gastrointestinal toxicities remains elusive. (Takebe et al., *Pharmacology & Therapeutics*, 2014, 141: 140-149).

The skilled artisan will appreciate that a "loading dose" of a drug is an initial higher dose of a drug given at the beginning of a course of treatment before dropping down to a lower "maintenance dose." A loading dose is typically useful for drugs that achieve their therapeutic threshold level relatively slowly. An initial loading dose or doses are administered for the drug to reach the appropriate therapeutic level more rapidly than if administered only at a lower fixed dose.

The present disclosure balances a need for a therapeutic agent dose regimen that exhibits activity (efficacy) in the treatment of solid tumor cancers while mitigating gastrointestinal toxicity. There is also a need for a dose regimen in which 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof demonstrates therapeutic efficacy and durable response in solid tumor cancer patients without adversely impacting efficacy, or causing dose limiting, or dose schedule limiting gastrointestinal toxicities.

Disclosed is a method of treating a solid tumor cancer patient comprising administering to a patient in need of treatment 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, wherein

a) a loading dose of at least one dose and up to 12 doses at 75-150 mg/dose are administered twice or three times per week during a 28 day cycle; followed by
b) a maintenance dose of 50 mg/dose administered three times per week; and optionally
c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid.

Disclosed is a compound 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide or a pharmaceutically acceptable salt or hydrate thereof, for use

in the treatment of a solid tumor cancer, wherein said compound or a pharmaceutically acceptable salt or hydrate thereof is administered:

a) at a loading dose of at least one dose and up to 12 doses at 75-150 mg/dose are administered twice or three times per week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid.

In one aspect, there is provided a compound 4,4,4-Trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for use in the treatment of a solid tumor cancer , wherein said compound or the pharmaceutically acceptable salt or hydrate thereof is to be administered:

a. at a loading dose of at least one dose and up to 12 doses at 75-150 mg/dose twice or three times per week for at least one week during a 28 day cycle; followed by

b. a maintenance dose of 50 mg/dose three times per week.

Disclosed is the use of 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for preparation of a medicament for treating a solid tumor cancer wherein said medicament is administered:

a) at a loading dose of at least one dose and up to 12 doses at 75-150 mg/dose administered twice or three times per week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid.

In another aspect, there is provided use of 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, in the manufacture of a medicament for the treatment of a solid tumor cancer, wherein said medicament is to be administered:

a) at a loading dose of at least one dose and up to 12 doses at 75-150 mg/dose twice or three times per week for at least one week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose three times per week.

Disclosed is a method of treating a solid tumor cancer comprising administering to a patient in need of treatment 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof,

a) a loading dose of at least one dose and up to 12 doses at 75-150 mg/dose administered twice or three times per week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid;

wherein the solid tumor cancer is selected from the group consisting of triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non-small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, leiomyosarcoma, and adenoid cystic carcinoma.

Disclosed is the compound 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for use in the treatment of a solid tumor cancer wherein said compound or a pharmaceutically acceptable salt or hydrate thereof is administered:

a) at a loading dose of at least one dose and up to 12 doses at 75-150 mg/dose administered twice or three times per week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid;

wherein the solid tumor cancer is selected from the group consisting of triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non-small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, leiomyosarcoma, and adenoid cystic carcinoma.

Disclosed is the use of 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for preparation of a medicament for treating a solid tumor cancer wherein said medicament is administered:

a) at a loading dose of at least one dose and up to 12 doses at 75-150 mg/dose administered twice or three times per week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid; and

wherein said solid tumor cancer is selected from the group consisting of triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non-small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, leiomyosarcoma, and adenoid cystic carcinoma.

Disclosed is a method of treating a solid tumor cancer comprising administering to a patient in need of treatment 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, wherein

a) a loading dose of at least one dose and up to 6 doses at 75-150 mg/dose administered twice or three times per week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid;

wherein the solid tumor cancer is selected from the group consisting of triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non-small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, leiomyosarcoma, and adenoid cystic carcinoma.

Disclosed is a compound 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof,

for use in the treatment of a solid tumor cancer wherein said compound or a pharmaceutically acceptable salt or hydrate thereof is administered:

a) at a loading dose of at least one dose and up to 6 doses at 75-150 mg/dose administered twice or three times per week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid;

wherein the solid tumor cancer is selected from the group consisting of triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non-small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, leiomyosarcoma, and adenoid cystic carcinoma.

Disclosed is the use of 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for preparation of a medicament for treatment of a solid tumor cancer; wherein said medicament is administered:

a) at a loading dose of at least one dose and up to 6 doses at 75-150 mg/dose administered twice or three times per week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid;

wherein the solid tumor cancer is selected from the group consisting of triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non-small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic

cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, leiomyosarcoma, and adenoid cystic carcinoma.

Disclosed is a method of treating a solid tumor cancer comprising administering to a patient in need of treatment 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof,

a) a loading dose of at least one dose and up to 3 doses at 75-150 mg/dose administered twice or three times per week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid;

wherein the solid tumor cancer is selected from the group consisting of triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non-small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, leiomyosarcoma, and adenoid cystic carcinoma.

Disclosed is a compound 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for use in the treatment of a solid tumor cancer wherein said compound or a pharmaceutically acceptable salt or hydrate thereof is administered:

a) at a loading dose of at least one dose and up to 3 doses at 75-150 mg/dose administered twice or three times per week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid;

wherein the solid tumor cancer is selected from the group consisting of triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non-small cell lung

cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, leiomyosarcoma, and adenoid cystic carcinoma.

Disclosed is the use of 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for preparation of a medicament for treatment of a solid tumor cancer; wherein said medicament is administered:

a) at a loading dose of at least one dose and up to 3 doses at 75-150 mg/dose administered twice or three times per week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid;

wherein the solid tumor cancer is selected from the group consisting of triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non-small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, leiomyosarcoma, and adenoid cystic carcinoma.

Disclosed is a method of treating leiomyosarcoma comprising administering to a patient in need of treatment 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof,

a) a loading dose of at least one dose and up to 3 doses at 75-150 mg/dose administered twice or three times per week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid.

Disclosed is the compound 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for use in the treatment of leiomyosarcoma wherein said compound or a pharmaceutically acceptable salt or hydrate thereof is administered:

a) at a loading dose of at least one dose and up to 3 doses at 75-150 mg/dose administered twice or three times per week during a 28 day cycle; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid.

Disclosed is the use of 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for preparation of a medicament for treatment of leiomyosarcoma wherein said medicament is administered:

a) at a loading dose of at least one dose and up to 3 doses at 75-150 mg/dose administered twice or three times per week; followed by

b) a maintenance dose of 50 mg/dose administered three times per week; and optionally

c) administering, during administration of the loading dose, 1-50 mg/day of a corticosteroid.

The compound 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide ("Compound 1"), or a pharmaceutically acceptable salt or hydrate thereof , is taught to be a Notch inhibitor in WO 2013/016081.

An "effective amount" means a dose of Compound 1, or pharmaceutically acceptable salt or hydrate thereof, or pharmaceutical composition containing the compound, or pharmaceutically acceptable salt or hydrate thereof, necessary to inhibit Notch signaling in a solid tumor cancer patient, and either destroy the target cancer cells

WE CLAIM:

1. A compound 4,4,4-Trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for use in the treatment of a solid tumor cancer , wherein said compound or the pharmaceutically acceptable salt or hydrate thereof is to be administered:
    a. at a loading dose of at least one dose and up to 12 doses at 75-150 mg/dose twice or three times per week for at least one week during a 28 day cycle; followed by
    b. a maintenance dose of 50 mg/dose three times per week.
2. The compound or the pharmaceutically acceptable salt or hydrate thereof for use of claim 1, wherein, during the administration of the loading dose, 1-80 mg/day of a corticosteroid is to be administered for one or more days of the 28 day cycle.
3. The compound or the pharmaceutically acceptable salt or hydrate thereof for use of claim 2, wherein the corticosteroid is to be administered at a dose of 1-50 mg/day.
4. The compound or the pharmaceutically acceptable salt or hydrate thereof for use of claim 2 or claim 3, wherein the corticosteroid is to be administered at a dose of 20 mg/day.
5. The compound or the pharmaceutically acceptable salt or hydrate thereof for use of any of claims 2-4, wherein the corticosteroid is to be administered for at least 14 days of the 28 day cycle.
6. The compound or the pharmaceutically acceptable salt or hydrate thereof for use of any of claims 2-5, wherein the corticosteroid is selected from the group consisting of hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone, and prednisone.
7. The compound or the pharmaceutically acceptable salt or hydrate thereof for use of any of claims 1-6, wherein said loading dose is at least one dose and up to 6 doses.

8. The compound or the pharmaceutically acceptable salt or hydrate thereof for use of any of claims 1-6 wherein said loading dose is at least one dose and up to 3 doses.
9. The compound or the pharmaceutically acceptable salt or hydrate thereof for use of any of claims 1-8, wherein the maintenance dose is to be administered over any remaining days of the 28 day cycle following administration of the loading dose and, optionally, over one or more additional 28 day cycles.
10. The compound or the pharmaceutically acceptable salt or hydrate thereof for use of any of claims 1-9, wherein said solid tumor cancer is selected from the group consisting of triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non-small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, leiomyosarcoma, and adenoid cystic carcinoma.
11. Use of 4,4,4-trifluoro-N-[(1S)-2-[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, in the manufacture of a medicament for the treatment of a solid tumor cancer, wherein said medicament is to be administered:
    a) at a loading dose of at least one dose and up to 12 doses at 75-150 mg/dose twice or three times per week for at least one week during a 28 day cycle; followed by
    b) a maintenance dose of 50 mg/dose three times per week.
12. The use of claim 11, wherein, during the administration of the loading dose, 1-80 mg/day of a corticosteroid is to be administered for one or more days of the 28 day cycle.
13. The use of claim 12, wherein the corticosteroid is to be administered at a dose of 1-50 mg/day.
14. The use of claim 12 or claim 13, wherein the corticosteroid is to be administered at a dose of 20 mg/day.

15. The use of any of claims 12-14, wherein the corticosteroid is to be administered for at least 14 days of the 28 day cycle.

16. The use of any of claims 12-15, wherein the corticosteroid is selected from the group consisting of hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone, and prednisone.

17. The use of any of claims 11-16, wherein said loading dose is at least one dose and up to 6 doses.

18. The use of any of claims 11-16, wherein said loading dose is at least one dose and up to 3 doses.

19. The use of any of claims 11-18, wherein the maintenance dose is to be administered over any remaining days of the 28 day cycle following administration of the loading dose and, optionally, over one or more additional 28 day cycles.

20. The use of any of claims 11-19, wherein said solid tumor cancer is selected from the group consisting of triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non-small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, hepatocellular carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, desmoid tumor, soft tissue sarcoma, leiomyosarcoma, and adenoid cystic carcinoma.