CLAIMS

1. A method of increasing complement-dependent cytotoxicity (CDC) of a parent polypeptide comprising an Fc domain of an immunoglobulin and a binding region, which method comprises introducing a mutation to the parent polypeptide in one or more amino acid residue(s) selected from the group corresponding to E430X, E345X, and S440W in the Fc region of a human IgG1 heavy chain.

2. The method according to claim 1, wherein the mutation in one or more amino acid residue(s) is selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, and S440W in the Fc region of a human IgG1 heavy chain or
from the group corresponding to E430G, E430S, E345K, and E345Q in the Fc region of a human IgG1 heavy chain.

3. A method of increasing CDC and antibody dependent cell-mediated cytotoxicity (ADCC) of a parent polypeptide comprising an Fc domain of an immunoglobulin and a binding region, which method comprises introducing a mutation to the parent polypeptide in one or more amino acid residue(s) corresponding to E430X, E345X, and S440W in the Fc region of a human IgG1 heavy chain.

4. The method according to claim 3, wherein the mutation in one or more amino acid residue(s) corresponding to E345R, E430T, and E430F in the Fc region of a human IgG1 heavy chain.

5. The method according to any one of claims 1 to 4, wherein the parent polypeptide is a parent antibody comprising an Fc domain of an immunoglobulin and an antigen-binding region.

6. A method of increasing complement-dependent cytotoxicity (CDC) of a parent antibody which is a bispecific antibody comprising a first polypeptide comprising a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and a second polypeptide comprising a second CH2-CH3 region of an immunoglobulin and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same antigen or on different antigens, and wherein the method comprises introducing a mutation to the first and/or second CH2-CH3 region in one or more amino acid residue(s) selected from the group corresponding to E430X,

E345X, S440Y and S440W in the Fc region of a human IgG1 heavy chain; and wherein the first CH2-CH3 region comprises a further amino acid mutation at a position selected from those corresponding to K409, T366, L368, K370, D399, F405, and Y407 in the Fc region of a human IgG1 heavy chain; and wherein the second CH2-CH3 region comprises a further amino acid mutation at a position selected from those corresponding to F405, T366, L368, K370, D399, Y407, and K409 in the Fc region of a human IgG1 heavy chain, and wherein the further amino acid mutation in the first CH2-CH3 region is different from the further amino acid mutation in the second CH2-CH3 region.

7. The method according to claim 6, wherein the mutation in one or more amino acid residue(s) is selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, S440Y, and S440W in the Fc region of a human IgG1 heavy chain.

8. The method according to any one of claims 6 or 7, wherein the method comprises introducing a mutation in both the first and second polypeptide of the bispecific antibody.

9. The method according to any one of claims 6 to 8, wherein the further amino acid mutation of the first CH2-CH3 region is at the position corresponding to K409, such as K409R, in the Fc region of a human IgG1 heavy chain; and wherein the further amino acid mutation of the second CH2-CH3 region is at the position corresponding to F405, such as F405L, in the Fc region of a human IgG1 heavy chain.

10. The method according to any one of claims 1 to 9, said method comprises introducing the mutation in one of more positions other than S440Y and S440W, and further introducing a mutation
(i) in each of the amino acid residues corresponding to K439 and S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W,
(ii) in each of the amino acid residues corresponding to K447 and 448 in the Fc region of a human IgG1 heavy chain, such as K447K/R/H and 448E/D in the Fc region of a human IgG1 heavy chain, preferably K447K and 448E in the Fc region of a human IgG1 heavy chain, or
(iii) in each of the amino acid residues corresponding to K447, 448 and 449 in the Fc region of a human IgG1 heavy chain, such as K447D/E, 448K/R/H and 449P in the Fc

region of a human IgG1 heavy chain, preferably K447E, 448K and 449P in the Fc region of a human IgG1 heavy chain.

11. The method according to claim 10, wherein the method comprises introducing the mutation in one of more positions other than S440Y and S440W, and further introducing a mutation in each of the amino acid residues corresponding to K439 and/or S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation in in S440 is not S440Y or S440W.

12. The method according to claim 11, wherein the mutation in the position corresponding to K439 in the Fc region of a human IgG1 heavy chain is K439D/E, and/or the mutation in the position corresponding to S440 in the Fc region of a human IgG1 heavy chain is S440K/R.

13. A method of increasing complement-dependent cytotoxicity (CDC) of a combination of at least a first and a second parent polypeptide, wherein the at least first and second parent polypeptide each comprises an Fc domain of an immunoglobulin and a binding region, wherein the method comprises
introducing to the at least first and/or second parent polypeptide a mutation in one or more amino acid residue(s) selected from the group corresponding to E430X, E345X, S440Y, and S440W in the Fc region of a human IgG1 heavy chain.

14. The method according to claim 13, wherein the method comprises introducing to the at least first and/or second parent polypeptide a mutation in one or more amino acid residues selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, S440Y, and S440W in the Fc region of a human IgG1 heavy chain.

15. The method according to claim 14, wherein the method comprises introducing a mutation which may be the same or different to both the first and second parent polypeptide.

16. The method according to claim 14, wherein the method comprises
(i) introducing a mutation to the first parent polypeptide in one or more amino acid residues selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, S440Y, and S440W in the Fc region of a human IgG1 heavy chain,
(ii) providing the second parent polypeptide which does not comprise a mutation in one

or more amino acid residues selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, S440Y, and S440W in the Fc region of a human IgG1 heavy chain.

17. The method according to any one of claims 13 to 16, wherein the mutation in one or more positions is another than S440Y and S440W, and wherein the method further comprises the steps of
(i) introducing to the first parent polypeptide a second mutation in the amino acid residue corresponding to position K439 in the Fc region of a human IgG1 heavy chain; and
(ii) introducing to the second parent polypeptide a second mutation in the amino acid residue corresponding to S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation is not S440Y or S440W; wherein steps (i) and (ii) may alternatively be
(iii) introducing the for the first parent polypeptide a second mutation in the amino acid residue corresponding to position S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation is not S440Y or S440W;
(iv) introducing to the second parent polypeptide a second mutation in the amino acid residue corresponding to position K439 in the Fc region of a human IgG1 heavy chain.

18. The method according to claim 17, wherein the mutation in the position corresponding to K439 in the Fc region of a human IgG1 heavy chain is K439D/E, and/or the mutation in the position corresponding to S440 in the Fc region of a human IgG1 heavy chain is S440K/R.

19. The method according to any one of claims 13 to 18, wherein the first and second parent polypeptide is a first and second parent antibody each comprising an Fc domain of an immunoglobulin and an antigen-binding region.

20. The method according to claim 19, wherein the first and/or second parent antibody is a bispecific antibody which comprises a first polypeptide comprising a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and a second polypeptide comprising a second CH2-CH3 region and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same antigen or on different antigens, and wherein said first CH2-CH3 region comprises a further amino acid mutation at a position selected from those corresponding to K409, T366, L368, K370, D399, F405, and Y407 in the Fc region of a human IgG1 heavy chain; and wherein the second CH2-CH3 region comprises a further

amino acid mutation at a position selected from those corresponding to F405, T366, L368, K370, D399, Y407, and K409 in the Fc region of a human IgG1 heavy chain, and wherein the further amino acid mutation in the first CH2-CH3 region is different from the further amino acid mutation in the second CH2-CH3 region.

21. The method according to claim 20, wherein the first CH2-CH3 region comprises a further amino acid mutation at the position corresponding to K409, such as K409R, in the Fc region of a human IgG1 heavy chain; and wherein the second CH2-CH3 region comprises a further amino acid mutation at the position corresponding to F405, such as F405L, in the Fc region of a human IgG1 heavy chain.

22. The method according to any one of claims 1 to 2 and 5 to 21, wherein the method does not alter antibody dependent cell-mediated cytotoxicity (ADCC) of the parent polypeptide or parent antibody.

23. The method according to any one of claims 1 to 22, wherein
a) the method does not alter binding of the parent polypeptide or parent antibody to neonatal Fc receptor (FcRn) as determined by the method disclosed in Example 34 and/or
b) the method does not increase or decrease binding of the parent polypeptide or parent antibody to neonatal Fc receptor (FcRn) by more than 30%, such as of more than 20%, 10% or 5% as measured by a change in the absorbance at OD405 nm as determined by the method disclosed in Example 34 and/or
c) the method does not increase the apparent affinity of the parent polypeptide or parent antibody to mouse neonatal Fc receptor (FcRn) by more than a factor 0.5 or does not decrease the apparent affinity of the parent polypeptide or parent antibody to mouse FcRn by more than a factor 2 as determined by the method disclosed in Example 34 and/or
d) the method does not alter the plasma clearance rate of the parent polypeptide or parent antibody as determined by the method disclosed in Example 37 and/or
e) the method does not increase or decrease the plasma clearance rate of the parent polypeptide or parent antibody by more than a factor 3.0, such as by more than a factor 2.5, factor 2.0, factor 1.5 or factor 1.2 as determined by the method disclosed in Example 37 and/or
f) the method does not alter target independent fluid phase complement activation of the variant as determined by the method as determined by the method disclosed in Example 36 and/or

g) the method does not alter the plasma half-life of the parent polypeptide or parent antibody.

24. A variant of a parent polypeptide comprising an Fc domain of an immunoglobulin and a binding region, wherein the variant comprises one or more mutation(s) selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, and S440W in the Fc region of a human IgG1 heavy chain and provided that the variant does not contain any further mutations in the Fc domain which alter the binding of the variant to neonatal Fc receptor (FcRn).

25. A variant of a parent polypeptide comprising an Fc domain of an immunoglobulin and a binding region, wherein the variant comprises one or more mutation(s) selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, and S440W in the Fc region of a human IgG1 heavy chain and provided that the variant does not contain any further mutations in the Fc domain which increase or decrease the binding of the variant to neonatal Fc receptor (FcRn) by more than 30%, such as of more than 20%, 10% or 5% as measured by a change in the absorbance at OD405 nm as determined by the method disclosed in Example 34.

26. The variant according to any one of claims 24 or 25, wherein the one or more mutation(s) is selected from the group corresponding to E430G, E430S, E345K, and E345Q in the Fc region of a human IgG1 heavy chain.

27. The variant according to any of claims 24 to 26, wherein
a) the variant does not contain any further mutations in the Fc domain which alter antibody dependent cell-mediated cytotoxicity (ADCC) of the variant and/or
b) the variant does not contain any further mutations in the Fc domain which alter the plasma clearance rate of the variant as determined by the method disclosed in Example 37 and/or
c) the variant does not contain any further mutations in the Fc domain which increase or decrease the plasma clearance rate of the variant by more than a factor 3.0, such as by by more than a factor 2.5, factor 2.0, factor 1.5 or factor 1.2 as determined by the method disclosed in Example 37 and/or
d) the variant does not contain any further mutations in the Fc domain which alter the serum half-life of the variant and/or
e) the variant does not contain any further mutations in the Fc domain which alter target independent fluid phase complement activation of the variant as determined by the method disclosed in Example 36 and/or

f) the variant does not contain any further mutations in the Fc domain.
g) the variant comprises only one mutation.

28. The variant according to any of claims 24 to 27, wherein the variant comprises a combination of two mutations in the amino acid residues selected from the group corresponding to E345X/E430X, E345X/S440Y, E345X/S440W, E430X/S440Y, and E430X/S440W in the Fc region of a human IgG1 heavy chain.

29. A variant of a parent polypeptide comprising an Fc domain of an immunoglobulin and a binding region, wherein the variant comprises a first mutation selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, S440Y, and S440W in the Fc region of a human IgG1 heavy chain; and a second mutation selected from the group corresponding to
(i) an amino acid residue corresponding to K439 and S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W, and if the first mutation is S440Y or S440W the second mutation is in the amino acid residue corresponding to K439 in the Fc region of a human IgG1 heavy chain,
(ii) an amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448P in the Fc region of a human IgG1 heavy chain; or
(iii) an amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448K/R/H and 449P in the Fc region of a human IgG1 heavy chain.

30. The variant according to claim 29, wherein the variant comprises a first mutation selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, and E345Y in the Fc region of a human IgG1 heavy chain, and a second mutation in an amino acid residue corresponding to K439 and S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y and S440W.

31. The variant according to claim 30, wherein the mutation in the amino acid residue corresponding to K439 is K439D/E and the amino acid residue corresponding to S440 is S440K/R.

32. The variant according to any one of claims 24 to 31, wherein the parent polypeptide is a parent antibody comprising an Fc domain of an immunoglobulin and an antigen-binding region.

33. A variant of a parent antibody which is a bispecific antibody comprising a first polypeptide comprising a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and a second polypeptide comprising a second CH2-CH3 region of an immunoglobulin and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same or on different antigens, and wherein the first and/or second CH2-CH3 regions comprise one or more mutation(s) selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, S440Y, and S440W in the Fc region of a human IgG1 heavy chain, and wherein
the first polypeptide comprises a further mutation in an amino acid residue selected from those corresponding to K409, T366, L368, K370, D399, F405, and Y407 in the Fc region of a human IgG1 heavy chain; and
the second polypeptide comprises a further mutation in an amino acid residue selected from those corresponding to F405, T366, L368, K370, D399, Y407 and K409 in the Fc region of a human IgG1 heavy chain, and wherein the further mutation in the first polypeptide is different from the further mutation in the second polypeptide.

34. The variant according to claim 33, wherein
(i) the first polypeptide comprises a further mutation in the amino acid residue corresponding to K409, such as K409R, in the Fc region of a human IgG1 heavy chain; and
(ii) the second polypeptide comprises a further mutation in the amino acid residue corresponding to F405, such as F405L, in the Fc region of a human IgG1 heavy chain; or wherein alternatively
(iii) the first polypeptide comprises a further mutation in the amino acid residue corresponding to F405, such as F405L, in the Fc region of a human IgG1 heavy chain; and
(iv) the second polypeptide comprises a further mutation in the amino acid residue corresponding to K409, such as K409R, in the Fc region of a human IgG1 heavy chain.

35. The variant according to any of claims 24 to 34, wherein the variant is conjugated to a drug, toxin or radiolabel, such as wherein the variant is conjugated to a toxin via a linker.

36. The variant according to any of claims 24 to 35, wherein the variant is part of a fusion protein.

37. A composition comprising a first and a second variant of a parent polypeptide each comprising an Fc domain of an immunoglobulin and a binding region, wherein the first and/or second variant comprises one or more mutation(s) selected from the group corresponding to E430X, E345X, S440Y and S440W in the Fc region of a human IgG1 heavy chain.

38. The composition according to claim 37, wherein the first and/or second variant comprises one or more mutation(s) selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, S440Y, and S440W in the Fc region of a human IgG1 heavy chain.

39. The composition according to claim 38, wherein both the first and second variant comprises one or more mutation(s) which may be the same or different.

40. The composition according to claim 38, wherein the first variant comprises one or more mutation(s) selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, S440Y, and S440W in the Fc region of a human IgG1 heavy chain, and wherein
the second variant does not comprise one or more mutation(s) in an amino acid residue selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, S440Y, and S440W in the Fc region of a human IgG1 heavy chain.

41. The composition according to any one of claims 37 to 40 wherein
(i) the first variant further comprises a mutation in the position corresponding to K439 in the Fc region of a human IgG1 heavy chain, and
(ii) the second variant further comprises a mutation in the position corresponding to S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation is not S440Y or S440W; or
wherein (i) and (ii) may alternatively be
(iii) the first variant further comprises a mutation in the position corresponding to S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation is not S440Y or S440W; and
(iv) the second variant further comprises a mutation in the position corresponding to K439 in the Fc region of a human IgG1 heavy chain.

42. The composition according to claim 41, wherein the mutation in position K439 in the Fc region of a human IgG1 heavy chain is K439D/E, and/or the mutation in position S440 in the Fc region of a human IgG1 heavy chain is S440K/R.

43. The composition according to any one of claims 37 to 42, wherein
(i) the first variant further comprises a pro-drug, and
(ii) the second variant comprises an activator for the pro-drug on the first variant; or wherein (i) and (ii) may alternatively be
(iii) the second variant comprises a pro-drug, and
(iv) the first variant comprises an activator for the pro-drug on the second variant.

44. The composition according to any of claims 37 to 43, wherein the first and second parent polypeptide is a first and second parent antibody each comprising an Fc domain of an immunoglobulin and an antigen-binding region.

45. The variant according to claims 24 to 36, the composition according to claim 44, wherein the variant or the first and the second antibody is each a human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgM, or IgE antibody, optionally each a human full-length antibody, such as each a human full-length IgG1 antibody.

46. The method according to claims 1 to 5 or 13 to 19, the variant according to claims 24 to 31, composition according to claim 45, wherein the parent antibody such as the first or second parent antibody, the variant or the first and the second antibody is each selected from a monospecific, bispecific or multispecific antibody.
47. The composition according to claim 46, wherein the first and/or second parent antibody is each a bispecific antibody which comprises a first polypeptide comprising a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and a second polypeptide comprising a second CH2-CH3 region and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same antigen or on different antigens, and wherein said first CH2-CH3 region comprises a further amino acid mutation at a position selected from those corresponding to K409, T366, L368, K370, D399, F405, and Y407 in the Fc region of a human IgG1 heavy chain; and wherein the second CH2-CH3 region comprises a further amino acid mutation at a position selected from those corresponding to F405, T366, L368, K370, D399, Y407, and K409 in the Fc region of a human IgG1 heavy chain, and wherein the further amino acid mutation in the first CH2-CH3 region is different from the further amino acid mutation in the second CH2-CH3 region.

48. The composition according to claim 47, wherein the further amino acid mutation of the first CH2-CH3 region is at the position corresponding to K409, such as K409R, in the Fc region of a human IgG1 heavy chain; and wherein the further amino acid

mutation of the second CH2-CH3 region is at the position corresponding to F405, such as F405L, in the Fc region of a human IgG1 heavy chain.

49. The composition according to any one of claims 37 to 46, wherein the first and the second variant of the composition bind different epitopes on the same or on different antigens.

50. The composition according to any one of claims 37 to 49, wherein one or both of the first and second variants are conjugated to a drug, toxin or radiolabel, such as wherein one or both of the first and second variants are conjugated to a toxin via a linker.

51. The composition according to any one of claims 37 to 50, wherein one or both of the first and second variants are part of a fusion protein.

52. The composition according to any one of claims 37 to 46 and 49 to 51, wherein the first and/or second variant of the composition comprises only one mutation.
53. A composition comprising the variant according to any one of claims 24 to 36 or the composition according to any one of claims 37 to 52 and a pharmaceutically acceptable carrier.

54. A kit-of-parts comprising a first variant and a second variant as defined in any one of claims 24 to 36 for simultaneous, separate or sequential use in therapy.

55. The variant, composition or kit-of-parts according to any one of claims 24 to 54 for treatment of a disease, such as cancer.

56. Use of the variant, the composition or the kit-of-parts according to any one of claims 24 to 54 for the manufacture of a medicament for the treatment of cancer.

57. The variant, composition or kit-of-parts according to any one of claims 24 to 54, for use in imaging at least a part of the body of a human or other mammal.

CLAIMS

1. A method of increasing complement-dependent cytotoxicity (CDC) of a parent polypeptide comprising an Fc domain of an immunoglobulin and a binding region, which method comprises introducing a mutation to the parent polypeptide in an amino acid residueselected from the group corresponding to E430G, E430S, E430F and E430T in the Fc region of a human IgG1 heavy chain, wherein the method does not alter binding of the parent polypeptide to neonatal Fc receptor (FcRn) compared to the parent polypeptide without the mutation.

2. A method of increasing CDC and antibody dependent cell-mediated cytotoxicity (ADCC) of a parent polypeptide comprising an Fc domain of an immunoglobulin and a binding region, which method comprises introducing a mutation to the parent polypeptide in one or more amino acid residue(s) corresponding to E430G, E430S, E430F and, E430T in the Fc region of a human IgG1 heavy chain.

3. The method according to any one of claims 1 to 2, wherein the parent polypeptide is a parent antibody comprising an Fc domain of an immunoglobulin and an antigen-binding region.

4. A method of increasing complement-dependent cytotoxicity (CDC) of a parent antibody which is a bispecific antibody comprising a first polypeptide comprising a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and a second polypeptide comprising a second CH2-CH3 region of an immunoglobulin and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same antigen or on different antigens, and wherein the method comprises introducing a mutation to the first and/or second CH2-CH3 region in one or more amino acid residue(s) selected from the group corresponding to E430G, E430S, E430F and, E430T in the Fc region of a human IgG1 heavy chain; and wherein
the first CH2-CH3 region comprises a further amino acid mutation at a position selected from those corresponding to K409, T366, L368, K370, D399, F405, and Y407 in the Fc region of a human IgG1 heavy chain; and wherein the second CH2-CH3 region comprises a further amino acid mutation at a position selected from those corresponding to F405, T366, L368, K370, D399, Y407, and K409 in the Fc region of a human IgG1 heavy chain, and wherein the further amino acid mutation in the first CH2-CH3 region is different from the further amino acid mutation in the second CH2-CH3 region.

5. The method according to claim 4, wherein the method comprises introducing a mutation in both the first and second polypeptide of the bispecific antibody.

6. The method according to any one of claims 4 to 5, wherein the further amino acid mutation of the first CH2-CH3 region is at the position corresponding to K409, such as K409R, in the Fc region of a human IgG1 heavy chain; and wherein the further amino acid mutation of the second CH2-CH3 region is at the position corresponding to F405, such as F405L, in the Fc region of a human IgG1 heavy chain.

7. The method according to any one of claims 1 to 6, said method comprises further introducing a mutation
(i) in each of the amino acid residues corresponding to K439 and S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W,
(ii) in each of the amino acid residues corresponding to K447 and 448 in the Fc region of a human IgG1 heavy chain, such as K447K/R/H and 448E/D in the Fc region of a human IgG1 heavy chain, preferably K447K and 448E in the Fc region of a human IgG1 heavy chain, or
(iii) in each of the amino acid residues corresponding to K447, 448 and 449 in the Fc region of a human IgG1 heavy chain, such as K447D/E, 448K/R/H and 449P in the Fc region of a human IgG1 heavy chain, preferably K447E, 448K and 449P in the Fc region of a human IgG1 heavy chain.

8. The method according to claim 7, wherein the mutation in the position corresponding to K439 in the Fc region of a human IgG1 heavy chain is K439D/E, and/or the mutation in the position corresponding to S440 in the Fc region of a human IgG1 heavy chain is S440K/R.

9. A method of increasing complement-dependent cytotoxicity (CDC) of a combination of at least a first and a second parent polypeptide, wherein the at least first and second parent polypeptide each comprises an Fc domain of an immunoglobulin and a binding region, wherein the method comprises
introducing to the at least first and/or second parent polypeptide a mutation in one or more amino acid residue(s) selected from the group corresponding to E430G, E430S, E430F and, E430T in the Fc region of a human IgG1 heavy chain.

10. The method according to claim 9, wherein the method comprises introducing a mutation which may be the same or different to both the first and second parent polypeptide.

11. The method according to claim 9, wherein the method comprises
(i) introducing a mutation to the first parent polypeptide in one or more amino acid residues selected from the group corresponding to E430G, E430S, E430F and, E430T in the Fc region of a human IgG1 heavy chain,
(ii) providing the second parent polypeptide which does not comprise a mutation in one or more amino acid residues selected from the group corresponding to E430G, E430S, E430F and E430T in the Fc region of a human IgG1 heavy chain.

12. The method according to any one of claims 9 to 11, wherein the method further comprises the steps of
(i) introducing to the first parent polypeptide a second mutation in the amino acid residue corresponding to position K439 in the Fc region of a human IgG1 heavy chain; and
(ii) introducing to the second parent polypeptide a second mutation in the amino acid residue corresponding to S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation is not S440Y or S440W; wherein steps (i) and (ii) may alternatively be
(iii) introducing the for the first parent polypeptide a second mutation in the amino acid residue corresponding to position S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation is not S440Y or S440W;
(iv) introducing to the second parent polypeptide a second mutation in the amino acid residue corresponding to position K439 in the Fc region of a human IgG1 heavy chain.

13. The method according to claim 12, wherein the mutation in the position corresponding to K439 in the Fc region of a human IgG1 heavy chain is K439D/E, and/or the mutation in the position corresponding to S440 in the Fc region of a human IgG1 heavy chain is S440K/R.

14. The method according to any one of claims 9 to 13, wherein the first and second parent polypeptide is a first and second parent antibody each comprising an Fc domain of an immunoglobulin and an antigen-binding region.

15. The method according to claim 14, wherein the first and/or second parent antibody is a bispecific antibody which comprises a first polypeptide comprising a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and a second polypeptide comprising a second CH2-CH3 region and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same antigen or on different antigens, and wherein said first CH2-CH3 region comprises a further amino acid mutation at a position selected from those corresponding to K409, T366, L368, K370, D399, F405, and Y407 in the Fc region of a human IgG1 heavy chain; and wherein the second CH2-CH3 region comprises a

further amino acid mutation at a position selected from those corresponding to F405, T366, L368, K370, D399, Y407, and K409 in the Fc region of a human IgG1 heavy chain, and wherein the further amino acid mutation in the first CH2-CH3 region is different from the further amino acid mutation in the second CH2-CH3 region.

16. The method according to claim 15, wherein the first CH2-CH3 region comprises a further amino acid mutation at the position corresponding to K409, such as K409R, in the Fc region of a human IgG1 heavy chain; and wherein the second CH2-CH3 region comprises a further amino acid mutation at the position corresponding to F405, such as F405L, in the Fc region of a human IgG1 heavy chain.

17. The method according to any one of claims 1 and 3 to 16, wherein the method does not alter antibody dependent cell-mediated cytotoxicity (ADCC) of the parent polypeptide or parent antibody.

18. The method according to any one of claims 1 to 17, wherein the method does not
a) alter binding of the parent polypeptide or parent antibody to neonatal Fc receptor (FcRn) as determined by the method disclosed in Example 34 and/or
b) increase or decrease binding of the parent polypeptide or parent antibody to neonatal Fc receptor (FcRn) by more than 30%, such as of more than 20%, 10% or 5% as measured by a change in the absorbance at OD405 nm as determined by the method disclosed in Example 34 and/or
c) increase the apparent affinity of the parent polypeptide or parent antibody to mouse neonatal Fc receptor (FcRn) by more than a factor 0.5 or does not decrease the apparent affinity of the parent polypeptide or parent antibody to mouse FcRn by more than a factor 2 as determined by the method disclosed in Example 34 and/or
d) alter the plasma clearance rate of the parent polypeptide or parent antibody as determined by the method disclosed in Example 37 and/or
e) increase or decrease the plasma clearance rate of the parent polypeptide or parent antibody by more than a factor 3.0, such as by more than a factor 2.5, factor 2.0, factor 1.5 or factor 1.2 as determined by the method disclosed in Example 37 and/or
f) alter target independent fluid phase complement activation of the variant as determined by the method as determined by the method disclosed in Example 36 and/or
g) alter the plasma half-life of the parent polypeptide or parent antibody.

19. A variant of a parent polypeptide comprising an Fc domain of an immunoglobulin and a binding region, wherein the variant comprises a mutation selected from the group

corresponding to E430G, E430S, E430F and E430T in the Fc region of a human IgG1 heavy chain, wherein the variant has increased complement-dependent cytotoxicity (CDC) and wherein the mutation in the Fc domain does not alter binding of the variant to neonatal Fc receptor (FcRn).

20. A variant of a parent polypeptide comprising an Fc domain of an immunoglobulin and a binding region, wherein the variant comprises a mutation selected from the group corresponding to E430G, E430S, E430F and E430T in the Fc region of a human IgG1 heavy chain , wherein the variant has increased complement-dependent cytotoxicity (CDC) and wherein the mutation in the Fc domain does not alter binding of the variant to neonatal Fc receptor (FcRn) and provided that the variant does not contain any further mutations in the Fc domain which alter the binding of the variant to neonatal Fc receptor (FcRn).

21. A variant of a parent polypeptide comprising an Fc domain of an immunoglobulin and a binding region, wherein the variant comprises a mutation selected from the group corresponding to E430G, E430S, E430F and E430T in the Fc region of a human IgG1 heavy chain , wherein the variant has increased complement-dependent cytotoxicity (CDC) and wherein the mutation in the Fc domain does not alter binding of the variant to neonatal Fc receptor (FcRn) and provided that the variant does not contain any further mutations in the Fc domain which increase or decrease the binding of the variant to neonatal Fc receptor (FcRn) by more than 30%, such as of more than 20%, 10% or 5% as measured by a change in the absorbance at OD405 nm as determined by the method disclosed in Example 34.

22. The variant according to any of claims 19 to 21, wherein
a) the variant does not contain any further mutations in the Fc domain which alter antibody dependent cell-mediated cytotoxicity (ADCC) of the variant and/or
b) the variant does not contain any further mutations in the Fc domain which alter the plasma clearance rate of the variant as determined by the method disclosed in Example 37 and/or
c) the variant does not contain any further mutations in the Fc domain which increase or decrease the plasma clearance rate of the variant by more than a factor 3.0, such as by by more than a factor 2.5, factor 2.0, factor 1.5 or factor 1.2 as determined by the method disclosed in Example 37 and/or
d) the variant does not contain any further mutations in the Fc domain which alter the serum half-life of the variant and/or
e) the variant does not contain any further mutations in the Fc domain which alter target independent fluid phase complement activation of the variant as determined by the method disclosed in Example 36 and/or

f) the variant does not contain any further mutations in the Fc domain.
g) the variant comprises only one mutation.

23. The variant according to any one of claims 19 to 22, wherein the variant comprises a combination of two mutations in the amino acid residues selected from the group corresponding to E345X/E430G,S,F,T, E430G,S,F,T/S440Y, and E430G,S,F,T/S440W in the Fc region of a human IgG1 heavy chain , wherein X is K, Q, R or Y.

24. A variant of a parent polypeptide comprising an Fc domain of an immunoglobulin and a binding region, wherein the variant comprises a first mutation selected from the group corresponding to E430G, E430S, E430F and E430T in the Fc region of a human IgG1 heavy chain; and a second mutation selected from the group corresponding to
(i) an amino acid residue corresponding to K439 and S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W, ,
(ii) an amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448P in the Fc region of a human IgG1 heavy chain; or
(iii) an amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448K/R/H and 449P in the Fc region of a human IgG1 heavy chain.

25. The variant according to claim 24, wherein the variant comprises a first mutation selected from the group corresponding to E430G, E430S, E430F and E430T in the Fc region of a human IgG1 heavy chain, and a second mutation in an amino acid residue corresponding to K439 or S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y and S440W.

26. The variant according to claim 25, wherein the mutation in the amino acid residue corresponding to K439 is K439D/E and the amino acid residue corresponding to S440 is S440K/R.

27. The variant according to any one of claims 19 to 26, wherein the parent polypeptide is a parent antibody comprising an Fc domain of an immunoglobulin and an antigen-binding region.

28. A variant of a parent antibody which is a bispecific antibody comprising a first polypeptide comprising a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and a second polypeptide comprising a second CH2-CH3 region of an immunoglobulin and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same or on different antigens, and wherein the first and/or second

CH2-CH3 regions comprise one or more mutation(s) selected from the group corresponding to E430G, E430S, E430F, E430T, and wherein
the first polypeptide comprises a further mutation in an amino acid residue selected from those corresponding to K409, T366, L368, K370, D399, F405, and Y407 in the Fc region of a human IgG1 heavy chain; and
the second polypeptide comprises a further mutation in an amino acid residue selected from those corresponding to F405, T366, L368, K370, D399, Y407 and K409 in the Fc region of a human IgG1 heavy chain, and wherein the further mutation in the first polypeptide is different from the further mutation in the second polypeptide.

29. The variant according to claim 28, wherein
(i) the first polypeptide comprises a further mutation in the amino acid residue corresponding to K409, such as K409R, in the Fc region of a human IgG1 heavy chain; and
(ii) the second polypeptide comprises a further mutation in the amino acid residue corresponding to F405, such as F405L, in the Fc region of a human IgG1 heavy chain; or
wherein alternatively
(iii) the first polypeptide comprises a further mutation in the amino acid residue corresponding to F405, such as F405L, in the Fc region of a human IgG1 heavy chain; and
(iv) the second polypeptide comprises a further mutation in the amino acid residue corresponding to K409, such as K409R, in the Fc region of a human IgG1 heavy chain.

30. The variant according to any one of claims 19 to 29, wherein the variant is
a) conjugated to a drug, toxin or radiolabel, such as wherein the variant is conjugated to a toxin via a linker and/or
b) part of a fusion protein.

31. A composition comprising a first and a second variant of a parent polypeptide each comprising an Fc domain of an immunoglobulin and a binding region, wherein the first and/or second variant comprises a mutation selected from the group corresponding to E430G, E430S, E430F and E430T in the Fc region of a human IgG1 heavy chain.

32. The composition according to claim 31, wherein both the first and second variant comprises a mutation selected from the group corresponding to E430G, E430S, E430F and E430T in the Fc region of a human IgG1 heavy chain, which may be the same or different.

33. The composition according to claim 31, wherein the first variant comprises a mutation selected from the group corresponding to E430G, E430S, E430F and E430T in the Fc region of

a human IgG1 heavy chain, and wherein
the second variant does not comprise one or more mutation(s) in an amino acid residue selected from the group corresponding to E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, S440Y, and S440W in the Fc region of a human IgG1 heavy chain.

34. The composition according to any one of claims 31 to 33 wherein
(i) the first variant further comprises a mutation in the position corresponding to K439 in the Fc region of a human IgG1 heavy chain, and
(ii) the second variant further comprises a mutation in the position corresponding to S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation is not S440Y or S440W; or
wherein (i) and (ii) may alternatively be
(iii) the first variant further comprises a mutation in the position corresponding to S440 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation is not S440Y or S440W; and
(iv) the second variant further comprises a mutation in the position corresponding to K439 in the Fc region of a human IgG1 heavy chain.

35. The composition according to claim 34, wherein the mutation in position K439 in the Fc region of a human IgG1 heavy chain is K439D/E, and/or the mutation in position S440 in the Fc region of a human IgG1 heavy chain is S440K/R.

36. The composition according to any one of claims 31 to 35, wherein
(i) the first variant further comprises a pro-drug, and
(ii) the second variant comprises an activator for the pro-drug on the first variant; or
wherein (i) and (ii) may alternatively be
(iii) the second variant comprises a pro-drug, and
(iv) the first variant comprises an activator for the pro-drug on the second variant.

37. The composition according to any one of claims 31 to 36, wherein the first and second parent polypeptide is a first and second parent antibody each comprising an Fc domain of an immunoglobulin and an antigen-binding region.

38. The variant according to claims 19 to 30, the composition according to claim 37, wherein the variant or the first and the second antibody is each a human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgM, or IgE antibody, optionally each a human full-length antibody, such as each a human full-length IgG1 antibody.

39. The method according to claims 1 to 3 or 9 to 14, the variant according to claims 19 to 26, composition according to claim 38, wherein the parent antibody such as the first or second parent antibody, the variant or the first and the second antibody is each selected from a monospecific, bispecific or multispecific antibody.

40. The composition according to claim 39, wherein the first and/or second parent antibody is each a bispecific antibody which comprises a first polypeptide comprising a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and a second polypeptide comprising a second CH2-CH3 region and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same antigen or on different antigens, and wherein said first CH2-CH3 region comprises a further amino acid mutation at a position selected from those corresponding to K409, T366, L368, K370, D399, F405, and Y407 in the Fc region of a human IgG1 heavy chain; and wherein the second CH2-CH3 region comprises a further amino acid mutation at a position selected from those corresponding to F405, T366, L368, K370, D399, Y407, and K409 in the Fc region of a human IgG1 heavy chain, and wherein the further amino acid mutation in the first CH2-CH3 region is different from the further amino acid mutation in the second CH2-CH3 region.

41. The composition according to claim 40, wherein the further amino acid mutation of the first CH2-CH3 region is at the position corresponding to K409, such as K409R, in the Fc region of a human IgG1 heavy chain; and wherein the further amino acid mutation of the second CH2-CH3 region is at the position corresponding to F405, such as F405L, in the Fc region of a human IgG1 heavy chain.

42. The composition according to any one of claims 31 to 41, wherein the first and the second variant of the composition bind different epitopes on the same or on different antigens.

43. The composition according to any one of claims 31 to 42, wherein one or both of the first and second variants

a) are conjugated to a drug, toxin or radiolabel, such as wherein one or both of the first and second variants are conjugated to a toxin via a linker and/or

b) part of a fusion protein.

44. The composition according to any one of claims 31 to 39 and 42 to 43, wherein the first and/or second variant of the composition comprises only one mutation.

45. A composition comprising the variant according to any one of claims 19 to 30 or the composition according to any one of claims 31 to 44 and a pharmaceutically acceptable carrier.

46. A kit-of-parts comprising a first variant and a second variant as defined in any one of claims 19 to 30 for simultaneous, separate or sequential use in therapy.

47. The variant, composition or kit-of-parts according to any one of claims 19 to 46 for treatment of a disease, such as cancer.

48. Use of the variant, the composition or the kit-of-parts according to any one of claims 19 to 46 for the manufacture of a medicament for the treatment of cancer.

49. The variant, composition or kit-of-parts according to any one of claims 19 to 46, for use in imaging at least a part of the body of a human or other mammal.

50. A variant of a parent polypeptide comprising an Fc domain of an immunoglobulin and a binding region, wherein the variant comprises a mutation selected from the group corresponding to E430G, E430S, E430F and E430T in the Fc region of a human IgG1 heavy chain and wherein the variant has increased complement-dependent cytotoxicity (CDC) and provided that the variant does not have altered binding to the neonatal Fc receptor (FcRn) compared to the parent polypeptide for treatment of cancer.