearly 1 year after approval, abemaciclib has finally entered the NRDL in January 2022, making it a more affordable CDK4/6 inhibitor option to patients than palbociclib. Despite palbociclib being the first-in-class to enter the Chinese market, it is yet to be included in the NRDL. The branded agent did, however, drop in price by 54% in January 2021, shortly following the approval of the first palbociclib generic, in an attempt to garner some utilization in this competitive market.

Upon disease progression, fulvestrant, a selective estrogen receptor degrader (SERD), is the hormone agent of choice for second and subsequent lines of therapies in the USA and EU5 [3]. In urban mainland China, there is no defined algorithm, with docetaxel-based chemotherapy alone or with EC for second line (data not shown) and capecitabine or gemcitabine-based chemotherapy for third line identified as the most commonly utilized options among physicians surveyed (Table 10). For fourth and subsequent lines, physicians in China did not report a specific standard of care and often included multiple therapies including hormone therapy alone, chemotherapies, or targeted therapies. With large patient numbers receiving the next line of therapy, current treatment options are tolerable, but there still exists a need for alternative treatment options to keep fewer patients from needing to receive a subsequent line of therapy.

This study included some limitations that are important to note. First, the possibility that physician responses may have been subject to recall bias. However, the authors note that the physicians were asked to limit their responses to a consideration of only the last 6 months, to help reduce the impact of this bias on study results. Physicians only reported answers based on their own patient pools and practices, thereby limiting the generalizability of the responses. Moreover, as described in the methods, definitions of ORR, PFS, and relapse versus refractory patients were not provided to physicians in the survey questions, and respondent answers were directional estimates based on their own clinical experience and practice. The researchers attempted to distribute physician recruitment in a representative manner, including physicians from major urban hubs across a variety of regions in China; however, due to the focus on urban populations, the survey results may or may not have been reflective of HR+/HER2(−) breast cancer treatment patterns across the larger Chinese population. The authors also note that new agents have been approved in China for HR+/HER2(−) breast cancer since the survey study was conducted (detailed in Supplementary Table 1), including abemaciclib, tucidi-nostat (chidamide), utidelone, dalpiciclib, and envafolimab [21–23, 25, 26]. The approval of these agents may alter the treatment patterns that were reported by physicians in this study. Regional differences in guidelines, physician preferences, regulatory approvals, and availability of drugs make it challenging to compare and validate treatment patterns in China against that in the US, EU, or Japan. The answers obtained in our survey align closely with national guidelines published at the time that the survey was conducted (September 2019) and shed light on this otherwise little understood but increasingly important market segment. As such, we conduct annual surveys to closely monitor the changes in this vast and rapidly evolving market.

Conclusions

The survey revealed that physicians in urban mainland China prescribed different treatment modalities and regimens for their HR+/HER2(−) breast cancer patients in 2019. Regimens used in refractory or relapsed patients varied among breast oncologists in China and no apparent standard of care was reported.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The database used for this research, named CancerM Pact, does not collect or use patient-level data, or any data involving...
Consent to participate  As the survey data in this research did not collect or use patient-level data, or any data involving people, medical records, or human samples, informed consent was not necessary.

Consent to publish  As the survey data in this research did not collect or use patient-level data, or any data involving people, medical records, or human samples, consent to publish was not necessary.

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