

CLAIMS

1. A method of predicting whether an individual susceptible to or suffering from cancer or a myeloproliferative disorder is likely to develop resistance to treatment with a tyrosine kinase inhibitor, the method comprising determining whether the individual has a

5 polymorphic variant of a *BIM* (*BCL2L11*) gene which comprises, in 5' to 3' order, the nucleotide sequence set out in SEQ ID NO: 5 followed immediately by the nucleotide sequence set out in SEQ ID NO: 7, preferably in which the polymorphic variant of the *BIM* (*BCL2L11*) gene lacks the nucleotide sequence set out in SEQ ID NO: 6.

2. A method according to Claim 1, which comprises: (a) detecting the presence of a
10 nucleic acid amplification product comprising a sequence set out in SEQ ID NO: 1 as an indicator of the individual having the polymorphic variant of the *BIM* (*BCL2L11*) gene, or (b) detecting the presence of a nucleic acid amplification product comprising a sequence set out in SEQ ID NO: 2 as an indicator of the individual lacking the polymorphic variant of the *BIM* (*BCL2L11*) gene.

15 3. A method according to Claim 1 or 2, in which the method comprises nucleic acid amplification product using a nucleotide sequence (a) as set out in SEQ ID NO: 3, or a (b) as set out in SEQ ID NO: 4, or a combination of (a) and (b), for example, as a primer set.

4. A method according to any of Claims 1, 2 or 3, in which (a) if the individual is determined to have the polymorphic variant of the *BIM* (*BCL2L11*) gene, then the individual
20 is likely to develop resistance to treatment with a tyrosine kinase inhibitor, or in which (b) if the individual is determined not to have the polymorphic variant of the *BIM* (*BCL2L11*) gene, then the individual is less likely to develop resistance to treatment with a tyrosine kinase inhibitor.

5. A method of choosing a therapy for an individual with cancer or a myeloproliferative
25 disorder, the method comprising determining whether a patient is likely to develop resistance to treatment with a tyrosine kinase inhibitor by a method according to any preceding claim, and where the individual is determined as being likely to develop such resistance, choosing a therapy comprising any one or more of the following:

(a) more frequent monitoring of the patient;

30 (b) more frequent blood and bone marrow tests;

(c) bone marrow transplantation;

(d) administration of a more potent tyrosine kinase inhibitor (TKI), such as nilotinib or dasatinib;

(e) administration of a BH3-mimetic, e.g., ABT-263, for example in combination with a TKI;

(f) increasing the dose of a tyrosine kinase inhibitor, e.g. imatinib, for example beyond the standard dose of 400mg/day to 600 or 800 mg/day; or

(g) treatment with a drug that inhibits the pro-survival effect of the BCL2 group of proteins.

6. A method of determining the likelihood of success of a particular therapy on an individual with cancer or a myeloproliferative disorder, the method comprising comparing the therapy with the therapy determined by a method according to Claim 5.

7. A method according to any preceding claim, in which:

(a) the cancer or myeloproliferative disorder comprises chronic myelogenous leukaemia (CML) and in which the resistance to treatment with a tyrosine kinase inhibitor comprises for example BCR-ABL-independent TKI-resistance, such as resistance to a tyrosine kinase inhibitor such as imatinib;

(b) the cancer or myeloproliferative disorder comprises gastrointestinal stromal tumour (GIST), and in which the resistance to treatment with a tyrosine kinase inhibitor comprises for example c-KIT/PDGFR-independent TKI-resistance, such as resistance to a tyrosine kinase inhibitor such as imatinib;

(c) the cancer or myeloproliferative disorder comprises non-small cell lung cancer (NSCLC), and in which the resistance to treatment with a tyrosine kinase inhibitor comprises for example EGFR-independent TKI-resistance, such as resistance to a tyrosine kinase inhibitor such as erlotinib or gefitinib, or other kinase inhibitors, e.g. sunitinib, nilotinib, and sorafenib;

(d) the cancer or myeloproliferative disorder comprises a myeloproliferative disorder such as selected from the group consisting of: polycythaemia vera, essential thrombocythaemia, and primary myelofibrosis, and in which the resistance to

treatment with a tyrosine kinase inhibitor comprises for example JAK2-independent TKI-resistance, such as resistance to JAK inhibitors; or

(e) in which the cancer or myeloproliferative disorder is selected from the group consisting of: haematologic malignancies, chronic lymphocytic leukaemia, acute lymphoblastic leukaemia, acute myeloid leukaemia, multiple myeloma, myeloproliferative disorders (including polycythaemia vera, essential thrombocythaemia, and primary myelofibrosis), solid tumours, small cell lung cancer, breast cancer, colorectal cancer, ovarian cancer, melanoma and neuroblastoma.

8. A polymorphic variant of a *BIM* (*BCL2L11*) gene which comprises, in 5' to 3' order, the nucleotide sequence set out in SEQ ID NO: 5 followed immediately by the nucleotide sequence set out in SEQ ID NO: 7.

9. A polymorphic variant of a *BIM* (*BCL2L11*) gene characterised by lacking the nucleotide sequence set out in SEQ ID NO: 6.

10. A nucleotide sequence as set out in SEQ ID NO: 1 or SEQ ID NO: 2, which is obtainable from a *BIM* polymorphic variant according to Claim 8 or 9, for example by nucleic acid amplification.

11. A polymorphic variant of a *BIM* (*BCL2L11*) gene according to Claim 8 or 9 or a nucleotide sequence according to Claim 10, which is associated with:

(i) resistance to treatment with tyrosine kinase inhibitors for chronic myelogenous leukaemia in the absence of BCR-ABL reactivation (BCR-ABL-independent TKI-resistance);

(ii) resistance to treatment with tyrosine kinase inhibitors for gastrointestinal stromal tumours (GIST) in the absence of c-KIT/PDGFR reactivation (c-KIT/PDGFR-independent TKI-resistance);

(iii) resistance to treatment with tyrosine kinase inhibitors for non-small cell lung cancer (NSCLC) in the absence of EGFR reactivation (EGFR-independent TKI-resistance); or

(iv) resistance to treatment with tyrosine kinase inhibitors for a myeloproliferative disorder in the absence of JAK2 reactivation (JAK2-independent TKI-resistance);

in an individual comprising such a polymorphism.

12. A nucleotide sequence (a) as set out in SEQ ID NO: 3, or a (b) as set out in SEQ ID NO: 4, or a combination of (a) and (b), for example, a primer set.

13. A method of detecting the presence or absence of a *BIM (BCL2L1)* polymorphism according to Claim 8 or 9 in an individual, the method comprising detecting a nucleic acid amplification product comprising a sequence set out in SEQ ID NO: 1 or a sequence set out in SEQ ID NO: 2, for example by use of a primer set according to Claim 12.

14. A method of treatment of a patient suffering from cancer or a myeloproliferative disorder, the method comprising determining whether the cancer or myeloproliferative disorder is a BCR-ABL-independent TKI-resistant CML cancer, a c-KIT/PDGFR-independent TKI-resistant GIST cancer, an EGFR-independent TKI-resistant NSCLC cancer or a JAK2-independent TKI-resistant myeloproliferative disorder by a method according to any of Claims 1 to 7, and treating the patient by performing a step selected from (a) to (g) as set out in Claim 5.

15. A method according to Claim 13 or 14, which comprises detecting a nucleic acid amplification product comprising a sequence set out in SEQ ID NO: 1, for example by use of a primer set according to Claim 5.

16. A polymorphic variant, nucleotide sequence or method substantially as hereinbefore described with reference to and as shown in Figures 1 to 26 of the accompanying drawings.

CLAIMS

1. A method of predicting whether an individual susceptible to or suffering from cancer or a myeloproliferative disorder is likely to develop resistance to treatment with a tyrosine kinase inhibitor, the method comprising determining whether the individual has a polymorphic variant of a *BIM* (*BCL2L11*) gene which lacks the nucleotide sequence set out in SEQ ID NO: 6.
2. A method according to Claim 1, in which the polymorphic variant of a *BIM* (*BCL2L11*) gene comprises, in 5' to 3' order, the nucleotide sequence set out in SEQ ID NO: 5 followed immediately by the nucleotide sequence set out in SEQ ID NO: 7.
3. A method according to Claim 1 or 2, which comprises: (a) detecting the presence of a nucleic acid amplification product comprising a sequence set out in SEQ ID NO: 1 as an indicator of the individual having the polymorphic variant of the *BIM* (*BCL2L11*) gene, or (b) detecting the presence of a nucleic acid amplification product comprising a sequence set out in SEQ ID NO: 2 as an indicator of the individual lacking the polymorphic variant of the *BIM* (*BCL2L11*) gene.
4. A method according to Claim 1, 2 or 3, in which the method comprises nucleic acid amplification using a nucleotide sequence (a) as set out in SEQ ID NO: 3, or a (b) as set out in SEQ ID NO: 4, or a combination of (a) and (b), for example, as a primer set.
5. A method according to any preceding claim, in which (a) if the individual is determined to have the polymorphic variant of the *BIM* (*BCL2L11*) gene, then the individual is likely to develop resistance to treatment with a tyrosine kinase inhibitor, or in which (b) if the individual is determined not to have the polymorphic variant of the *BIM* (*BCL2L11*) gene, then the individual is less likely to develop resistance to treatment with a tyrosine kinase inhibitor.
6. A method of choosing a therapy for an individual with cancer or a myeloproliferative disorder, the method comprising determining whether a patient is likely to develop resistance to treatment with a tyrosine kinase inhibitor by a method according to any preceding claim, and where the individual is determined as being likely to develop such resistance, choosing a therapy comprising any one or more of the following:
 - (a) more frequent monitoring of the patient;

- (b) more frequent blood and bone marrow tests;
- (c) bone marrow transplantation;
- (d) administration of a more potent tyrosine kinase inhibitor (TKI), such as nilotinib or dasatinib;
- 5 (e) administration of a BH3-mimetic, e.g., ABT-263, for example in combination with a TKI;
- (f) increasing the dose of a tyrosine kinase inhibitor, e.g. imatinib, for example beyond the standard dose of 400mg/day to 600 or 800 mg/day; or
- (g) treatment with a drug that inhibits the pro-survival effect of the BCL2 group of
10 proteins.
- 7. A method according to any preceding claim, in which:
 - (a) the cancer or myeloproliferative disorder comprises chronic myelogenous leukaemia (CML) and in which the resistance to treatment with a tyrosine kinase inhibitor comprises for example BCR-ABL-independent TKI-resistance, such as resistance to a
15 tyrosine kinase inhibitor such as imatinib;
 - (b) the cancer or myeloproliferative disorder comprises gastrointestinal stromal tumour (GIST), and in which the resistance to treatment with a tyrosine kinase inhibitor comprises for example c-KIT/PDGFR-independent TKI-resistance, such as resistance to a tyrosine kinase inhibitor such as imatinib;
 - 20 (c) the cancer or myeloproliferative disorder comprises non-small cell lung cancer (NSCLC), and in which the resistance to treatment with a tyrosine kinase inhibitor comprises for example EGFR-independent TKI-resistance, such as resistance to a tyrosine kinase inhibitor such as erlotinib or gefitinib, or other kinase inhibitors, e.g. sunitinib, nilotinib, and sorafenib;
 - 25 (d) the cancer or myeloproliferative disorder comprises a myeloproliferative disorder such as selected from the group consisting of: polycythaemia vera, essential thrombocythaemia, and primary myelofibrosis, and in which the resistance to treatment with a tyrosine kinase inhibitor comprises for example JAK2-independent TKI-resistance, such as resistance to JAK inhibitors; or

- (e) in which the cancer or myeloproliferative disorder is selected from the group consisting of: haematologic malignancies, chronic lymphocytic leukaemia, acute lymphoblastic leukaemia, acute myeloid leukaemia, multiple myeloma, myeloproliferative disorders (including polycythaemia vera, essential thrombocythaemia, and primary myelofibrosis), solid tumours, small cell lung cancer, breast cancer, colorectal cancer, ovarian cancer, melanoma and neuroblastoma.
8. An isolated polymorphic variant of a *BIM* (*BCL2L1*) gene which comprises, in 5' to 3' order, the nucleotide sequence set out in SEQ ID NO: 5 followed immediately by the nucleotide sequence set out in SEQ ID NO: 7.
9. An isolated polymorphic variant of a *BIM* (*BCL2L1*) gene characterised by lacking the nucleotide sequence set out in SEQ ID NO: 6.
10. An isolated nucleotide sequence as set out in SEQ ID NO: 1, which is obtainable from a *BIM* polymorphic variant according to Claim 8 or 9, for example by nucleic acid amplification.
11. An isolated polymorphic variant of a *BIM* (*BCL2L1*) gene according to Claim 8 or 9 or a nucleotide sequence according to Claim 10, which is associated with:
- (i) resistance to treatment with tyrosine kinase inhibitors for chronic myelogenous leukaemia in the absence of BCR-ABL reactivation (BCR-ABL-independent TKI-resistance);
 - (ii) resistance to treatment with tyrosine kinase inhibitors for gastrointestinal stromal tumours (GIST) in the absence of c-KIT/PDGFR reactivation (c-KIT/PDGFR-independent TKI-resistance);
 - (iii) resistance to treatment with tyrosine kinase inhibitors for non-small cell lung cancer (NSCLC) in the absence of EGFR reactivation (EGFR-independent TKI-resistance); or
 - (iv) resistance to treatment with tyrosine kinase inhibitors for a myeloproliferative disorder in the absence of JAK2 reactivation (JAK2-independent TKI-resistance);
- in an individual comprising such a polymorphism.
12. An isolated nucleotide sequence (a) as set out in SEQ ID NO: 3, or a (b) as set out in SEQ ID NO: 4, or a combination of (a) and (b), for example, a primer set.

13. An isolated nucleotide sequence having the sequence set out in SEQ ID NO: 6.
14. A method of detecting the presence or absence of a *BIM* (*BCL2L1*) polymorphism according to Claim 8 or 9 in an individual, the method comprising detecting a nucleic acid amplification product comprising a sequence set out in SEQ ID NO: 1 for example by use of a primer set according to Claim 12.
15. An isolated polymorphic variant of a *BIM* (*BCL2L1*) gene according to any of Claims 8, 9 or 11 or a nucleotide sequence according to Claim 10 or 12 for use in a method of treatment of a patient suffering from cancer or a myeloproliferative disorder.
16. An isolated polymorphic variant of a *BIM* (*BCL2L1*) gene or a nucleotide sequence according to Claim 15 for use in a method as specified therein, the method comprising determining whether the cancer or myeloproliferative disorder is a BCR-ABL-independent TKI-resistant CML cancer, a c-KIT/PDGFR-independent TKI-resistant GIST cancer, an EGFR-independent TKI-resistant NSCLC cancer or a JAK2-independent TKI-resistant myeloproliferative disorder by a method according to any of Claims 1 to 5, and treating the patient by performing a step selected from (a) to (g) as set out in Claim 6.