CDK4 AND 6 INHIBITOR IN COMBINATION WITH FULVESTRANT FOR THE TREATMENT OF HORMONE RECEPTOR-POSITIVE, HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2-NEGATIVE ADVANCED OR METASTATIC BREAST CANCER IN PATIENTS PREVIOUSLY TREATED WITH A CDK4 AND 6 INHIBITOR

FIELD

[0001] The disclosure relates to the field of treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer in patients previously treated with a CDK4 and 6 inhibitor.

BACKGROUND

[0002] The combination therapy of CDK4 and 6 inhibitors with an endocrine therapy (ET) as a first-line treatment of locally advanced or metastatic hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer has dramatically improved outcomes (Finn et al. 2016; Tripathy et al. 2018; Johnston et al. 2019). Nevertheless, these therapies are not curative, and most metastatic breast cancer patients will experience disease progression. More recently, abemaciclib has shown significant improvement in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) in the adjuvant setting (Johnston et al. 2020) in patients with early breast cancer at high risk of recurrence. As the use of CDK4 and 6 inhibitors increases in earlier lines of therapy, there exists a need for additional methods for treating patients who experience disease progression or recurrence on or after the CDK4 and 6-based therapy.

SUMMARY

[0002a] In a first aspect of the present disclosure, there is provided a use of a CDK4 and 6 inhibitor in the manufacture of a medicament for treating a patient with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer previously treated with a CDK4 and 6 inhibitor-containing therapy, wherein the CDK4 and 6 inhibitor is to be administered in combination with fulvestrant.

[0002b] In another aspect of the present disclosure, there is provided a use of a CDK4 and 6 inhibitor in the manufacture of a medicament for treating a patient with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), advanced or metastatic breast cancer after a prior CDK4 and 6 inhibitor-containing therapy, wherein the CDK4 and 6 inhibitor is to be administered in simultaneous, separate, or sequential combination with fulvestrant.

[0002c] In yet another aspect of the present disclosure, there is provided a use of abemaciclib in the manufacture of a medicament for treating a patient with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer previously treated with a CDK4 and 6 inhibitor-containing therapy selected from abemaciclib, ribociclib, and palbociclib, wherein the abemaciclib is to be administered in combination with fulvestrant, and wherein abemaciclib is to be administered twice daily as a 150 mg oral dose on days 1-28 of each 28 day cycle, and wherein fulvestrant is to be administered as a 500 mg intramuscular dose on day 1 and 15 of a first 28 day cycle, and on day 1 of a second and any subsequent 28 day cycle.

[0002d] In a further aspect of the present disclosure, there is provided a use of abemaciclib in the manufacture of a medicament for treating a patient with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer previously treated with a CDK4 and 6 inhibitor-containing therapy selected from abemaciclib, ribociclib, and palbociclib, wherein the abemaciclib is used in simultaneous, separate, or sequential combination with fulvestrant, and wherein abemaciclib is to be administered twice daily as a 150 mg oral dose on days 1-28 of each 28 day cycle, and wherein fulvestrant is to be administered as a 500 mg intramuscular dose on day 1 and 15 of a first 28 day cycle, and on day 1 of a second and any subsequent 28 day cycle.

[0003] In an example, the disclosure provides a method of treating a patient with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer who has been previously treated with a CDK4 and 6 inhibitor-containing therapy, the method comprising administering to the patient a CDK4 and 6 inhibitor in combination with fulvestrant. In some further examples, the method comprises administering to the patient a CDK4 and 6 inhibitor comprising abemaciclib,

palbociclib, or ribociclib in combination with fulvestrant. In some preferred examples, the method comprises administering to the patient abemaciclib in combination with fulvestrant. In alternative examples, the method comprises administering to the patient palbociclib in combination with fulvestrant. In another examples, the method comprises administering to the patient ribociclib in combination with fulvestrant.

[0004] In some examples, the patient may have been administered a prior CDK4 and 6 inhibitor-containing therapy as a monotherapy. In some other examples, the patient may have been administered a prior CDK4 and 6 inhibitor-containing therapy in combination with an additional therapy. In some further examples, the prior CDK4 and 6 inhibitor-containing therapy comprises abemaciclib, palbociclib, or ribociclib. In further examples, the prior CDK4 and 6 inhibitor-containing therapy comprises abemaciclib. In some further examples, the prior CDK4 and 6 inhibitor-containing therapy comprises palbociclib. In yet some further examples, the prior CDK4 and 6 inhibitor-containing therapy comprises ribociclib.

[0005] In some examples, the patient may have been administered a prior CDK4 and 6 inhibitor-containing therapy in combination with an endocrine therapy. In some examples, the prior endocrine therapy comprises tamoxifen. In some examples, the prior endocrine therapy comprises an aromatase inhibitor. In some further examples, the aromatase inhibitor comprises letrozole, anastrozole, or exemestane.

[0006] In further examples, the patient may have been administered a combination of a CDK4 and 6 inhibitor with an endocrine therapy for the first line (or initial) treatment of HR+, HER2- advanced or metastatic breast cancer. In some examples, the first line treatment comprises an endocrine therapy selected from tamoxifen and an aromatase inhibitor. In some examples, the first line treatment comprises ribociclib as the CDK4 and 6 inhibitor. In some examples, the first line treatment comprises palbociclib as the CDK4 and 6 inhibitor. In some examples, the first line treatment comprises abemaciclib as the CDK 4 and 6 inhibitor.

[0007] In further examples, the patient may have been administered a prior CDK4 and 6 inhibitor-containing therapy as a monotherapy. In some other examples, the patient may have been administered a prior CDK4 and 6 inhibitor-

containing therapy in combination with an additional therapy. In some further examples, the prior CDK4 and 6 inhibitor-containing therapy comprises abemaciclib, palbociclib, or ribociclib.

[0008] In further examples, the prior CDK4 and 6 inhibitor-containing therapy comprises abemaciclib. In some further examples, the prior CDK4 and 6 inhibitor-containing therapy comprises palbociclib. In yet some further examples, the prior CDK4 and 6 inhibitor-containing therapy comprises ribociclib.

[0009] In some further examples, the method of treating comprises a patient with advanced or metastatic breast cancer and who has received a prior CDK4 and 6 inhibitor therapy comprising abemaciclib. In such further examples, the prior therapy comprising abemaciclib may have been administered: (i) in combination with endocrine therapy (e.g., tamoxifen or an aromatase inhibitor) for the adjuvant treatment in an adult patient with HR+, HER2- node positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA approved test; (ii) in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR+, HER2- advanced or metastatic breast cancer; (iii) in combination with fulvestrant for the treatment of women with HR+, HER2- advanced or metastatic breast cancer; or (iv) as monotherapy for the treatment of adult patients with HR+, HER2- advanced or metastatic breast cancer with disease progression following endocrine therapy.

[0010] In some further examples, the method of treating comprises a patient with advanced or metastatic breast cancer and who has received a prior CDK4 and 6 inhibitor therapy comprising palbociclib. In such further examples, the prior therapy comprising palbociclib may have been administered: (i) in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR+, HER2- advanced or metastatic breast cancer; or (ii) in combination with fulvestrant for the treatment of women with HR+, HER2- advanced or metastatic breast cancer following endocrine therapy.

[0011] In some further examples, the method of treating comprises a patient with advanced or metastatic breast cancer and who has received a prior CDK4 and 6 inhibitor therapy comprising ribociclib. In such further examples, the prior therapy comprising ribociclib may have been administered: (i) in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of pre/perimenopausal or postmenopausal women with HR+, HER2- advanced or metastatic breast cancer; or (ii) in combination with fulvestrant for the treatment of

postmenopausal women with HR+, HER2- advanced or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on endocrine therapy.

[0012] In some further examples, the method according to any of the above examples comprises administering abemaciclib as a 150 mg oral dose twice daily on days 1-28 of each 28 day cycle. In yet further examples, the above method comprises administering fulvestrant as a 500 mg intramuscular dose on day 1 and 15 of a first 28 day cycle (cycle 1), and on day 1 of a second and any subsequent 28 day cycle (cycle 2 and subsequent cycles).

[0013] In another example, the disclosure provides a method of treating a patient with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer previously treated with a CDK4 and 6 inhibitor-containing therapy selected from abemaciclib, ribociclib, and palbociclib, the method comprising administering to the patient an effective amount of abemaciclib in combination with fulvestrant, wherein abemaciclib is administered twice daily as a 150 mg oral dose on days 1-28 of each 28 day cycle, and wherein fulvestrant is administered as a 500 mg intramuscular dose on day 1 and 15 of a first 28 day cycle, and on day 1 of a second and any subsequent 28 day cycle.

[0014] In any of the above examples, the method may comprise administering the CDK4 and 6 inhibitor in simultaneous, separate, or sequential combination with fulvestrant.

[0015] In any of the above examples, the method may be administered for a time sufficient to provide the patient progression-free survival.

[0016] In any of the above examples, the patient is human. In further examples, the patient may be an adult male, or an adult premenopausal, perimenopausal, or postmenopausal woman.

[0017] In another example, the disclosure provides a CDK4 and 6 inhibitor for use in simultaneous, separate or sequential combination with fulvestrant, in the treatment of a patient with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), advanced or metastatic breast cancer wherein the patient had received a prior CDK4 and 6 inhibitor-containing therapy.

[0018] In another example, the disclosure provides a combination comprising a therapeutically effective amount of CDK4 and 6 inhibitor and fulvestrant for simultaneous, separate or sequential use in providing treatment to a patient with HR+, HER2- advanced or metastatic

breast cancer with disease progression on or after a prior therapy of a CDK4 and 6 inhibitor, for a time period sufficient to provide progression free survival.

[0019] In another example, the disclosure provides a CDK4 and 6 inhibitor for use in simultaneous, separate or sequential combination with fulvestrant for the treatment of a patient with HR+, HER2- advanced or metastatic breast cancer with disease progression on or after a prior therapy of a CDK4 and 6 inhibitor.

[0020] In another example, the disclosure provides for the use of a CDK4 and 6 inhibitor in the manufacture of a medicament for the treatment of a patient with HR+, HER2- advanced or metastatic breast cancer who has received a prior therapy of a CDK4 and 6 inhibitor, wherein the medicament is to be administered in simultaneous, separate or sequential combination with fulvestrant. In some examples, the patient experienced disease progression on the prior therapy of a CDK4 and 6 inhibitor.

[0021] In another example, the disclosure provides for the use of a CDK4 and 6 inhibitor in the manufacture of a medicament for the treatment of a patient with HR+, HER2- advanced or metastatic breast cancer with disease recurrence on or after a prior therapy of a combination of a CDK4 and 6 inhibitor with endocrine therapy for the adjuvant treatment of early breast cancer, wherein the medicament is to be administered in simultaneous, separate or sequential combination with fulvestrant.

[0022] These examples as well as other examples will be apparent in light of the description that follows.

DETAILED DESCRIPTION

[0023] Methods, uses, and compositions for the treatment of a patient with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer, and who has been previously treated with a CDK4 and 6 inhibitor-containing therapy, comprising administering to the patient a CDK4 and 6 inhibitor in combination with fulvestrant are disclosed herein. While there has been significant interest and an increased use of therapies that include a CDK4 and 6 inhibitor in the treatment of breast cancer, no clinical evidence exists that serves to guide standard of care therapy for patients with relapsed or progressive metastatic disease that occurs on or after an administered CDK4 and 6 containing therapy. For example, the 2020 ESMO and 2021 NCCN clinical guidelines support

We Claim:

1. Use of a CDK4 and 6 inhibitor in the manufacture of a medicament for treating a patient with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer previously treated with a CDK4 and 6 inhibitor-containing therapy, wherein the CDK4 and 6 inhibitor is to be administered in combination with fulvestrant.
2. Use of a CDK4 and 6 inhibitor in the manufacture of a medicament for treating a patient with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), advanced or metastatic breast cancer after a prior CDK4 and 6 inhibitor-containing therapy, wherein the CDK4 and 6 inhibitor is to be administered in simultaneous, separate, or sequential combination with fulvestrant.
3. The use according to claim 1 or claim 2, wherein the previous CDK4 and 6 inhibitor-containing therapy comprised abemaciclib, palbociclib, or ribociclib.
4. The use according to claim 3, wherein the previous CDK4 and 6 inhibitor-containing therapy comprised abemaciclib.
5. The use according to claim 3, wherein the previous CDK4 and 6 inhibitor-containing therapy comprised palbociclib.
6. The use according to claim 3, wherein the previous CDK4 and 6 inhibitor-containing therapy comprised ribociclib.
7. The use according to any of claims 1-6, wherein the prior CDK4 and 6 inhibitor-containing therapy was a combination of a CDK4 and 6 inhibitor with endocrine therapy for the adjuvant treatment of early breast cancer.
8. The use according to claim 7, wherein the prior adjuvant treatment comprised an endocrine therapy selected from tamoxifen and an aromatase inhibitor.
9. The use according to any one of claims 7-8, wherein the prior adjuvant treatment was administered to a patient at a high risk of recurrence.
10. The use according to any one of claims 7-9, wherein the prior adjuvant treatment was administered to a patient with a Ki-67 score ≥20% as determined by an FDA approved test.
11. The use according to any of claims 1-6, wherein the prior CDK4 and 6 inhibitor-containing therapy was a combination of a CDK4 and 6 inhibitor with endocrine therapy for the initial treatment of advanced or metastatic breast cancer.

12. The use according to any of claims 1-6, wherein the prior CDK4 and 6 inhibitor-containing therapy was a combination of a CDK4 and 6 inhibitor with an aromatase inhibitor for the initial treatment of advanced or metastatic breast cancer.
13. The use according to claim 11, wherein the previous CDK4 and 6 inhibitor-containing therapy was administered in combination with an aromatase inhibitor.
14. The use according to claim 12 or claim 13, wherein the aromatase inhibitor previously administered in combination with the CDK4 and 6 inhibitor-containing therapy comprised letrozole, anastrozole, or exemestane.
15. The use according to any one of claims 1-14, wherein a CDK4 and 6 inhibitor selected from abemaciclib, palbociclib, and ribociclib, is to be administered in combination with fulvestrant.
16. The use according to claim 15, wherein the CDK4 and 6 inhibitor is abemaciclib.
17. The use according to claim 15, wherein the CDK4 and 6 inhibitor is palbociclib.
18. The use according to claim 15, wherein the CDK4 and 6 inhibitor is ribociclib.
19. The use according to claim 16, wherein abemaciclib is to be administered as a 150 mg oral dose twice daily on days 1-28 of each 28 day cycle.
20. The use according to claim 19, wherein fulvestrant is to be administered as a 500 mg intramuscular dose on day 1 and 15 of a first 28 day cycle (cycle 1), and on day 1 of a second and any subsequent 28 day cycle (cycle 2 and subsequent cycles).
21. Use of abemaciclib in the manufacture of a medicament for treating a patient with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer previously treated with a CDK4 and 6 inhibitor-containing therapy selected from abemaciclib, ribociclib, and palbociclib, wherein the abemaciclib is to be administered in combination with fulvestrant, and wherein abemaciclib is to be administered twice daily as a 150 mg oral dose on days 1-28 of each 28 day cycle, and wherein fulvestrant is to be administered as a 500 mg intramuscular dose on day 1 and 15 of a first 28 day cycle, and on day 1 of a second and any subsequent 28 day cycle.
22. Use of abemaciclib in the manufacture of a medicament for treating a patient with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer previously treated with a CDK4 and 6 inhibitor-containing therapy selected from abemaciclib, ribociclib, and palbociclib, wherein the

abemaciclib is used in simultaneous, separate, or sequential combination with fulvestrant, and wherein abemaciclib is to be administered twice daily as a 150 mg oral dose on days 1-28 of each 28 day cycle, and wherein fulvestrant is to be administered as a 500 mg intramuscular dose on day 1 and 15 of a first 28 day cycle, and on day 1 of a second and any subsequent 28 day cycle.

23. The use of any one of claims 1-22, wherein the administration is for a time sufficient to provide progression-free survival.
24. The use according to any one of claims 1-23, wherein the patient is an adult man or an adult premenopausal, perimenopausal, or postmenopausal woman.