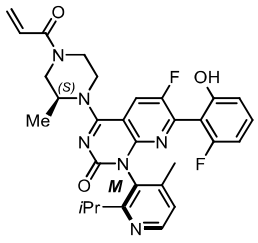
milestone for proof-of-concept, mutant-selective KRAS inhibition, it was positioned as a tool compound for preclinical studies. We identified a series of novel acrylamide-based molecules that utilize a previously unexploited surface groove in $KRAS^{G12C}$ to substantially enhance potency and selectivity. Intensive electrophile-screening and structure-based design culminated in the discovery of AMG 510, the first $KRAS^{G12C}$ inhibitor to reach clinical testing in humans (See www.clinicaltrials.gov NCT03600883). Here we present compelling clinical activity of AMG 510.

SUMMARY

[0006] In one aspect, the present disclosure relates to a use of a compound having the following structure: , or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the compound is to be administered to the subject at a total daily amount of 960 mg.

[0006a] Provided herein are methods of treating cancer comprising administering to a subject in need thereof Compound A in a daily dose of 180 mg, 360 mg, 720 mg, or 960 mg. In various cases, the daily dose is 180 mg. In various cases, the daily dose is 360 mg. In various cases, the daily dose is 720 mg. In various cases, the daily dose is 960 mg. The dose can be administered orally. The dose can be administered as a single daily dose. In various cases, the subject is administered Compound A for at least one months, or at least three months, or at least six months.

[0007] The subjects administered Compound in the methods disclosed herein have cancer. The cancer can be a solid tumor. The cancer can be a KRAS G12C mutated cancer. In some cases, the cancer is non-small cell lung cancer. In some cases, the cancer is colorectal cancer. In some cases, the cancer is pancreatic cancer. In various cases, the subject is one who, prior to start of therapy with Compound A, had undergone at least one (e.g., at least two) other systemic cancer therapy.

[0008] In various cases, a subject administered Compound A for at least a month does not exhibit any grade 3 or grade 4 adverse events associated with Compound A therapy. In some cases, the subject does not exhibit any grade 3 or grade 4 adverse events associated with Compound A therapy after at least three months of administration of Compound A. In various cases, the subject exhibits an at least stable disease after administration with Compound A. In some cases, the subject exhibits an at least partial response after administration with Compound A.

[0009] In various cases, the methods disclosed herein can further comprise administration of a chemotherapeutic. In some cases, the chemotherapeutic comprises an anti-PD1 antibody. In some cases, the anti-PD1 antibody is Pembrolizumab (Keytruda), Nivolumab, AUNP-12, AMG 404, or Pidilizumab. In some cases, the chemotherapeutic comprises an anti-PDL1 antibody. In some cases, the anti-PDL1 antibody is Atezolizumab, MPDL3280A, Avelumab or Durvalumab. In some cases, the chemotherapeutic comprises a MEK inhibitor. In some cases, the MEK inhibitor is trametinib, pimasertib, PD-325901, MEK162, TAK-733, GDC-0973 or AZD8330. In some cases, the chemotherapeutic comprises a CDK4/6 inhibitor. In some cases, the CDK4/6 inhibitor comprises abemaciclib, or palbociclib. In some cases, the chemotherapeutic comprises a PI3K inhibitor. In some cases, the PI3K inhibitor comprises AMG 511 or buparlisib.

BRIEF DESCRIPTION OF THE FIGURES

[0010] In the Figures that follow, PD indicates progressive disease, PR indicates partial response and SD indicates stable disease.

[0011] Figure 1 shows CA 19-9 and CAE biomarker response in patient having metastatic colon adenocarcinoma and administered Compound A at a total daily dose of 360 mg.

[0012] Figure 2 shows non-small cell lung cancer (NSCLC) tumor responses, as measured by radiographic scans every six weeks, for nine NSCLC cancer patients receiving Compound A at various total daily doses as shown.

[0013] Figure 3 shows the response and treatment duration of NSCLC patients administered Compound A at the following total daily doses – top four bars 960 mg; next six bars 720 mg; next bar 360 mg; and bottom three bars 180 mg.

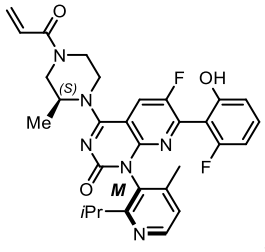
[0014] Figure 4 shows colorectal cancer (CRC) and other solid tumor responses, as measured by radiographic scans every six weeks, for CRC and other solid tumor cancer patients receiving Compound A at various total daily doses as shown.

[0015] Figure 5 shows the response and treatment duration of CRC and Other solid tumor patients administered Compound A at the following total daily doses – top two bars 960 mg; next five bars 720 mg; next eleven bars 360 mg; and bottom three bars 180 mg.

CLAIMS

What is claimed:

1. Use of a compound having the following structure:



, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the compound is to be administered to the subject at a total daily amount of 960 mg.

2. The use of claim 1, wherein the cancer is non-small cell lung cancer, small intestine cancer, appendix cancer, colorectal cancer, endometrial cancer, pancreatic cancer, skin cancer, gastric cancer, nasal cavity cancer, or bile duct cancer.

3. The use of claim 1, wherein the cancer is non-small cell lung cancer.

4. The use of claim 1, wherein the cancer is locally advanced or metastatic non-small cell lung cancer.

5. The use of claim 1, wherein the cancer is colorectal cancer.

6. The use of claim 1, wherein the cancer is pancreatic cancer.

7. The use of any one of claims 1 to 6, wherein the cancer is a KRAS G12C mutated cancer.

8. The use of any one of claims 1 to 7, wherein the subject, prior to start of treatment with the medicament, had undergone at least one other systemic cancer therapy.

9. The use of any one of claims 1 to 8, wherein the subject had undergone at least two other systemic cancer therapies.

10. The use of any one of claims 1 to 9, wherein the medicament is to be administered orally.

11. The use of any one of claims 1 to 10, wherein the medicament is to be administered once daily.

12. The use of any one of claims 1 to 11, wherein the medicament is to be administered as a tablet.

13. The use of any one of claims 1 to 12, further comprising that a chemotherapeutic is to be administered to the subject.

14. The use of claim 13, wherein the chemotherapeutic comprises an anti-PD1 antibody.

15. The use of claim 14, wherein the anti-PD1 antibody is pembrolizumab, nivolumab, or AMG 404.

16. The use of claim 15, wherein the anti-PD1 antibody is prembrolizumab.

17. The use of claim 15, wherein the anti-PD1 antibody is AMG 404.

18. The use of claim 13, wherein the chemotherapeutic comprises an anti-PDL1 antibody.

19. The use of claim 18, wherein the anti-PDL1 antibody is atezolizumab, a velumab or durvalumab.

20. The use of claim 19, wherein the anti-PDL1 antibody is atezolizumab.

21. The use of claim 13, wherein the chemotherapeutic comprises a MEK inhibitor.

22. The use of claim 21, wherein the MEK inhibitor is trametinib, pimasertib, PD-325901, MEK162, TAK-733, GDC-0973 or AZD8330.

23. The use of claim 22, wherein the MEK inhibitor is trametinib.

24. The use of claim 13, wherein the chemotherapeutic comprises a CDK4/6 inhibitor.

25. The use of claim 24, wherein the CDK4/6 inhibitor is abemaciclib, or palbociclib.

26. The use of claim 25, wherein the CDK4/6 inhibitor is palbociclib.

27. The use of claim 13, wherein the chemotherapeutic comprises a PI3K inhibitor.

28. The use of claim 27, wherein the PI3K inhibitor is AMG 511 or buparlisib.