[0024] FIGs. 6 and **7** summarize other treatment exposure events, dose discontinuation or dose adjustments during the study.

[0025] FIG. 8 depicts the tumor burden in patient target lesions for the combination of Cabozantinib + Nivolumab +/- Ipilimumab.

[0026] FIG. 9 shows the responses when the combination of Cabozantinib + Nivolumab (CaboNivo) and Cabozantinib + Nivolumab + Ipilimumab (CaboNivoIpi) was tested against various tumor types.

[0027] FIG. 10 shows the preliminary time to response and durability of response by cabozantinib dose (CR+PR).

[0028] FIG. **11** depicts median progression free survival.

[0029] FIG. 12 depicts median overall survival.

[0030] FIG. 13 depicts the study design for an expansion study of cabozantinib plus nivolumab (CaboNivo) alone or with Ipilimumab (CaboNivoIpi) in patients with metastatic urothelial carcinoma and other genitourinary tumors.

DETAILED DESCRIPTION

[0031] Disclosed herein is a method of treating urothelial carcinoma, as well as other forms of cancer described herein, in a human patient, comprising administering to the human patient a therapeutically effective dose of Cabozantinib or a pharmaceutically acceptable salt thereof alone or in combination with one or more therapeutic agent. The one or more agents can be selected from the group consisting of an anti-CTLA4 monoclonal antibody and an IgG4 anti-PD-1 monoclonal antibody. The one or more agents can be selected from the group consisting of the anti-CTLA4 monoclonal antibody ipilimumab and the IgG4 anti-PD-1 monoclonal antibody nivolumab. The form of cancer is selected from the group consisting of urothelial carcinoma, urachal adenocarcinoma, squamous cell carcinoma of the bladder, castration-resistant prostate cancer, renal cell carcinoma-sarcomatoid tumor, trophoblastic tumor, germ cell cancer, and penile cancer.

[0032] "Pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA,

Preferably, the lubricant functions to facilitate compression of the tablets and ejection of the tablets from the die cavity. Such lubricants may be hydrophilic or hydrophobic, and examples include magnesium stearate, Lubritab.RTM., stearic acid, talc, and other lubricants known in the art or to be developed which exhibit acceptable or comparable properties, or mixtures thereof. Examples of lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, zinc stearate, and the like, or mixtures thereof.

[0050] The lubricant should be selected to aid in the flow of the powder in the hopper and into the die. Magnesium stearate exhibits excellent properties in combination with the other preferred excipients of the formulation. Magnesium stearate contributes to reducing friction between the die wall and tablet formulation during compression, as well as to the easy ejection of the Cabozantinib tablets. It also resists adhesion to punches and dies.

[0051] Preferably, the lubricant is magnesium stearate (non-bovine) used in an amount of from about 0.5 to about 1.0 percent by weight on a solid basis of the directly compressible formulation.

Film Coating

[0052] The pharmaceutical composition containing Cabozantinib or a pharmaceutically acceptable salt thereof can also comprise an optional film coating when it is a tablet. The film coat concentration can be about 1 to about 10 percent by weight on a solid basis of the directly compressible formulation. Film coating suspensions may include combinations of the following components: hypromeollose, carboxymethylcellulose sodium, carnauba wax, cellulose acetate phthalate, cetyl alcohol, confectioner's sugar, ethyl cellulose, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, liquid glucose, maltodextrin, methyl cellulose, microcrystalline wax, Opadry and Opadry II, polymethacrylates, polyvinyl alcohol, shellac, sucrose, talc, titanium dioxide, and zein.

Other Adjuvants

[0053] Other pharmaceutically acceptable adjuvants known in the pharmaceutical formulation art may also be used in the pharmaceutical compositions of this disclosure. These include, but are not limited to, preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispersing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. If desired, a pharmaceutical

mixture. This final blend is then ready for tablet compression. The resulting uncoated core tablets are subsequently film coated. The film coating comprises Opadry Yellow, which contains hypromellose, titanium dioxide, triacetin, and iron oxide yellow.

[0098] More particularly, the formulation process comprises:

a) Delumping unmilled Cabozantinib or a pharmaceutically acceptable salt thereof;

b) Premixing the delumped Cabozantinib or a pharmaceutically acceptable salt thereof with Avicel PH102, lactose anhydrous 60M, and croscarmellose sodium to form a binder solution;

c) Wet high shear granulation of the binder solution to produce wet granules;

d) Wet screening of the wet granules to produce wet screened granules;

e) Fluid bed drying of the wet screened granules to produce dried granules;

f) Dry milling of the dried granules to produce dried milled granules;

g) Blending the dried milled granules with colloidal silicon and croscarmellose to produce an extragranular blend;

h) Lubricant blending of the extragranular blend and magnesium stearate to produce a final blend;

i) Tablet compression of the final blend to form an uncoated core tablet; and

j) Film coating of the uncoated core tablet.

[0099] Cabozantininb can be administered as a CABOMETYX tablet. CABOMETYX is a tablet comprising Cabozantinib (S)-malate, microcrystalline cellulose, anhydrous lactose, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide magenisum stearate, and film coating comprising hypromellose, titanium dioxide, triacetin, and iron oxide yellow.

[00100] In an embodiment, the Cabozantinib (S)-malate is administered as a tablet formulation comprising approximately:

30-32 percent by weight of Cabozantinib, (S)-malate salt;

38-40 percent by weight of microcrystalline cellulose;

18-22 percent by weight of lactose;

2-4 percent by weight of hydroxypropyl cellulose;

4-8 percent by weight of croscarmellose sodium;

0.2-0.6 percent by weight of colloidal silicon dioxide;

0.5-1 percent by weight of magnesium stearate; and further comprising:

2.5-3.5 percent by weight of hydroxypropyl cellulose;

5.5-6.5 percent by weight of croscarmellose sodium;

0.25-0.35 percent by weight of colloidal silicon dioxide;

0.7-0.8 percent by weight of magnesium stearate; and further comprising:

3.9-4.1 percent by weight of a film coating material comprising hypromellose, titanium dioxide, triacetin, and iron oxide yellow.

[00113] In another embodiment the Cabozantinib (S)-malate is administered as a tablet formulation selected from the group consisting of:

Ingredient	**Theoretical Quantity (mg/unit dose)**		
	20-mg Tablet	**40-mg Tablet**	**60-mg Tablet**
Cabozantinib (S)-malate	25.34	50.69	76.03
Microcrystalline Cellulose, PH-102	31.08	62.16	93.24
Lactose Anhydrous, 60M	15.54	31.07	46.61
Hydroxypropyl Cellulose, EXF	2.400	4.800	7.200
Croscarmellose Sodium	4.800	9.600	14.40
Colloidal Silicon Dioxide	0.2400	0.4800	0.7200
Magnesium Stearate (Non-Bovine)	0.6000	1.200	1.800
Opadry® Yellow (03K92254)	3.200	6.400	9.600
Total tablet weight	83.20	166.4	249.6

[00114] In another embodiment, the Cabozantinib (S)-malate is administered to treat urothelial cancer or another form of cancer as disclosed herein as a tablet formulation containing 20, 40, or 60 mg of Cabozantinib. 60 mg tablets are yellow film-coated, oval shaped with no score, debossed with “XL” on one side and “60” on the other side of the tablet; available in bottles of 30 tablets: NDC 42388-023-26. 40 mg tablets are yellow film-coated, triangle shaped with no score, debossed with “XL” on one side and “40” on the other side of the tablet; available in bottles of 30 tablets: NDC 42388-025-26. 20 mg tablets are yellow film-coated, round shaped with no score, debossed with “XL” on one side and “20” on the other side of the tablet; available in bottles of 30 tablets: NDC 42388-024-26.

[00115] In a further embodiment, the 60 mg of Cabozantinib is administered once daily as the CABOMETYX tablet formulation as described herein.

[00116] In another embodiment, the invention relates to the use of cabozantinib or a pharmaceutically acceptable salt thereof for the treatment of urothelial carcinoma or another form of cancer described herein. In one embodiment, the urothelial carcinoma is metastatic urothelial carcinoma that is relapsed or refractory. In one embodiment, the Cabozantinib or pharmaceutically acceptable salt thereof is administered at a dose of 20-60 mg once daily. In another embodiment, the Cabozantinib or pharmaceutically acceptable salt thereof is

administered at a dose of 20 mg once daily. In another embodiment, the Cabozantinib or pharmaceutically acceptable salt thereof is administered at a dose of 40 mg once daily. In another embodiment, the Cabozantinib or pharmaceutically acceptable salt thereof is administered at a dose of 60 mg once daily. In another embodiment, the Cabozantinib is administered as the (S)-malate. In another embodiment, the Cabozantinib is administered as Cabometyx tablets. In one embodiment, ORR was improved in patients with lung and/or liver metastases as compared to patients without lung and/or liver metastases.

[00117] In another embodiment, the invention relates to the treatment of urothelial carcinoma or another form of cancer described herein, comprising administering to a patient in need of such treatment, comprising administering a therapeutically effective amount of Cabozantinib or a pharmaceutically acceptable salt thereof. In one embodiment, the urothelial carcinoma is metastatic urothelial carcinoma that is relapsed or refractory. In one embodiment, the Cabozantinib or pharmaceutically acceptable salt thereof is administered at a dose of 20-60 mg once daily. In another embodiment, the Cabozantinib or pharmaceutically acceptable salt thereof is administered at a dose of 20 mg once daily. In another embodiment, the Cabozantinib or pharmaceutically acceptable salt thereof is administered at a dose of 40 mg once daily. In another embodiment, the Cabozantinib or pharmaceutically acceptable salt thereof is administered at a dose of 60 mg once daily. In another embodiment, the Cabozantinib is administered as the (S)-malate. In another embodiment, the Cabozantinib is administered as Cabometyx tablets. In one embodiment, ORR was improved in patients with lung and/or liver metastases as compared to patients without lung and/or liver metastases.

[00118] In another embodiment, the invention relates to use of Cabozantinib or a pharmaceutically acceptable salt thereof in combination with nivolumab to treat urothelial carcinoma or another form of cancer as described herein. In one embodiment, the cabozantinib or pharmaceutically acceptable salt thereof is administered concurrently (at the same time) or sequentially (one after the other) with nivolumab. In one embodiment, the urothelial carcinoma is metastatic urothelial carcinoma. In one embodiment, the urothelial carcinoma is metastatic urothelial carcinoma that is relapsed or refractory. In one embodiment, the Cabozantinib or a pharmaceutically acceptable salt thereof is administered at a dose of 20-60 mg once daily. In another embodiment, the Cabozantinib or pharmaceutically acceptable salt thereof is administered at a dose of 20 mg once daily. In another embodiment, the Cabozantinib or pharmaceutically acceptable salt thereof is administered at a dose of 40 mg once daily. In another embodiment, the Cabozantinib or pharmaceutically acceptable