

Claims

What is claimed is:

1. An *in vitro* method of predicting the sensitivity of the growth of a tumor cell to an AKT inhibitor, comprising determining the presence of a mutation to AKT, wherein the presence of a mutation to AKT correlates with sensitivity of the cell to the AKT inhibitor.
2. The method of claim 1, wherein the presence of the mutation to AKT correlates with increased sensitivity of the cell to an ATP competitive AKT inhibitor.
3. The method of claim 1, wherein the presence of the mutation to AKT correlates with decreased sensitivity of the cell to an an allosteric AKT inhibitor.
4. The method of claim 1, wherein the presence of the mutation to AKT correlates with decreased sensitivity of the cell to a pan-PI3K AKT inhibitor.
5. The method of any one of claims 1-4, wherein the mutation corresponds to, or aligns with, a mutation depicted in Table 1, Table 2, Figure 2, Figure 3, Figure 16 or Figure 17.
6. The method of claim 5, wherein the mutation corresponds to, or aligns with, L52, K189 or D323.
7. The method of any one of claims 1-6, wherein the AKT is AKT1, AKT2 or AKT3.
8. The method of claim 7, wherein the AKT is AKT1.
9. The method of any one of claims 1-8, wherein the mutation to AKT disrupts the interaction between the PH-domain and the kinase domain of AKT.

10. The method of any one of claims 1-9, wherein the mutation to AKT increases phosphorylation of AKT.
11. The method of claim 10, wherein in the increase in phosphorylation is due to constitutive phosphorylation.
12. The method of any one of claims 1-11, wherein the method further comprises determining the PTEN status of the cell, wherein PTEN loss correlates with increased sensitivity to the inhibitor.
13. The method of claim 12, wherein the tumor cell is an ovarian or prostate cancer tumor cell.
14. The method of any one of claims 1-13, wherein the method further comprises determining the presence of a PI3K mutation of the cell, wherein the presence of a PI3K mutation correlates with increased sensitivity to inhibition by the inhibitor.
15. The method of claim 14, wherein said PI3K mutations are one or both of H1047R and H1047L.
16. The method of any one of claims 1-15, wherein the method further comprises determining the pAKT profile of the cell, wherein a high activity profile for pAKT correlates with increased sensitivity to inhibition by the inhibitor.
17. The method of any one of claims 1-16, wherein the method further comprises determining the pAKT profile of the cell, wherein a low activity profile for pAKT correlates with decreased sensitivity to inhibition by the inhibitor.
18. The method of any one of claims 1-17, wherein the method further comprises determining the Her2 and/or Her3 status of the cell, wherein a Her2+

and/or Her3+ status of the cell correlates with increased sensitivity to inhibition by the inhibitor.

19. The method of any one of claims 1-18, wherein the method further comprises determining the presence of a Met kinase mutation of the cell, wherein the presence of a Met kinase mutation correlates with sensitivity of the cell to the AKT inhibitor.

20. The method of any one of claims 1-19, wherein the method further comprises determining the presence of a B-Raf or K-Ras mutation of the cell, wherein the presence of a B-Raf or K-Ras mutation correlates with a decrease in sensitivity of the cell to the AKT inhibitor.

21. The method of any one of claims 1-20, wherein the method further comprises determining the localization profile of FOXO3a in the cell, wherein a cytoplasmic localization profile of FOXO3a correlates with sensitivity of the cell to inhibition by the Akt inhibitor.

22. The method of any one of claims 1-12 or 14-21, wherein the tumor cell is a prostate, ovarian, breast, gastric, or pancreatic cancer cell.

23. The method of claim 23, wherein the tumor cell is an endocrine resistant breast cancer cell.

24. The method of any one of claims 1-23, wherein the method further comprises determining the INPP4B, PHLPP, and/or PP2A status of the cell, wherein INPP4B, PHLPP, and/or PP2A loss correlates with increased sensitivity to the inhibitor.

25. The method of any one of claims 1-24, wherein the AKT inhibitor is (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one, or a pharmaceutically acceptable salt thereof.

26. The method of any one of claims 1-25, further comprising obtaining a physiological sample from a patient for determining the presence of the mutation to AKT.
27. The method of claim 26, further comprising determining the presence of the mutation to AKT in the physiological sample.
28. The method of any one of claims 1-27, further comprising informing a patient for whom the presence of a mutation to AKT is determined that an AKT inhibitor should be administered.
29. The method of any one of claims 1-27, further comprising informing a patient for whom the presence of a mutation to AKT is determined that an AKT inhibitor should not be administered.
30. Use of GDC-0068 or a salt thereof in the manufacture of a medicament for treating a cancer cell comprising one or more of a PI3k, PTEN, and AKT mutation.

Claims

What is claimed is:

1. An *in vitro* method of predicting the sensitivity of the growth of a tumor cell to an AKT inhibitor, comprising determining the presence of a mutation to AKT, wherein the presence of a mutation to AKT correlates with sensitivity of the cell to the AKT inhibitor, wherein the mutation corresponds to, or aligns with, L52, K189 or D323.
2. The method of claim 1, wherein the presence of the mutation to AKT correlates with increased sensitivity of the cell to an ATP competitive AKT inhibitor.
3. The method of claim 1, wherein the presence of the mutation to AKT correlates with decreased sensitivity of the cell to an an allosteric AKT inhibitor.
4. The method of claim 1, wherein the presence of the mutation to AKT correlates with decreased sensitivity of the cell to a pan-PI3K AKT inhibitor.
5. The method of any one of claims 1-4, wherein the AKT is AKT1, AKT2 or AKT3.
6. The method of claim 5, wherein the AKT is AKT1.
7. The method of any one of claims 1-6, wherein the mutation to AKT disrupts the interaction between the PH-domain and the kinase domain of AKT.
8. The method of any one of claims 1-7, wherein the mutation to AKT increases phosphorylation of AKT.
9. The method of claim 8, wherein in the increase in phosphorylation is due to constitutive phosphorylation.

10. The method of any one of claims 1-9, wherein the method further comprises determining the PTEN status of the cell, wherein PTEN loss correlates with increased sensitivity to the inhibitor.
11. The method of claim 10, wherein the tumor cell is an ovarian or prostate cancer tumor cell.
12. The method of any one of claims 1-11, wherein the method further comprises determining the presence of a PI3K mutation of the cell, wherein the presence of a PI3K mutation correlates with increased sensitivity to inhibition by the inhibitor.
13. The method of claim 12, wherein said PI3K mutations are one or both of H1047R and H1047L.
14. The method of any one of claims 1-13, wherein the method further comprises determining the pAKT profile of the cell, wherein a high activity profile for pAKT correlates with increased sensitivity to inhibition by the inhibitor.
15. The method of any one of claims 1-14, wherein the method further comprises determining the pAKT profile of the cell, wherein a low activity profile for pAKT correlates with decreased sensitivity to inhibition by the inhibitor.
16. The method of any one of claims 1-15, wherein the method further comprises determining the Her2 and/or Her3 status of the cell, wherein a Her2+ and/or Her3+ status of the cell correlates with increased sensitivity to inhibition by the inhibitor.
17. The method of any one of claims 1-16, wherein the method further comprises determining the presence of a Met kinase mutation of the cell, wherein the presence of a Met kinase mutation correlates with sensitivity of the cell to the AKT inhibitor.
18. The method of any one of claims 1-17, wherein the method further comprises determining the presence of a B-Raf or K-Ras mutation of the cell, wherein the

presence of a B-Raf or K-Ras mutation correlates with a decrease in sensitivity of the cell to the AKT inhibitor.

19. The method of any one of claims 1-18, wherein the method further comprises determining the localization profile of FOXO3a in the cell, wherein a cytoplasmic localization profile of FOXO3a correlates with sensitivity of the cell to inhibition by the Akt inhibitor.

20. The method of any one of claims 1-10 or 12-19, wherein the tumor cell is a prostate, ovarian, breast, gastric, or pancreatic cancer cell.

21. The method of claim 20, wherein the tumor cell is an endocrine resistant breast cancer cell.

22. The method of any one of claims 1-21, wherein the method further comprises determining the INPP4B, PHLPP, and/or PP2A status of the cell, wherein INPP4B, PHLPP, and/or PP2A loss correlates with increased sensitivity to the inhibitor.

23. The method of any one of claims 1-22, wherein the AKT inhibitor is (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one, or a pharmaceutically acceptable salt thereof.

24. The method of any one of claims 1-23, further comprising obtaining a physiological sample from a patient for determining the presence of the mutation to AKT.

25. The method of claim 24, further comprising determining the presence of the mutation to AKT in the physiological sample.

26. The method of any one of claims 1-25, further comprising informing a patient for whom the presence of a mutation to AKT is determined that an AKT inhibitor should be administered.

27. The method of any one of claims 1-25, further comprising informing a patient for whom the presence of a mutation to AKT is determined that an AKT inhibitor should not be administered.

28. Use of GDC-0068 or a salt thereof in the manufacture of a medicament for treating a cancer cell having a mutation corresponding to, or aligning with, L52, K189 or D323.