

useful in, assessing or predicting responsiveness to eribulin in patients having cancer and, in particular, breast cancer.

SUMMARY

5 The disclosure is based, at least in part, on the observation that a low level of expression, *e.g.*, the absence of expression, of the biomarkers identified herein is indicative of responsiveness to eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate). Specifically, the absence of expression or a low level of expression of these biomarkers, including, for example, one or more of
10 those biomarkers set forth in Table 1, in a subject is indicative that the subject will be responsive to treatment with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate).

 Accordingly, in one example, the present disclosure provides a method for determining whether eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), may be used to treat a subject having breast cancer, by
15 assaying a sample derived from the subject to determine the level of expression in the sample of a biomarker selected from the group of biomarkers listed in Table 1, wherein a low level of expression of the biomarker is indicative that eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), will be effective
20 in treating the subject having breast cancer. In another example, the present disclosure provides a method for determining whether eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), may be used to treat a subject having breast cancer, by determining the level of expression of a biomarker selected from the group of biomarkers listed in Table 1 in a sample derived from the
25 subject, wherein a low level of expression of the biomarker is indicative that eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), will be effective in treating the subject having breast cancer. In one aspect, the present disclosure refers to a method for determining whether eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, may be used to treat a subject having breast
30 cancer, the method comprising determining the level of expression of a biomarker selected from the group of biomarkers listed in Table 1 in a sample derived from said subject, wherein a low level of expression of the biomarker is indicative that eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, will be effective in treating said subject. In a further example, the present disclosure provides a method for
35 predicting whether eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), may be used to treat a subject having breast cancer, by determining the level of expression of a biomarker selected from the group of biomarkers listed in Table 1 in a sample derived from the subject, and predicting that eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin
40 mesylate), will be effective in treating a subject having breast cancer when there is a low level of expression of the biomarker in the sample. In one example of the foregoing aspects of the disclosure, the methods may further include obtaining a sample from a subject.

In yet another example, the present disclosure provides a method for determining the sensitivity of a breast tumor, for example, derived from a subject having breast cancer, to treatment with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), by determining the level of expression of a biomarker selected from the group of biomarkers listed in Table 1 in the tumor, wherein a low level of expression of the biomarker in the tumor indicates that the tumor is sensitive to treatment with eribulin, or an analog thereof. In one aspect, the present disclosure refers to a method for determining the sensitivity of a breast tumor to treatment with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, the method comprising determining the level of expression of a biomarker selected from the group of biomarkers listed in Table 1 in said tumor, wherein a low level of expression of the biomarker in said tumor indicates that said tumor is sensitive to treatment with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof. In yet another example, the present disclosure provides a method for determining the sensitivity of a breast tumor, for example, derived from a subject having breast cancer, to treatment with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), by determining the level of expression of a biomarker selected from the group of biomarkers listed in Table 1 in the tumor, and identifying the tumor as being sensitive to treatment with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), when the biomarker is expressed in the tumor at a low level.

In one aspect, the present disclosure refers to eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, for use in a method of treating a subject having breast cancer, the method comprising identifying a subject having breast cancer in which a biomarker selected from the group of biomarkers listed in Table 1 has a low level of expression, and administering a therapeutically effective amount of eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, to said subject. In another aspect, the present disclosure refers to eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, for use in a method of treating a subject having breast cancer, the method comprising assaying a sample derived from said subject to determine the level of expression in said sample of a biomarker selected from the group of biomarkers listed in Table 1, and administering a therapeutically effective amount of eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, to said subject when a low level of expression of the biomarker is detected in said sample.

In further examples of the disclosure, methods are provided for treating a subject having breast cancer. The methods include identifying a subject having breast cancer in which a biomarker selected from the group of biomarkers listed in Table 1 is expressed at a low level, and administering a therapeutically effective amount of eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), to the subject. In yet a further example, the present disclosure provides methods of treating a subject having breast cancer, by assaying a sample derived from the subject to determine the level of expression in the sample of a biomarker selected from the group of biomarkers listed in Table 1, and administering a therapeutically effective amount of eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), to the subject when a low level of expression of the biomarker is detected in the sample. In one example of the foregoing aspects of the disclosure, the methods may further include obtaining a sample from a subject.

In further examples of the disclosure, methods are provided for treating a subject having breast cancer that is sensitive to eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof. The methods include identifying a subject having breast cancer that is sensitive to eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, (*e.g.*, a breast cancer in which a biomarker selected from the group of biomarkers listed in Table 1 is expressed at a low level), and administering a therapeutically effective amount of eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), to the subject. In yet a further example, the present disclosure provides methods of treating a subject having breast cancer that is sensitive to eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, by

assaying a sample derived from the subject to determine the level of expression in the sample of a biomarker selected from the group of biomarkers listed in Table 1, and administering a therapeutically effective amount of eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), to the subject when a
5 low level of expression of the biomarker is detected in the sample. In one example of the foregoing aspects of the disclosure, the methods may further include obtaining a sample from a subject.

In various examples, the subject has not been previously treated with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate).
10 Alternatively, the subject has been previously treated with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof. In certain examples, the breast cancer is an Estrogen Receptor (ER) negative breast cancer and/or a Progesterone Receptor (PR) negative breast cancer and/or a Her-2 negative breast cancer.

In various examples, the level of expression of at least 2, at least 3, at least 4 or at
15 least 5 biomarkers selected from the group of biomarkers listed in Table 1 is determined.

In particular examples, a predictive gene signature comprising a sub-combination of 2 or more biomarkers selected from the group of biomarkers listed in Table 1 is used. In various examples, the level of expression of at least 2, at least 3, at least 4 or at least 5 biomarkers selected from the group of biomarkers listed in Table 1 is determined. For
20 example, the predictive gene signature may include at least 2 biomarkers, *e.g.*, DYSF and EDIL3; GNAT1 and ERGIC3; KRT24 and PAPLN; MANSC1 and PDGFB; PCDH1 and PDGFB; or PHOSPHO2 and PSENEN. In another example, the predictive gene signature may include at least 3 biomarkers, *e.g.*, COL7A1, YTHDF1 and ZIC5; CKLF, IL10 and TUBB6; CDC20, CFL1 and TMEM79; HYAL2, NCBP1 and SNX11;
25 or CEP152, NCBP1 and SATB1. In another example, the predictive gene signature may include at least 4 biomarkers, *e.g.*, APBB2, CCL26, PSENEN and SATB1; ANG, JAM3, KLHL17 and PAPLN; ITFG3, MAD2L1BP, NMU and PDGFB; SPTA1, TYROBP, SNX11 and PSENEN; GRAMD4, GNAT1, TMIGD2 and YTHDF1; or GRAMD4, HYAL2, PHOSPHO2 and TUBB6. In another example, the predictive gene
30 signature may include at least 5 biomarkers, *e.g.*, CCL26, CDC20, ERGIC3, EDIL3 and PCDH1; DYSF, NMU, PHOSPHO2, PSENEN and SNX11; APBB2, CKLF, CYP4F3, TUBB6 and YTHDF1; or CEP152, MAD2L1BP, SPTA1, TMEM79 and ZIC5.

In particular examples, the predictive gene signature may include 2 or more of biomarkers ABI3, ANG, APBB2, CCL26, CDC20, CEP152, CFL1, CKLF, COL7A1,

CYP4F3, DYSF, GNAT1, GRAMD4, HYAL2, IL10, ITFG3, JAM3, KLHL17, KRT24, MAD2L1BP, MANSC1, MOBKL1B, NCBP1, NMU, PCDH1, PHOSPHO2, SPTA1, TMIGD2, TYROBP, ZIC5, ERGIC3, PDGFB, PSENEN, SATB1, SNX11, TMEM79 and YTHDF1, *e.g.*, ABI3 and ANG; APBB2 and CCL26; GNAT1 and GRAMD4; IL10 and ITFG3; MACSC1 and MOBKL1B; NMU and PCDH1; or TYROBP and ZIC5. In other examples, the predictive gene signature includes at least 3 of the previously recited biomarkers, *e.g.*, ABI3, ANG and APBB2; CCL26, CKLF and COL7A1; DYSF, GNAT1 and HYAL2; JAM3, KLHL17 and KRT24; NCBP1, NMU and PCDH1; SPTA1, TMIGD2 and TYROBP; or ZIC5, MAD2L1BP and CDC20. In other examples, the predictive gene signature includes at least 4 of the previously recited biomarkers, *e.g.*, ABI3, ANG, APBB2 and CCL26; CEP152, CFL1, CKLF and COL7A1; KRT24, MANSC1, MOBKL1B and SPTA1; TYROBP, TMIGD2, PHOSPHO2 and NMU; ABI3, GNAT1, KLHL17 and SPTA1; or CEP152, HYAL2, PCDH1 and TMIGD2. In yet further examples, the predictive gene signature includes at least 5 of the previously recited biomarkers, *e.g.*, CKLF, COL7A1, GRAMD4, JAM3 and PCDH1; APBB2, CEP152, DYSF, IL10 and TYROBP; CYP4F3, HYAL2, ITFG3, KLHL17 and KRT24; NCBP1, SPTA1, TMIGD2, IL10 and JAM3; or CCL26, PHOSPHO2, SPTA1, TMIGD2 and ZIC5.

In other examples, the predictive gene signature may include 2 or more of biomarkers ERGIC3, PDGFB, PSENEN, SATB1, SNX11, TMEM79 or YTHDF1, or any sub-combination thereof, *e.g.*, ERGIC3 and PDGFB; ERGIC3 and PSENEN; ERGIC3 and SATB1; ERGIC3 and SNX11; ERGIC3 and TMEM79; ERGIC3 and YTHDF1; PDGFB and PSENEN; PDGFB and SATB1; PDGFB and SNX11; PDGFB and TMEM79; PDGFB and YTHDF1; PSENEN and SATB1; PSENEN and SNX11; PSENEN and TMEM79; PSENEN and YTHDF1; SATB1 and SNX11; SATB1 and TMEM79; SATB1 and YTHDF1; SNX11 and TMEM79; SNX11 and YTHDF1; or TMEM79 and YTHDF1. In other examples, the predictive gene signature includes at least 3 biomarkers, for example, ERGIC3, PDGFB and PSENEN; SATB1, SNX11 and TMEM79; SNX11, TMEM79 and YTHDF1; or ERGIC3, PDGFB and SATB1. In further examples, the predictive gene signature includes at least 4 biomarkers, for example, ERGIC3, PDGFB, PSENEN and SATB1; SNX11, TMEM79, YTHDF1 and ERGIC3; or ERGIC3, PDGFB, PSENEN and YTHDF1. In further examples, the predictive gene signature includes at least 5 biomarkers, for example, ERGIC3, PDGFB, PSENEN, SATB1 and SNX11; ERGIC3, PDGFB, PSENEN, SATB1 and TMEM79; or PSENEN, SATB1, SNX11, TMEM79 and YTHDF1. In yet further examples, the predictive gene signature includes at least 6 biomarkers, for example, ERGIC3, PDGFB, PSENEN, SATB1, SNX11 and TMEM79; PDGFB, PSENEN, SATB1, SNX11,

TMEM79 and YTHDF1; or ERGIC3, PSENEN, SATB1, SNX11, TMEM79 and YTHDF1. In yet another example, the predictive gene signature includes 7 biomarkers, for example, ERGIC3, PDGFB, PSENEN, SATB1, SNX11, TMEM79 and YTHDF1.

In various examples, the biomarker is not one or more of SPTA1, PAPLN, PCDH1, TMIGD2 and/or KRT24. In a particular example, the biomarker is not SPTA1, PAPLN, PCDH1, TMIGD2 and KRT24. In one example, the biomarker is not SPTA1. In another example, the biomarker is not PAPLN. In another example, the biomarker is not PCDH1. In another example, the biomarker is not TMIGD2. In yet another example, the biomarker is not KRT24.

In particular examples, the predictive gene signature may include 2 or more of biomarkers ABI3, ANG, APBB2, CCL26, CDC20, CEP152, CFL1, CKLF, COL7A1, CYP4F3, DYSF, GNAT1, GRAMD4, HYAL2, IL10, ITFG3, JAM3, KLHL17, MAD2L1BP, MANSC1, MOBKL1B, NCBP1, NMU, PHOSPHO2, TYROBP, ZIC5, ERGIC3, PDGFB, PSENEN, SATB1, SNX11, TMEM79, YTHDF1, EDIL3 and TUBB6, *e.g.*, ABI3 and ANG; GRAMD4 and HYAL2; NMU and PHOSPHO2; ZIC5 and PSENEN; or SNX11 and MOBKL1B. In other examples, the predictive gene signature includes at least 3 of the previously recited biomarkers, *e.g.*, APBB2, CDC20 and CKLF; COL7A1, DYSF and GNAT1; NCBP1, SATB1 and EDIL3; PSENEN, DYSF and GNAT1; MANSC1, ZIC5 and CFL1; or CKLF, GRAMD4 and NMU. In other examples, the predictive gene signature includes at least 4 of the previously recited biomarkers, *e.g.*, ANG, CCL26, CEP152 and JAM3; APBB2, CYP4F3, ITFG3 and TYROBP; CYP4F3, MANSC1, PDGFB and YTHDF1; TUBB6, DYSF, PHOSPHO2 and CDC20; or CKLF, KLHL17, HYAL2 and ZIC5. In yet further examples, the predictive gene signature includes at least 5 of the previously recited biomarkers, *e.g.*, IL10, CEP152, COL7A1, TYROBP and ERGIC3; TMEM79, SNX11, PSENEN, GNAT1 and GRAMD4; JAM3, SNX11, KLHL17, MOBKL1B and ERGIC3; or NMU, PHOSPHO2, PDGFB, CFL1 and ANG.

In various methods and or kits of the disclosure, the biomarker is not ABI3, is not ANG, is not APBB2, is not CCL26, is not CDC20, is not CEP152, is not CFL1, is not CKLF, is not COL7A1, is not CYP4F3, is not DYSF, is not GNAT1, is not GRAMD4, is not HYAL2, is not IL10, is not ITFG3, is not JAM3, is not KLHL17, is not KRT24, is not MAD2L1BP, is not MANSC1, is not MOBKL1B, is not NCBP1, is not NMU, is not PCDH1, is not PHOSPHO2, is not SPTA1, is not TMIGD2, is not TYROBP, is not ZIC5, is not ERGIC3, is not PDGFB, is not PSENEN, is not SATB1, is not SNX11, is not TMEM79, is not EDIL3, is not PAPLN, is not TUBB6 and/or is not YTHDF1.

In certain examples, the biomarker is not expressed at a detectable level. In another example, the biomarker is expressed at a low level as compared to a control. Expression can be determined directly or indirectly by any suitable method. In certain examples, the level of expression of the biomarker is determined at the nucleic acid level using any suitable method. For example, the level of expression of the biomarker can be determined by detecting cDNA, mRNA or DNA. In particular examples, the level of expression of the biomarker is determined by using a technique selected from the group consisting of polymerase chain reaction (PCR) amplification reaction, reverse-transcriptase PCR analysis, quantitative reverse-transcriptase PCR analysis, Northern blot analysis, RNAase protection assay, digital RNA detection/ quantitation (*e.g.*, nanoString) and combinations or sub-combinations thereof.

In certain examples, the level of expression of the biomarker can be determined by detecting miRNA. Specifically, mRNA expression can be assessed indirectly by assessing levels of miRNA, wherein an elevated level of an miRNA which controls the expression of an mRNA is indicative of a low level of expression of the mRNA encoding the biomarker.

In other examples, the level of expression of the biomarker is determined at the protein level using any suitable method. For example, the presence or level of the protein can be detected using an antibody or antigen binding fragment thereof, which specifically binds to the protein. In particular examples, the antibody or antigen binding fragment thereof is selected from the group consisting of a murine antibody, a human antibody, a humanized antibody, a bispecific antibody, a chimeric antibody, a Fab, Fab', F(ab')₂, ScFv, SMIP, affibody, avimer, versabody, nanobody, and a domain antibody, or an antigen binding fragment of any of the foregoing. In particular examples, the antibody or antigen binding portion thereof is labeled, for example, with a label selected from the group consisting of a radio-label, a biotin-label, a chromophore-label, a fluorophore-label, and an enzyme-label. In certain examples, the level of expression of the biomarker is determined by using a technique selected from the group consisting of an immunoassay, a western blot analysis, a radioimmunoassay, immunofluorimetry, immunoprecipitation, equilibrium dialysis, immunodiffusion, electrochemiluminescence immunoassay (ECLIA), ELISA assay, immunopolymerase chain reaction and combinations or sub-combinations thereof. In particular examples, the immunoassay is a solution-based immunoassay selected from the group consisting of electrochemiluminescence, chemiluminescence, fluorogenic chemiluminescence, fluorescence polarization, and time-resolved fluorescence. In other examples, the immunoassay is a sandwich immunoassay selected from the group consisting of electrochemiluminescence, chemiluminescence,

and fluorogenic chemiluminescence. Other assays which rely on agents capable of detecting the protein, such as those relying upon a suitable binding partner or enzymatic activity, can also be used (*e.g.*, use of a ligand to detect a receptor molecule).

Samples can be obtained from a subject by any suitable method, and may
5 optionally have undergone further processing step(s) (*e.g.*, freezing, fractionation, fixation, guanidine treatment, etc). Any suitable sample derived from a subject can be used, such as any tissue (*e.g.*, biopsy), cell, or fluid, as well as any component thereof, such as a fraction or extract. In various examples, the sample is a fluid obtained from the subject, or a component of such a fluid. For example, the fluid can be blood, plasma,
10 serum, sputum, lymph, cystic fluid, nipple aspirate, urine, or fluid collected from a biopsy (*e.g.*, lump biopsy). In other examples, the sample is a tissue or component thereof obtained from the subject. For example, the tissue can be tissue obtained from a biopsy (*e.g.*, lump biopsy), breast tissue, connective tissue, and/or lymphatic tissue. In a particular example, the tissue is breast tissue, or a component thereof (*e.g.*, cells
15 collected from the breast tissue). In a particular example, the component of the breast tissue are breast tissue cells. In another example, the component of the breast tissue are circulating breast tumor cells.

In one example, the subject is a human.

In another example, the present disclosure provides a kit for predicting whether
20 eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), may be used to treat a subject having breast cancer, including reagents for determining the level of expression of a biomarker selected from the group of biomarkers listed in Table 1; and instructions for use of the kit to predict whether eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin
25 mesylate), may be used to treat a subject having breast cancer. In one aspect, the present disclosure refers to use of a kit in the methods disclosed herein, the kit comprising reagents for determining the level of expression of a biomarker selected from the group of biomarkers listed in Table 1; and instructions for use of the kit to predict whether eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, may be used
30 to treat a subject having breast cancer. For example, the reagent for determining the level of expression of the biomarker can be a probe for identifying a null mutation in the biomarker. The reagent for determining the level of expression of the biomarker can be a probe for amplifying and/or detecting the biomarker. In yet another example, the reagent for determining the level of expression of the biomarker can be an antibody, for
35 example, an antibody specific for the product of the expression of the wild type or null mutant version of the biomarker.

In a particular example, the kit further includes reagents for obtaining a biological sample from a subject. In another example, the kit includes a control sample.

In another example, the present disclosure provides methods for determining
40 whether eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*,

eribulin mesylate), may be used to treat a subject having breast cancer by determining and/or identifying whether the subject carries at least one gene, selected from the group of biomarkers set forth in Table 1, which contains a null mutation. In another example, the present disclosure provides methods for predicting whether eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), may be used to treat a subject having breast cancer by assaying a sample derived from the subject to determine whether the subject carries at least one gene, selected from the group of biomarkers set forth in Table 1, which contains a null mutation. In a further example, the present disclosure provides methods for determining the sensitivity of a breast tumor to treatment with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof by determining and/or identifying whether said tumor is characterized by at least one gene, selected from the group of biomarkers set forth in Table 1, which contains a null mutation. In yet another example, the present disclosure is directed to methods for treating a subject having breast cancer with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof by identifying whether at least one gene, selected from the group of biomarkers set forth in Table 1, which contains a null mutation and administering a therapeutically effective amount of eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate) to the subject.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the high throughput siRNA screening methods in Breast Cancer Cell Lines performed as described in Example 1.

Figure 2 depicts the identification and selection of certain genes for further consideration as biomarkers of efficacy of eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof.

Figure 3 depicts the confirmation assays performed as described in Example 1.

Figure 4 depicts the results of the QuantiTect SYBR Assays to determine the relative quantities of cDNAs after treatment with siRNA as set forth in Example 1.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for determining whether eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin mesylate), may be used to treat a subject having breast cancer, methods for predicting whether eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof (*e.g.*, eribulin

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CLAIMS

What is claimed is:

1. A method for determining whether eribulin, an analog thereof, or a
5 pharmaceutically acceptable salt thereof, may be used to treat a subject having breast cancer, the method comprising
determining the level of expression of a biomarker selected from the group of biomarkers listed in Table 1 in a sample derived from said subject, wherein a low level of expression of the biomarker is indicative that eribulin, an analog thereof, or a
10 pharmaceutically acceptable salt thereof, will be effective in treating said subject.
2. A method for determining the sensitivity of a breast tumor to treatment with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, the method comprising
15 determining the level of expression of a biomarker selected from the group of biomarkers listed in Table 1 in said tumor, wherein a low level of expression of the biomarker in said tumor indicates that said tumor is sensitive to treatment with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof.
- 20 3. The method of claim 2, wherein a sample of the breast tumor is obtained from a subject having breast cancer.
4. Eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, for use in a method of treating a subject having breast cancer, the method comprising
25 identifying a subject having breast cancer in which a biomarker selected from the group of biomarkers listed in Table 1 has a low level of expression, and
administering a therapeutically effective amount of eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, to said subject.
- 30 5. Eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, for use in a method of treating a subject having breast cancer, the method comprising
assaying a sample derived from said subject to determine the level of expression in said sample of a biomarker selected from the group of biomarkers listed in Table 1, and
35 administering a therapeutically effective amount of eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, to said subject when a low level of expression of the biomarker is detected in said sample.

6. The method of any one of claims 1-3, wherein (a) the pharmaceutically acceptable salt of eribulin is eribulin mesylate.
- 5 7. The method of any one of claims 1 to 3, wherein (a) at least 2 biomarkers selected from the group of biomarkers listed in Table 1 have a low level of expression; or (b) at least 3 biomarkers selected from the group of biomarkers listed in Table 1 have a low level of expression; or (c) at least 4 biomarkers selected from the group of biomarkers listed in Table 1 have a low level of expression; or (d) at least 5 biomarkers
10 selected from the group of biomarkers listed in Table 1 have a low level of expression.
8. The method of any one of claims 1 to 3, wherein said biomarker is not expressed at a detectable level.
- 15 9. The method of any one of claims 1 to 3, wherein (a) the level of expression of said biomarker is determined at the nucleic acid level; optionally wherein the level of expression of said biomarker is determined by (i) detecting cDNA; or (ii) detecting mRNA or miRNA; or (iii) detecting DNA; or (iv) using a technique selected from the group consisting of polymerase chain reaction (PCR) amplification reaction, reverse-
20 transcriptase PCR analysis, quantitative reverse-transcriptase PCR analysis, Northern blot analysis, RNAase protection assay, digital RNA detection/ quantitation, and combinations or sub-combinations thereof; or (b) the level of expression of said biomarker is determined at the protein level; optionally wherein the presence of the protein is detected using an antibody or antigen binding fragment thereof, which
25 specifically binds to the protein; optionally wherein (i) the antibody or antigen binding fragment thereof is selected from the group consisting of a murine antibody, a human antibody, a humanized antibody, a bispecific antibody, a chimeric antibody, a Fab, Fab', F(ab')₂, ScFv, SMIP, affibody, avimer, versabody, nanobody, a domain antibody, and an antigen binding fragment of any of the foregoing; or (ii) wherein the antibody or
30 antigen binding fragment thereof is labeled; optionally wherein the antibody or antigen binding fragment thereof is labeled with a label selected from the group consisting of a radio-label, a biotin-label, a chromophore-label, a fluorophore-label, and an enzyme-label.
- 35 10. The method of any one of claims 1-3, wherein (a) said subject has not been previously treated with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof; or (b) said subject has been previously treated with eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof.

11. The method of any one of claims 1-3 wherein said breast cancer is (a) an Estrogen Receptor (ER) negative breast cancer; or (b) a Progesterone Receptor (PR) negative breast cancer; or (c) a HER-2 negative breast cancer; or (d) an Estrogen Receptor (ER) negative and Progesterone Receptor (PR) negative breast cancer; or (e) an Estrogen Receptor (ER) negative and HER-2 negative breast cancer; or (f) a Progesterone Receptor (PR) negative and HER-2 negative breast cancer; or (g) an Estrogen Receptor (ER) negative, Progesterone Receptor (PR) negative and HER-2 negative breast cancer.
12. The method of claim 9, wherein the level of expression of said biomarker is determined by using a technique selected from the group consisting of an immunoassay, a western blot analysis, a radioimmunoassay, immunofluorimetry, immunoprecipitation, equilibrium dialysis, immunodiffusion, electrochemiluminescence immunoassay (ECLIA), ELISA assay, immunopolymerase chain reaction and combinations or sub-combinations thereof; optionally wherein
- (a) the immunoassay is a solution-based immunoassay selected from the group consisting of electrochemiluminescence, chemiluminescence, fluorogenic chemiluminescence, fluorescence polarization, and time-resolved fluorescence; or
- (b) the immunoassay is a sandwich immunoassay selected from the group consisting of electrochemiluminescence, chemiluminescence, and fluorogenic chemiluminescence.
13. The method of any one of claims 1-3, wherein (i) said sample comprises a fluid, or component thereof, obtained from said subject; optionally wherein the fluid is selected from the group consisting of blood, lymph, serum, plasma, cystic fluid, nipple aspirates, urine, sputum, and fluid collected from a biopsy; or (ii) the sample comprises a tissue, or component thereof, obtained from said subject; optionally wherein (a) said tissue is selected from the group consisting of breast tissue, connective tissue, lymphatic tissue, tissue obtained from a biopsy and tissue obtained from a lump biopsy; or (b) the tissue is breast tissue or a component thereof; optionally wherein said component of said breast tissue comprises breast tissue cells; optionally wherein said breast tissue cells are circulating breast tumor cells.
14. The method of any one of claims 1-3, wherein said subject is a human subject.
15. The use of a kit in the methods of claims 1 to 14, the kit comprising reagents for determining the level of expression of a biomarker selected from the group of biomarkers listed in Table 1; and

instructions for use of the kit to predict whether eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, may be used to treat a subject having breast cancer.

- 5 16. The use of the kit of claim 15, wherein (a) the pharmaceutically acceptable salt of eribulin is eribulin mesylate; or (b) the reagent for determining the level of expression of the biomarker is a probe for identifying a null mutation in the biomarker; or (c) the reagent for determining the level of expression of the biomarker is a probe for amplifying and/or detecting the biomarker; or (d) the reagent for determining the level of
10 expression of the biomarker is an antibody; or (e) the kit further comprises reagents for obtaining a biological sample from a subject; or (f) the kit further comprises a control sample.
- 15 17. The method of any one of claims 1-3, wherein the biomarker is TUBB6.
18. Eribulin, an analog thereof, or a pharmaceutically acceptable salt thereof, for use as in claim 4 or 5, wherein the biomarker is TUBB6.