[0017] The present disclosure relates to 25-hydroxyvitamin D therapy as adjunctive therapy and/or to treat cancer in a patient. In one aspect, the present invention provides a pharmaceutical composition comprising (a) a sustained release formulation of 30 μg to 300 μg 25-hydroxyvitamin D and (b) an agent selected from the group consisting of: cinacalcet, a bisphosphonate, calcitonin, a hormone, a monoclonal antibody, a corticosteroid, denosumab, zoledronic acid, azacitidine, axathioprine, bevacizumab, bleomycin, capecitabine, carboplatin, chlorabucil, cisplatin, cyclophosphamide, cytarabine, daunorubicin, docetaxel, doxifluridine, doxorubicin, epirubicin, etoposide, fluorouracil, gemcitabine, herceptin, idarubicin, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, tafluposide, teniposide, tioguanine, retinoic acid, valrubicin, vinblastine, vincristine, vindesine, vinorelbine, and any combination thereof. In another aspect, the present invention refers to a kit comprising (a) a sustained release formulation of 30 μg to 300 μg 25-hydroxyvitamin D and (b) an agent selected from the group consisting of:cinacalcet, a bisphosphonate, calcitonin, a hormone, a monoclonal antibody, denosumab, zoledronic acid, azacitidine, axathioprine, bevacizumab, bleomycin, capecitabine, carboplatin, chlorabucil, cisplatin, cyclophosphamide, cytarabine, daunorubicin, docetaxel, doxifluridine, doxorubicin, epirubicin, etoposide, fluorouracil, gemcitabine, herceptin, idarubicin, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, tafluposide, teniposide, tioguanine, retinoic acid, valrubicin, vinblastine, vincristine, vindesine, vinorelbine, and any combination thereof. In yet another aspect, the present invention refers to the use of (a) a sustained release formulation of 30 μg to 300 μg 25-hydroxyvitamin D and (b) an agent selected from the group consisting of: cinacalcet, a bisphosphonate, calcitonin, a hormone, a monoclonal antibody, denosumab, zoledronic acid, azacitidine, axathioprine, bevacizumab, bleomycin, capecitabine, carboplatin, chlorabucil, cisplatin, cyclophosphamide, cytarabine, daunorubicin, docetaxel, doxifluridine, doxorubicin, epirubicin, etoposide, fluorouracil, gemcitabine, herceptin, idarubicin, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, tafluposide, teniposide, tioguanine, retinoic acid, valrubicin, vinblastine, vincristine, vindesine, vinorelbine, and any combination thereof, in the manufacture of a medicament for: (A) treating or preventing iatrogenic hypocalcemia and secondary hyperparathyroidism in a patient; (B) increasing bone mineral density in a patient; (C) decreasing the blood level of a bone resorption marker in a patient; (D) treating bone pain in a patient; (E) increasing the time to the first post-treatment skeletal-related event in a

patient; (F) effectively and safely restoring blood 25-hydroxyvitamin D levels to at least 30 ng/mL and to maintain blood 25-hydroxyvitamin D levels at such optimal levels; (G) lowering elevated serum parathyroid hormone levels in a patient having a bone metastasis; (H) stabilizing serum calcium levels in a patient having a bone metastasis; (I) treating hungry bone syndrome; (J) managing iatrogenic hypocalcemia and secondary hyperparathyroidism in a patient with a bone metastasis; (K) inhibiting the proliferation and migration of cancer cells; (L) mitigating the progression of cancer in the bone; (M) treating a patient having cancer and a bone metastasis; (N) treating cancer in a patient; or (O) mitigating cancer progression and/or a skeletal related event in a patient with a bone metastasis from a solid tumor. In one example, a method of treating or preventing iatrogenic hypocalcemia and/or secondary hyperparathyroidism in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D. In another example, a method of increasing bone mineral density in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D.

[0018] In another example, a method of decreasing the blood level of a bone resorption marker in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D. In another example, a method of treating bone pain in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D.

[0019] In another example, a method of increasing the time to the first post-treatment skeletal-related event in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D. In another example, a method of treating a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D to effectively and safely restore blood 25-hydroxyvitamin D levels to at least 30 ng/mL and to maintain blood 25-hydroxyvitamin D levels at such optimal levels.

[0020] In any of the methods disclosed herein, the agent that increases the risk of hypocalcemia is optionally selected from the group consisting of an antiresorptive agent, an anti-convulsant agent, a corticosteroid, an anti-hypercalcemia agent, an antimicrobial agent, and combinations thereof. In one example, the agent that increases the risk of hypocalcemia

is an antiresorptive agent, optionally selected from the group consisting of bisphosphonates (e.g., zoledronic acid, alendronate, risedronate, ibandronate, etidronate, and pamidronate), selective estrogen receptor modulators (e.g., raloxifene), calcitonin, hormones (e.g., estrogen), and monoclonal antibodies (e.g., denosumab).

[0021] In one example, a method of lowering elevated serum parathyroid hormone levels in a patient having a bone metastasis and treated with an antiresorptive agent comprises administering an effective amount of 25-hydroxyvitamin D. In another example, a method of stabilizing serum calcium levels in a patient having a bone metastasis and treated with an antiresorptive agent comprises administering an effective amount of 25-hydroxyvitamin D. In still another example, a method of treating hungry bone syndrome comprises administering an effective amount of 25-hydroxyvitamin D to a patient in need of thereof.

[0022] In any of the methods of the present disclosure, the patient optionally has osteoporosis and/or cancer. In one example, a method of managing iatrogenic hypocalcemia and secondary hyperparathyroidism in a patient with a bone metastasis treated with an antiresorptive agent comprises administering an effective amount of 25-hydroxyvitamin D to prevent or reverse the iatrogenic hypocalcemia and lower the patient's serum parathyroid hormone level. In another example, a method of mitigating cancer progression and/or a skeletal related event in a patient with a bone tumor, optionally a bone metastasis from a solid tumor, comprises treating the patient with (a) an anticancer agent; (b) an antiresorptive agent; and (c) a 25-hydroxyvitamin D compound, wherein the combination of (a), (b), and (c) is effective to slow tumor growth and/or metastasis and/or increase the time to the first post-treatment skeletal-related event. In still another example, a method of treating a patient having cancer and a bone metastasis comprises the administration of (a) a prophylactic and continuing course of an effective amount of 25-hydroxyvitamin D to stabilize 25-hydroxyvitamin D levels and calcium levels in the patient without causing or exacerbating hypercalcemia; followed by (b) treatment with an agent known to increase the risk of iatrogenic hypocalcemia, wherein the treatment in step (a) prevents and/or treats the iatrogenic hypocalcemia in the patient.

[0023] In another example, a method of mitigating the progression of cancer in the bone in a patient comprises administering an effective amount of 25-hydroxyivtamin D. In another aspectexample, a method of inhibiting the proliferation and migration of cancer cells comprises administering an effective amount of 25-hydroxyvitamin D to a patient in need

thereof. In another example, a method of treating cancer in a patient comprises administering to the patient an effective amount of a combination of 25-hydroxyvitamin D and an anticancer agent. In any of the foregoing methods, the patient optionally has a cancer selected from the group consisting of bone cancer, bladder cancer, breast cancer, colon cancer, endometrial cancer, kidney cancer, leukemia, lung cancer, lymphoma, pancreatic cancer, prostate cancer, skin cancer, thyroid cancer, and metastatic forms thereof.

[0024] The present disclosure also relates to the use of 25-hydroxyvitamin D, optionally in a modified release formulation, as adjunctive therapy to treat hypocalcemia in a patient in need thereof. In one example, the disclosure provides a pharmaceutical composition comprising (a) 25-hydroxyvitamin D and (b) an agent that increases the risk of hypocalcemia and/or an anticancer agent. In another aspect, the disclosure provides a kit comprising (a) 25-hydroxyvitamin D; (b) an agent that increases the risk of hypocalcemia and/or an anticancer agent; and (c) instructions for co-administering effective amounts of (a) and (b) to a patient in need thereof.

[0025] In another example, a method according to the present disclosure comprises administering 25-hydroxyvitamin D in a modified release formulation, optionally an oral modified release formulation. In another example, the 25-hydroxyvitamin D is administered in a sterile intravenous formulation. In various examples, the 25-hydroxyvitamin D can be selected from the group consisting of 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, 25-hydroxyvitamin D_4, 25-hydroxyvitamin D_5, 25-hydroxyvitamin D_7 and combinations thereof.

[0026] For the compositions and methods described herein, optional features, including but not limited to components, compositional ranges thereof, substituents, conditions, and steps, are contemplated to be selected from the various aspects, embodiments, and examples provided herein.

[0027] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description, taken in conjunction with the drawings. While the compositions and methods are susceptible of embodiments in various forms, the description hereafter includes specific embodiments with the understanding that the disclosure is illustrative and is not intended to limit the invention to the specific embodiments described herein.

DETAILED DESCRIPTION

What is claimed is:

1. A pharmaceutical composition comprising (a) a sustained release formulation of 30 μg to 300 μg 25-hydroxyvitamin D and (b) an agent selected from the group consisting of: cinacalcet, a bisphosphonate, calcitonin, a hormone, a monoclonal antibody, a corticosteroid, denosumab, zoledronic acid, azacitidine, axathioprine, bevacizumab, bleomycin, capecitabine, carboplatin, chlorabucil, cisplatin, cyclophosphamide, cytarabine, daunorubicin, docetaxel, doxifluridine, doxorubicin, epirubicin, etoposide, fluorouracil, gemcitabine, herceptin, idarubicin, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, tafluposide, teniposide, tioguanine, retinoic acid, valrubicin, vinblastine, vincristine, vindesine, vinorelbine, and any combination thereof.

2. The pharmaceutical composition of claim 1, wherein the 25-hydroxyvitamin D is present in an amount of 30 μg, 60 μg, 90 μg, 120 μg, 150 μg, 180 μg, 210 μg, 240 μg, 270 μg, or 300 μg.

3. The pharmaceutical composition of claim 1 or 2, comprising 25-hydroxyvitamin D in a sustained release capsule or tablet formulation.

4. The pharmaceutical composition of claim 1 or 2, comprising 25-hydroxyvitamin D in a sustained release sterile intravenous formulation.

5. The pharmaceutical composition of any one of claims 1 to 4, wherein the 25-hydroxyvitamin D is selected from the group consisting of 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, 25-hydroxyvitamin D_4, 25-hydroxyvitamin D_5, 25-hydroxyvitamin D_7 and combinations thereof.

6. The pharmaceutical composition of claim 5, wherein the 25-hydroxyvitamin D comprises 25-hydroxyvitamin D_3 and/or 25-hydroxyvitamin D_2.

7. The pharmaceutical composition of claim 5, wherein the 25-hydroxyvitamin D comprises 25-hydroxyvitamin D_3.

8. The pharmaceutical composition of any of claims 1 to 7, comprising zoledronic acid.

9. The pharmaceutical composition of any of claims 1 to 8, comprising denosumab.

10. The pharmaceutical composition of claim 9, comprising denosumab in an amount from 60 mg to 120 mg.

11. The pharmaceutical composition of any one of claims 1 to 10, wherein the sustained release formulation comprises a waxy formulation.

12. The pharmaceutical composition of any one of claims 1 to 11, wherein the sustained release formulation consists essentially of about 20 wt% paraffin, about 20 wt% to about 25 wt% glycerol monostearate, about 10 wt% a mixture of lauroyl macrogolglycerides and lauroyl polyoxylglycerides, about 30 wt% to about 35 wt% mineral oil, and about 10 wt% to about 15 wt% hydroxyl propyl methylcellulose.

13. A kit comprising (a) a sustained release formulation of 30 μg to 300 μg 25-hydroxyvitamin D and (b) an agent selected from the group consisting of:cinacalcet, a bisphosphonate, calcitonin, a hormone, a monoclonal antibody, denosumab, zoledronic acid, azacitidine, axathioprine, bevacizumab, bleomycin, capecitabine, carboplatin, chlorabucil, cisplatin, cyclophosphamide, cytarabine, daunorubicin, docetaxel, doxifluridine, doxorubicin, epirubicin, etoposide, fluorouracil, gemcitabine, herceptin, idarubicin, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, tafluposide, teniposide, tioguanine, retinoic acid, valrubicin, vinblastine, vincristine, vindesine, vinorelbine, and any combination thereof.

14. The kit of claim 13, wherein the 25-hydroxyvitamin D_3 is present in an amount of 30 μg, 60 μg, 90 μg, 120 μg, 150 μg, 180 μg, 210 μg, 240 μg, 270 μg, or 300 μg.

15. The kit of claim 13 or 14, comprising 25-hydroxyvitamin D in a sustained release capsule or tablet formulation.

16. The kit of claim 13 or 14, comprising 25-hydroxyvitamin D in a sustained release sterile intravenous formulation.

17. The kit of any one of claims 13 to 16, wherein the 25-hydroxyvitamin D is selected from the group consisting of 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, 25-

hydroxyvitamin D_4, 25-hydroxyvitamin D_5, 25-hydroxyvitamin D_7 and combinations thereof.

18. The kit of claim 17, wherein the 25-hydroxyvitamin D comprises 25-hydroxyvitamin D_3 and/or 25-hydroxyvitamin D_2.

19. The kit of claim 17, wherein the 25-hydroxyvitamin D comprises 25-hydroxyvitamin D_3.

20. The kit of any of claims 13 to 19, comprising zoledronic acid.

21. The kit of any of claims 13 to 20, comprising denosumab.

22. The kit of claim 21, comprising denosumab in an amount from 60 mg to 120 mg.

23. The kit of any one of claims 13 to 22, wherein the sustained release formulation comprises a waxy formulation.

24. The kit of any one of claims 13 to 23, wherein the sustained release formulation consists essentially of about 20 wt% paraffin, about 20 wt% to about 25 wt% glycerol monostearate, about 10 wt% a mixture of lauroyl macrogolglycerides and lauroyl polyoxylglycerides, about 30 wt% to about 35 wt% mineral oil, and about 10 wt% to about 15 wt% hydroxyl propyl methylcellulose.

25. Use of (a) a sustained release formulation of 30 μg to 300 μg 25-hydroxyvitamin D and (b) an agent selected from the group consisting of: cinacalcet, a bisphosphonate, calcitonin, a hormone, a monoclonal antibody, denosumab, zoledronic acid, azacitidine, axathioprine, bevacizumab, bleomycin, capecitabine, carboplatin, chlorabucil, cisplatin, cyclophosphamide, cytarabine, daunorubicin, docetaxel, doxifluridine, doxorubicin, epirubicin, etoposide, fluorouracil, gemcitabine, herceptin, idarubicin, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, tafluposide, teniposide, tioguanine, retinoic acid, valrubicin, vinblastine, vincristine, vindesine, vinorelbine, and any combination thereof, in the manufacture of a medicament for: (A) treating or preventing iatrogenic hypocalcemia and secondary hyperparathyroidism in a patient; (B) increasing bone mineral density in a patient; (C)

decreasing the blood level of a bone resorption marker in a patient; (D) treating bone pain in a patient; (E) increasing the time to the first post-treatment skeletal-related event in a patient; (F) effectively and safely restoring blood 25-hydroxyvitamin D levels to at least 30 ng/mL and to maintain blood 25-hydroxyvitamin D levels at such optimal levels; (G) lowering elevated serum parathyroid hormone levels in a patient having a bone metastasis; (H) stabilizing serum calcium levels in a patient having a bone metastasis; (I) treating hungry bone syndrome; (J) managing iatrogenic hypocalcemia and secondary hyperparathyroidism in a patient with a bone metastasis; (K) inhibiting the proliferation and migration of cancer cells; (L) mitigating the progression of cancer in the bone; (M) treating a patient having cancer and a bone metastasis; (N) treating cancer in a patient; or (O) mitigating cancer progression and/or a skeletal related event in a patient with a bone metastasis from a solid tumor.

26. The use of claim 25, wherein the 25-hydroxyvitamin D_3 is present in an amount of 30 μg, 60 μg, 90 μg, 120 μg, 150 μg, 180 μg, 210 μg, 240 μg, 270 μg, or 300 μg.

27. The use of claim 25 or 26, comprising 25-hydroxyvitamin D in a sustained release capsule or tablet formulation.

28. The use of claim 25 or 26, comprising 25-hydroxyvitamin D in a sustained release sterile intravenous formulation.

29. The use of any one of claims 25 to 28, wherein the 25-hydroxyvitamin D is selected from the group consisting of 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, 25-hydroxyvitamin D_4, 25-hydroxyvitamin D_5, 25-hydroxyvitamin D_7 and combinations thereof.

30. The use of claim 29, wherein the 25-hydroxyvitamin D comprises 25-hydroxyvitamin D_3 and/or 25-hydroxyvitamin D_2.

31. The use of claim 29, wherein the 25-hydroxyvitamin D comprises 25-hydroxyvitamin D_3.

32. The use of any of claims 25 to 31, comprising zoledronic acid.

33. The use of any of claims 25 to 32, comprising denosumab.

34. The kit of claim 33, comprising denosumab in an amount from 60 mg to 120 mg.

35. The use of any one of claims 25 to 34, wherein the sustained release formulation comprises a waxy formulation.

36. The use of any one of claims 25 to 35, wherein the sustained release formulation consists essentially of about 20 wt% paraffin, about 20 wt% to about 25 wt% glycerol monostearate, about 10 wt% a mixture of lauroyl macrogolglycerides and lauroyl polyoxylglycerides, about 30 wt% to about 35 wt% mineral oil, and about 10 wt% to about 15 wt% hydroxyl propyl methylcellulose.

37. The use of any one of claims 25 to 36, wherein the patient is receiving or has previously received treatment with an agent that increases the risk of hypocalcemia.

38. The use of any one of claims 25 to 37, wherein the agent selected from the group is cinacalcet.

39. The use of any one of claims 25 to 38, wherein the patient has osteoporosis or cancer.

40. The use of claim 39, wherein the cancer is selected from the group consisting of bone cancer, bladder cancer, breast cancer, colon cancer, endometrial cancer, kidney cancer, leukemia, lung cancer, lymphoma, pancreatic cancer, prostate cancer, skin cancer, thyroid cancer, and metastatic forms thereof.

41. The use of any one of claims 25 to 40, wherein the patient has a metastatic bone cancer, metastatic prostate cancer, metastatic lung cancer, and/or metastatic breast cancer.

42. The use of any one of claims 25 to 41, wherein the patient has a bone tumor, optionally a bone metastasis from a solid tumor.

43. The use of any one of claims 25 to 42, wherein the patient has impaired renal function, optionally associated with Chronic Kidney Disease Stage 1, 2, 3, 4, or 5.

44. The use of any one of claims 25 to 43, wherein the sustained release formulation comprises 25-hydroxyvitamin D in an amount effective (A) to restore or maintain the patient's serum calcium level to at least about 8.0 mg/dL, optionally in a range of about 8.3 mg/dL to about 11.6 mg/dL; (B) to safely increase the patient's serum level of 25-hydroxyvitamin D to at least 30 ng/mL, optionally in a range of about 30 ng/mL to about 100 ng/mL; (C) to decrease the patient's serum parathyroid hormone level, optionally by 30% or more; (D) to decrease the patient's serum parathyroid hormone related peptide levels; (E) to safely increase the patient's serum level of 1,25-dihydroxyvitamin D to above the normal range, optionally at least to 50 pg/mL; (F) to achieve or maintain safe serum phosphorus levels and treat or prevent hypophosphatemia; (G) to have a positive effect on the patient's serum level of a marker of bone formation by more than what is accomplished with treatment with the antiresorptive agent alone; (H) to decrease the patient's serum level of a marker of bone resorption, optionally by at least 20%; (I) to maintain or decrease the patient's tumor burden; (J) to maintain or decrease the patient's serum level of a marker of tumor burden; (K) to inhibit the proliferation and/or migration of cancer cells.

45. The use of claim 44, option (H), wherein the marker of bone resorption is selected from the group consisting of PTHrP, FGF23, NTX, CTX, TRAC-5b, and combinations thereof.

46. The use of claim 44, option (J), wherein the marker of tumor burden is selected from the group consisting of CEA, CA 125, CA15-3, CA 27-29, prostate specific antigen (PSA), and combinations thereof.