

CLAIMS

1. A dosing regimen for treatment of a BK or JC polyomavirus infection in a human subject in need thereof, comprising
 - (a) parenterally administering to the subject a dosage of an antibody, or an antigen-binding fragment thereof, which specifically binds to a VP1 protein of the polyomavirus;
 - (b) measuring serum or tissue concentration of the antibody, or antigen-binding fragment thereof, in the subject; and
 - (c) administering a further dosage of the antibody, or antigen-binding fragment thereof, before the serum or tissue trough concentration (C_{trough}) falls below about 3-860 $\mu\text{g/mL}$;
wherein the dosing regimen maintains the serum or tissue concentration of the antibody, or antigen-binding fragment thereof, above the C_{trough} throughout the treatment.
2. The dosing regimen of claim 1, wherein:
 - (i) the C_{trough} in (c) is for plasma, and the dosing regimen comprises administering the further dosage before the plasma C_{trough} falls below about 150-860 $\mu\text{g/mL}$;
 - (ii) the C_{trough} in (c) is for renal tissue, and the dosing regimen comprises administering the further dosage before the C_{trough} in renal tissue falls below about 23.5-120 $\mu\text{g/mL}$; or
 - (iii) the C_{trough} in (c) is for bladder tissue, and the dosing regimen comprises administering the further dosage before the C_{trough} in bladder tissue falls below about 3-10 $\mu\text{g/mL}$.
3. The dosing regimen of claim 1 or 2, wherein the antibody, or antigen-binding fragment thereof, comprises
 - a heavy chain variable (V_H) region that comprises complementary determining region (CDR) $V_H\text{CDR1}$, $V_H\text{CDR2}$, and $V_H\text{CDR3}$ sequences of SEQ ID NOs: 6-8, respectively; and
 - a light chain variable (V_L) region that comprises $V_L\text{CDR1}$, $V_L\text{CDR2}$, and $V_L\text{CDR3}$ sequences of SEQ ID NOs: 9-11, respectively,and variants thereof which specifically bind to the VP1 protein.
4. The dosing regimen of claim 3, wherein
 - the V_H region comprises a sequence at least 80, 85, 90, 95, 97, 98, 99, or 100% identical to SEQ ID NO: 12, optionally wherein the V_H sequence has 1, 2, 3, 4, 5, or 6 alterations in the framework regions, optionally selected from one or more of V5Q, G9P, T10G, N30S, N30K, and N30Q; and
 - the V_L region comprises sequence at least 80, 85, 90, 95, 97, 98, 99, or 100% identical to SEQ ID NO: 13, optionally wherein the V_L sequence has 1, 2, 3, 4, 5, or 6 alterations in the framework regions.

5. The dosing regimen of claim 2 or 3, wherein the V_H region comprises, consists, or consists essentially of SEQ ID NO: 12 and the V_L region comprises, consists, or consists essentially of SEQ ID NO: 13.

6. The dosing regimen of any one of claims 1-5, wherein the dosing regimen comprises identifying the BK virus genotype or the JC virus in subject.

7. The dosing regimen of any one of claims 1-6, wherein the polyomavirus infection comprises a BK virus selected from one or more of genotype I, II, III, and IV, or wherein the polyomavirus infection comprises a JC virus.

8. The dosing regimen of any one of claims 1-7, wherein the subject is immuno-compromised.

9. The dosing regimen of any one of claims 1-8, wherein the subject is about to undergo, is undergoing, or has undergone a transplant procedure, optionally an organ transplant or cell-based transplant procedure.

10. The dosing regimen of claim 9, wherein the transplant procedure is selected from a kidney transplant and a hematopoietic cell transplant (HCT).

11. The dosing regimen of any one of claims 1-10, wherein the subject has or is at risk for having a condition selected from BK virus-associated nephropathy, BK virus-associated hemorrhagic cystitis, and JC virus-associated progressive multifocal leukoencephalopathy.

12. The dosing regimen of any one of claims 1-11, wherein the dosage in (a) is about 1 to about 100 mg/kg, or about 10-30 mg/kg, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, or 100 mg/kg, optionally wherein the dosage is administered intravenously or subcutaneously.

13. The dosing regimen of any one of claims 1-12, wherein the further dosage in (c) is the same as or different than the dosage in (a), optionally about 1 to about 100 mg/kg, or about 10-30 mg/kg, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, or 100 mg/kg, optionally wherein the dosage is administered intravenously or subcutaneously.

14. The dosing regimen of any one of claims 1-13, wherein the polyomavirus infection comprises a BK virus genotype I and wherein:

the tissue concentration, optionally renal tissue concentration, at the C_{trough} ranges from about 2618 to about 3775 to about 13,061-fold above the EC_{50} of the antibody, or antigen-binding fragment thereof; or

the tissue concentration, optionally bladder tissue concentration, at the C_{trough} ranges from about 500 to about 692 to about 1000-fold above the EC_{50} of the antibody, or antigen-binding fragment thereof,

wherein the EC_{50} is about 0.009 ± 0.010 $\mu\text{g/mL}$.

15. The dosing regimen of any one of claims 1-13, wherein the polyomavirus infection comprises a BK virus genotype II and wherein:

the tissue concentration, optionally renal tissue concentration, at C_{trough} ranges from about 589 to about 849 to about 2942-fold (for example, about 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000-fold) above the EC_{50} of the antibody, or antigen-binding fragment thereof; or

the tissue concentration, optionally bladder tissue concentration, at C_{trough} ranges from about 100 to about 156 to about 200-fold above the EC_{50} of the antibody, or antigen-binding fragment thereof,

wherein the EC_{50} is about 0.040 ± 0.025 $\mu\text{g/mL}$.

16. The dosing regimen of any one of claims 1-13, wherein the polyomavirus infection comprises a BK virus genotype III and wherein:

the tissue concentration, optionally renal tissue concentration, at the C_{trough} ranges from about 253 to about 365 to about 1265-fold above the EC_{50} of the antibody, or antigen-binding fragment thereof; or

the tissue concentration, optionally bladder tissue concentration, at the C_{trough} ranges from about 50 to about 67 to about 100-fold (for example, about 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100-fold) above the EC_{50} of the antibody, or antigen-binding fragment thereof,

wherein the EC_{50} is about 0.093 ± 0.057 $\mu\text{g/mL}$.

17. The dosing regimen of any one of claims 1-13, wherein the polyomavirus infection comprises a BK virus genotype IV and wherein:

the tissue concentration, optionally renal tissue concentration, at the C_{trough} ranges from about 1122 to about 1618 to about 5604-fold above the EC_{50} of the antibody, or antigen-binding fragment thereof; or

the tissue concentration, optionally bladder tissue concentration, at the C_{trough} ranges from about 100 to about 297 to about 500-fold above the EC_{50} of the antibody, or antigen-binding fragment thereof,

wherein the EC_{50} is about 0.021 ± 0.020 $\mu\text{g/mL}$.

18. The dosing regimen of any one of claims 1-13, wherein the polyomavirus infection comprises a JC virus and the tissue concentration at the C_{trough} is at least about 29 to about 110 to about 158 to about 547-fold above the EC_{50} of the antibody, or antigen-binding fragment thereof, wherein the EC_{50} is about $0.215 \pm 0.130 \mu\text{g/mL}$.

19. The dosing regimen of any one of claims 1-18, wherein time between (a) and (b) is about, at least about, or no more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days, or 1, 2, 3, 4, 5, 6, 7, or 8 weeks, or 1, 2, or 3 months.

20. The dosing regimen of any one of claims 1-19, comprising (b) measuring the serum or tissue levels in the subject about once every 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days, or about 1-3 times every 1, 2, 3, 4, 5, 6, 7, or 8 weeks, or about 1-6 times every 1, 2, or 3 months.

21. The dosing regimen of any one of claims 1-20, wherein the time between (a) and (c) is about, at least about, or no more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days, or 1, 2, 3, 4, 5, 6, 7, or 8 weeks, or 1, 2, or 3 months.

22. The dosing regimen of any one of claims 1-21, wherein at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% or more of the serum, circulating concentration of the antibody, or antigen-binding fragment thereof, penetrates an infected organ.

23. The dosing regimen of claim 22, wherein the infected organ is a bladder or a kidney or the central nervous system (CNS).

24. The dosing regimen of any one of claims 1-23, wherein the mean clearance of the antibody, or antigen binding fragment thereof, is about 0.0760-0.0996 mL/day/kg.

25. The dosing regimen of any one of claims 1-24, wherein the mean volume of distribution of the antibody, or antigen binding fragment thereof, is about 49.8-81.9 mL/kg.

26. A method for treating a BK or JC polyomavirus infection in a human subject in need thereof, comprising parenterally administering to the subject a dosage of an antibody, or an antigen-binding fragment thereof, which specifically binds to a VP1 protein of the polyomavirus, wherein the

dosage is about 10-30 mg/kg, or about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mg/kg.

27. The method of claim 26, wherein the antibody, or antigen-binding fragment thereof, comprises

a heavy chain variable (V_H) that comprises complementary determining region (CDR) V_H CDR1, V_H CDR2, and V_H CDR3 sequences of SEQ ID NOs: 6-8, respectively; and

a light chain variable (V_L) region that comprises V_L CDR1, V_L CDR2, and V_L CDR3 sequences of SEQ ID NOs: 9-11, respectively,

and variants thereof which specifically bind to the VP1 protein.

28. The method of claim 27, wherein

the V_H region comprises a sequence at least 80, 85, 90, 95, 97, 98, 99, or 100% identical to SEQ ID NO: 12, optionally wherein the V_H sequence has 1, 2, 3, 4, 5, or 6 alterations in the framework regions, optionally selected from one or more of V5Q, G9P, T10G, N30S, N30K, and N30Q; and

the V_L region comprises sequence at least 80, 85, 90, 95, 97, 98, 99, or 100% identical to SEQ ID NO: 13, optionally wherein the V_L sequence has 1, 2, 3, 4, 5, or 6 alterations in the framework regions.

29. The method of claim 27 or 28, wherein the V_H region comprises, consists, or consists essentially of SEQ ID NO: 12 and the V_L region comprises, consists, or consists essentially of SEQ ID NO: 13.

30. The method of any one of claims 26-29, wherein the polyomavirus infection comprises a BK virus selected from one or more of genotype I, II, III, and IV.

31. The method of any one of claims 26-30, wherein the polyomavirus infection comprises a JC virus.

32. The method of any one of claims 26-31, wherein the subject is immuno-compromised.

33. The method of any one of claims 26-32, wherein the subject is about to undergo, is undergoing, or has undergone a transplant procedure, optionally an organ transplant or cell-based transplant procedure.

34. The method of claim 33, wherein the transplant procedure is selected from a kidney transplant and a hematopoietic cell transplant (HCT).

35. The method of any one of claims 26-34, wherein the subject has or is at risk for having a condition selected from BK virus-associated nephropathy, BK virus-associated hemorrhagic cystitis, and JC virus-associated progressive multifocal leukoencephalopathy.

36. The method of any one of claims 26-35, wherein at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% or more of the serum, circulating concentration of the antibody, or antigen-binding fragment thereof, penetrates an infected organ.

37. The method of claim 36, wherein the infected organ is a bladder or a kidney.

38. The method of any one of claims 26-37, wherein the mean clearance of the antibody, or antigen binding fragment thereof, is about 0.0760-0.0996 mL/day/kg.

39. The method of any one of claims 26-38, wherein the mean volume of distribution of the antibody, or antigen binding fragment thereof, is about 49.8-81.9 mL/kg.

40. The dosing regimen or method of any one of claims 1-39, wherein the 10-30 mg/kg dosage provides optimal neutralizing activity (IC_{50}) by the subject's serum against the BK or JC polyomavirus, as measured in an *in vitro* or *ex vivo* viral assay.

41. The dosing regimen or method of any one of claims 1-40, which reduces BK or JC viremia and/or viruria in the subject, optionally by about or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 300%, 400%, 500%, 1000%, 2000%, 3000%, 4000%, or 5000% or more, relative to a control or prior to treatment with the antibody, or antigen-binding fragment thereof.

42. The dosing regimen or method of any one of claims 1-41, which reduces or improves one or more BK or JC virus-related symptoms in the subject, optionally one or more symptoms selected from blurred vision or other vision changes, brown or red urine, pain while urinating, reduced kidney function, difficulty urinating, cough, colds, trouble breathing, fever, muscle pain, muscle weakness, and/or seizures, optionally narrowed ureters, or kidney inflammation such as interstitial nephritis.

43. The dosing regimen or method of any one of claims 1-42, comprising administering the antibody, or antigen-binding fragment thereof, in a pharmaceutical composition that comprises histidine, a saccharide optionally sucrose, and a polyol optionally a polysorbate.

44. A pharmaceutical composition, comprising:
an antibody, or antigen-binding fragment thereof, which is formulated for parenteral administration at a dosage of about 10-30 mg/kg, and which comprises a heavy chain variable (V_H) that comprises complementary determining region (CDR) V_H CDR1, V_H CDR2, and V_H CDR3 sequences of SEQ ID NOs: 6-8, respectively, and a light chain variable (V_L) region that comprises V_L CDR1, V_L CDR2, and V_L CDR3 sequences of SEQ ID NOs: 9-11, respectively; and
a pharmaceutically-acceptable carrier that comprises histidine, a saccharide optionally sucrose, and a polyol optionally a polysorbate.

45. The pharmaceutical composition of claim 44, wherein the V_H region comprises a sequence at least 80, 85, 90, 95, 97, 98, 99, or 100% identical to SEQ ID NO: 12, optionally wherein the V_H sequence has 1, 2, 3, 4, 5, or 6 alterations in the framework regions, optionally selected from one or more of V5Q, G9P, T10G, N30S, N30K, and N30Q; and
the V_L region comprises sequence at least 80, 85, 90, 95, 97, 98, 99, or 100% identical to SEQ ID NO: 13, optionally wherein the V_L sequence has 1, 2, 3, 4, 5, or 6 alterations in the framework regions.

46. The pharmaceutical composition of claim 44 or 45, wherein the antibody, or antigen-binding fragment thereof, is formulated for parenteral administration at a dosage of about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mg/kg.

47. The pharmaceutical composition of any one of claims 44-46, which is formulated for intravenous administration.

48. The pharmaceutical composition of any one of claims 44-46, which is formulated for subcutaneous administration.

49. The pharmaceutical composition of any one of claims 44-48, for use in treating a BK or JC polyomavirus infection in a human subject in need thereof.

50. The pharmaceutical composition for use according to claim 49, wherein the polyomavirus infection comprises a BK virus selected from one or more of genotype I, II, III, and IV.

51. The pharmaceutical composition for use according to claim 49 or 50, wherein the polyomavirus infection comprises a JC virus.

52. The pharmaceutical composition for use according to any one of claims 49-51, wherein the subject is immuno-compromised.

53. The pharmaceutical composition for use according to any one of claims 49-52, wherein the subject is about to undergo, is undergoing, or has undergone a transplant procedure, optionally an organ transplant or cell-based transplant procedure.

54. The pharmaceutical composition for use according to claim 53, wherein the transplant procedure is selected from a kidney transplant and a hematopoietic cell transplant (HCT).

55. The pharmaceutical composition for use according to any one of claims 49-54, wherein the subject has or is at risk for having a condition selected from BK virus-associated nephropathy, BK virus-associated hemorrhagic cystitis, and JC virus-associated progressive multifocal leukoencephalopathy.