

SUMMARY

[0005] The aspects and embodiments of the present disclosure provide for methods and pharmaceutical compositions for treating subjects with cancer and neoplastic disease; such as those with advanced solid tumors, relapsed or refractory non-Hodgkin's lymphomas, glioblastoma multiforme, anaplastic astrocytoma, basal cell carcinoma, or other cancers. At least one embodiment provides a method for treating cancer and neoplastic disease comprising administering to a subject in need thereof a therapeutically effective amount of at least one BET inhibitor and a therapeutically effective amount of at least one chemotherapeutic agent. The chemotherapeutic agent may be an alkylating agent, such as temozolomide, or a mitotic inhibitor such as paclitaxel or paclitaxel protein-bound particles. An exemplary BET inhibitor is 4-[2-(cyclopropylmethylamino)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one. According to the method, administration of a BET inhibitor and chemotherapeutic agent may be concurrent or sequential.

[0005a] In one aspect, there is provided a use of a therapeutically effective amount of at least one bromodomain and extra-terminal protein (BET) inhibitor and at least one chemotherapeutic agent, which does not inhibit BET directly in the manufacture of a medicament for treating cancer or neoplastic disease.

[0006] In at least one embodiment, a BET inhibitor and chemotherapeutic agent of the combination therapy may be administered in a single pharmaceutical composition. Some embodiments provide a composition comprising a pharmaceutically effective amount of a BET inhibitor and temozolomide, formulated in a pharmaceutically acceptable carrier. Some embodiments provide a composition comprising a pharmaceutically effective amount of a BET inhibitor and protein-bound paclitaxel, formulated in a pharmaceutically acceptable carrier. In one embodiment, BET inhibitor and chemotherapeutic agent of the combination therapy may exist as separate pharmaceutical compositions administered either concurrently or sequentially. In another embodiment, BET inhibitor and chemotherapeutic agent are independent pharmaceutical compositions that are admixed before administration (i.e., admixed in a pharmaceutically acceptable solution for injection or infusion). In still another embodiment, BET inhibitor and chemotherapeutic agent are disposed as separate pharmaceutical compositions that are packaged together for administration (e.g., a blister-pack containing oral formulations, or packaging comprising an oral dosage form and an injectable dosage form).

[0007] In at least one embodiment, administering the BET inhibitor and the chemotherapeutic agent results in a synergistic inhibition of cell proliferation or increased cell death (e.g., tumor cell death) compared with administration of either the BET inhibitor or the chemotherapeutic agent alone. The chemotherapeutic agent can be an anti-proliferative or pro-apoptotic compound, and can be selected so as to show a synergistic anti-proliferative or pro-apoptotic effect when co-administered with a BET inhibitor. Combinatorial treatment with a BET inhibitor and a chemotherapeutic agent can result in a synergistic anti-cancer effect or can

CLAIMS

We claim:

1. Use of a therapeutically effective amount of at least one bromodomain and extra-terminal protein (BET) inhibitor and at least one chemotherapeutic agent, which does not inhibit BET directly in the manufacture of a medicament for treating cancer or neoplastic disease.

2. The use of claim 1, wherein administration of the BET inhibitor and the chemotherapeutic agent results in a synergistic reduction in cell proliferation in a tumor of the patient or a synergistic increase in apoptosis in a tumor of the patient as compared with administration of either the BET inhibitor or the chemotherapeutic agent alone.

3. The use of claim 1, wherein the therapeutic effective amount for both the BET inhibitor and chemotherapeutic agent when administered together can be at least 50% lower than that when the BET inhibitor and chemotherapeutic agent are used individually.

4. The use of claim 1, wherein the chemotherapeutic agent is selected from the group consisting of temozolomide, romidepsin, and protein-bound paclitaxel.