WHAT IS CLAIMED IS:

1. A method for treating a disease associated with target cells expressing CD138 comprising:
administering to a subject, in particular a human subject, in need thereof an immunoconjugate comprising
at least one engineered targeting antibody targeting CD138 expressing cells, and
at least one effector molecule, wherein said engineered targeting antibody is functionally attached to said effector molecule to form said immunoconjugate,
wherein preferably at least a part of the engineered targeting antibody confers IgG4 isotype properties, wherein
the immunoconjugate is administered in a multiple dose regimen comprising at least two doses, wherein the aggregate dose administered within an active treatment cycle is an aggregate maximum tolerable dose (AMTD) or a fraction of the AMTD and wherein said AMTD and/or said fraction exceeds the dose resulting in dose limiting toxicity (DLT) when the immunoconjugate is administered as a single dose, including as part of a multiple single dose regimen and/or exceeds the maximum tolerable dose (MTD) when the immunoconjugate is administered as a single dose, including as part of a multiple single dose regimen within said active treatment cycle.

2. The method of claim 1, wherein the immunoconjugate is administered in an active treatment cycle of 21 days, preferably at least three times within said 21 days.

3. The method of any one of the preceding claims, wherein the immunoconjugate is administered in equal doses.

4. The method of any one of the preceding claims, said multiple dose regimen lasts 3 weeks and is followed by a resting period.

5. The method of claim 4, wherein progression free survival or stable disease is maintained during the resting period.

6. The method of claim 5, wherein a level of said immunoconjugate in a body fluid of said subject, during said resting period is at least 0.5 µg/ml, at least 1µg/ml, at least 2µg/ml, at least 3 µg/ml, 4 µg/ml, 5 µg/ ml or 6µg/ml and/or wherein more than 80%, more than 90%, more than 95% of the CD138 of isolated target cells are occupied by said immunoconjugate within four to twenty four hours after completion of administration of the immunoconjugate.

7. The method of any one of the preceding claims, wherein said effector is a maytansinoid, in particular DM4, and wherein a total amount of maytansinoid administered to said patient within said 21 days is more than 2mg/m^2, more than 3mg/m^2, more than 4mg/m^2, more than 5mg/m^2, more than 6mg/m^2, more than 7mg/m^2, more than 8mg/m^2, more than 9mg/m^2 or more than more than 10mg/m^2.

8. The method of any one of the preceding claims wherein the AMTD exceeds the dose of said DLT by at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 80%, at least 90%, at least 100% or at least 120% and said MTD by at least 30%, at least 40%, at least 50%, at least 60%, at least 80%, at least 90%, at least 100%, at least 120% or at least 140%.

9. The method of any one of the preceding claims, wherein the AMTD is at least 240mg/m^2, preferably 300 mg/m^2, preferably 360 mg/m^2, preferably 420 mg/m^2 and the dose resulting in said DLT is 200 mg/m^2.

10. The method according to any one of the preceding claims, wherein the AMTD is at least 240mg/m^2, preferably 300 mg/m^2, preferably 360 mg/m^2, preferably 420 mg/m^2 and said MTD is at least 160 mg/m^2 or at least 180 mg/m^2.

11. The method according to any one of the preceding claims, wherein said active treatment cycle includes said administering being performed at least once a week, at preferably equal doses for at least three weeks and the active treatment cycle is preferably followed by a resting period of at least

one week, which together define a treatment cycle of at least 28 days, and wherein, after one, two or more treatment cycles, at least stable disease is achieved.

12. The method of claim 11, wherein said immunoconjugate is administered every 3rd day, every 4th day, every 5th day or every 6th day during said three weeks period.

13. The method of claim 11 or 12, wherein at least stable disease is maintained during three, four, five, six, seven treatment cycles.

14. The method of claim 13, wherein after reaching at least stable disease, the immunoconjugate is administered as a maintenance therapy less than twice within said active treatment cycle preferably as a repeated single dose of between 60 mg/m^2 and 280 mg/m^2, including about 70 mg/m^2 , about 80 mg/m^2, about 90 mg/m^2, about 100 mg/m^2 , about 110 mg/m^2, about 120 mg/m^2, about 130 mg/m^2, about 140 mg/m^2, 150 mg/m^2 , about 160 mg/m^2, about 170 mg/m^2, about 180 mg/m^2, about 190 mg/m^2, about 200 mg/m^2, about 210 mg/m^2, about 220 mg/m^2, about 230 mg/m^2, about 240 mg/m^2, about 250 mg/m^2, about 260 mg/m^2 and about 270 mg/m^2.

15. The method of claim 14, wherein at least progression free survival, stable disease and or a minor response is obtained for more than 3 months during said maintenance therapy.

16. A method according to any one of the preceding claims, wherein administration of said immunoconjugate as a repeated multiple dose in said active treatment cycle, results in an aggregate effective amount and a first level of the immunoconjugate in a body fluid of the subject and wherein, an amount equivalent to said aggregate effective amount is administered as a single dose or repeated single dose in said active treatment cycle, results in a second level of the immunoconjugate in a body fluid of said subject, wherein the first level is equal or below the second level, e.g. more than 10%, more than 20 % or more than 30% below the second level.

17. The method of claim 16, wherein the active treatment cycle lasts 21 days and/or the repeated multiple dose consists of 3 equal, preferably equidistant doses, more preferably administered on days 1, 8 and 15.

18. The method of claim 16 or 17, wherein said aggregate effective amount is more than 200mg/m^2, about 220mg/m^2, about 240mg/m^2, about 260mg/m^2, or about 280 mg/m^2.

19. A method for treating a disease associated with target cells expressing CD138, comprising:
administering to a patient in need thereof a pharmaceutical composition comprising an immunoconjugate and a pharmaceutically acceptable carrier in an active treatment cycle which is optionally followed by a resting period, wherein the immunoconjugate comprises
at least one targeting agent targeting CD138 expressing cells, and
at least one effector molecule, wherein said targeting agent is functionally attached to said effector molecule to form said immunoconjugate, and
wherein the dose of the immunoconjugate administered at least once a week is about 20mg/m^2, about 30mg/m^2, about 40mg/m^2, about 50mg/m^2, about 60mg/m^2, 70 mg/m^2, about 80mg/m^2, about 90mg/m^2, about 100mg/m^2, about 110mg/m^2, about 120mg/m^2, about 130mg/m^2, about 140mg/m^2, about 150mg/m^2 or about 160mg/m^2, about 170 mg/m^2, about 180 mg/m^2, about 190 mg/m^2, about 200 mg/m^2, about 210 mg/m^2, about 220 mg/m^2, about 230 mg/m^2, about 240 mg/m^2, about 250 mg/m^2, about 260 mg/m^2 , about 270 mg/m^2 or about 280 mg/m^2 and the pharmaceutical composition is administered for at least three weeks alone or in combination with a cytotoxic agent.

20. The method of claim 19, wherein the active treatment cycle lasts at least 21 day and the immunoconjugate is administered once a week at a dose from about 40mg/m^2 to about 140mg/m^2.

21. The method of any one of the of the preceding claims, wherein said administration is followed, after at least two 21 day treatment cycles, each

optionally followed by a resting period, by a further administration of said the immunoconjugate or pharmaceutical composition as a maintenance therapy.

22. The method of claim 21, wherein the maintenance therapy comprises administering the immunoconjugate or a pharmaceutical composition comprising the same (i) once every three to six weeks or (ii) at repeated multiple doses, wherein each individual dose of immunoconjugate is about 10mg/m^2, about 20mg/m^2, about 30mg/m^2, about 40mg/m^2, about 50mg/m^2, about 60mg/m^2, 70 mg/m^2, about 80mg/m^2, about 90mg/m^2 or about 100mg/m^2 lower than the individual dose of a primary therapy and/or wherein individual doses are administered in intervals exceeding the interval of the individual doses, e.g., by 1, 2, 3, 4, 5, 6, 7 days.

23. A method according to any one of the preceding claims, wherein administration of said immunoconjugate as a multiple dose regime results, 0-2 hours after completion of administration in a mean plasma level of at least 7 µg/ml , 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 50, 60 or 70 µg/ml.

24. A method according to any one of the preceding claims further comprising

determining 0-4 hours, including at about 1, 2, or 3, following an completion of administering said immunoconjugate or a pharmaceutical composition comprising the same, a reference level (RL) of an said immunoconjugate or of an efficacy blood parameter in a body fluid of a patient,
determining in a subsequent administration of said immunoconjugate, at 0-4 hours following an completion of said subsequent administration, a subsequent level (SL) of an said immunoconjugate or efficacy blood parameter,
comparing the RL to the SL,

(i) determining RL>SL,

and increasing the aggregate dose in a treatment cycle following said subsequent administration by 5- 100%, including 10-50% or 20-30%, and/or

(ii) determining RL<SL,

and decreasing the aggregate dose in a treatment cycle following said subsequent administration by 5- 100%, including 10-50% or 20-30%.

25. A method according to any one of the preceding claims further comprising

determining 0-2 hours following an completion of administering an individual dose of said immunoconjugate or a pharmaceutical composition comprising the same, a level of said immunoconjugate in a body fluid,

determining whether the level of the immunoconjugate is below or above 7 $\mu g/m^2$, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 $\mu g/m^2$,
increasing the individual dose in the next treatment cycle by at least $10mg/m^2$, $20mg/m^2$, about $30mg/m^2$, about $40mg/m^2$, about $50mg/m^2$, about $60mg/m^2$, $70\ mg/m^2$, about $80mg/m^2$, about $90mg/m^2$ or about $100mg/m^2$ if the level is below 7 $\mu g/m^2$, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 $\mu g/m^2$, or
maintaining or decreasing by at least $10mg/m^2$, $20mg/m^2$, about $30mg/m^2$, about $40mg/m^2$, about $50mg/m^2$, about $60mg/m^2$, about $70\ mg/m^2$, about $80mg/m^2$, about $90mg/m^2$ or about $100mg/m^2$, the individual dose in the next treatment cycle if the level is above 7 $\mu g/m^2$, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 $\mu g/m^2$.

26. A method according to any one of the preceding claims further comprising administering at least one cytotoxic agent, including two or three, at least once a week or once in a treatment cycle.

27. The method of claim 26, wherein said cytotoxic agent is lenalidomide and/or dexamethasone.

28. The method of claim 26 and any following claims, wherein said subject has not previously been exposed to an immunoconjugate comprising an antibody targeting CD138 expressing cells, to lenalidomide and/or to dexamethasone.

29. The method of claim 26 or 27, wherein said subject has previously been exposed to an immunoconjugate comprising an antibody targeting CD138 expressing cells, lenalidomide and/or dexamethasone.

30. The method of claim 29, wherein said subject responded to said exposure to an immunoconjugate comprising an antibody targeting CD138 expressing cells, lenalidomide and/or dexamethasone.

31. The method of claim 30, wherein said target cells expressing CD138 are refractory to exposure to an immunoconjugate comprising an antibody targeting CD138 expressing cells, lenalidomide and/or dexamethasone.

32. The method of claim 29, wherein said subject relapsed after said administration.

33. The method of claim 26 and any following claims, wherein lenalidomide is administered at a dose of 5 to 35 mg, preferably at about 25 mg, or at a dose of less than 25, 20, 15 or 10 mg, e.g., orally once a day for 21 days and/or wherein dexamethasone is administered at a dose of 20 to 50 mg, preferably at about 40 mg, or at a dose of less than 40 or 30 mg, e.g., orally once a day for 21 days.

34. The method of any one of the preceding claims, wherein said subject suffers from a solid tumor comprising target cells which express CD138 and wherein said solid tumor is refractory to cancer hormone therapy or chemotherapy or the subject has relapsed after hormone therapy or chemotherapy, wherein said administration results in at least tumor growth delay or tumor stasis.

35. The method of claim 34, wherein said immunoconjugate is administered in a repeated multiple dose regime with individual doses of 20mg/m^2 to 160mg/m^2.

36. The method of claim 34, wherein said solid tumor is estrogen receptor negative and/or progesterone receptor negative and/or Her2/neu negative.

37. The method of any one of the preceding claims, wherein the administration of said immunoconjugate or pharmaceutical composition is preceded by an administration of unconjugated antibody targeting CD138 expressing cells, wherein said immunoconjugate is administered 1-6, preferably 2-4, hours after completion of the administration of said unconjugated antibody.

38. The method of claim 37, wherein the unconjugated antibody is administered at a dose corresponding to a level of 10 to 30 µg/ml immunoconjugate in a body fluid of the subject, in particular a plasma level of the subject.

39. The method of claim 38, wherein the dose administered corresponds to about a difference between a theoretical and actual level of said immunoconjugate in a body fluid, 0-2 hours after completion of an administration of said immunoconjugate to said subject.

40. The method of claim 37 or any subsequent claims, wherein said antibody is administered at a dose of 10 to 40 mg/m^2, preferably 20-30 mg/m^2.

41. The method of claims 37 or any subsequent claims, wherein said immunoconjugate is administered at a individual dose that is up to 10mg/m^2 to 30mg/m^2 lower than the dose administered without said administration of said unconjugated antibody.

42. A kit comprising an antibody against the immunoconjugate according to any one of the preceding claims, and, in a separate container, instructions how to determine, a level of said immunoconjugate in a body fluid obtained from said subject by addition of said antibody to said body fluid.

CLAIMS

1. Use of an immunoconjugate in the manufacture of a medicament for treating a disease associated with target cells expressing CD138 in a human subject, the immunoconjugate comprising:
at least one engineered targeting antibody targeting CD138 expressing cells, and
at least one effector molecule,
wherein said engineered targeting antibody is functionally attached to said effector molecule to form said immunoconjugate,
wherein at least a part of the engineered targeting antibody confers IgG4 isotype properties, and wherein treating comprises administering the immunoconjugate in a multiple dose regimen comprising at least two doses, wherein the aggregate dose administered within an active treatment cycle is an aggregate maximum tolerable dose (AMTD) or a fraction of the AMTD and wherein said AMTD or said fraction exceeds the dose resulting in dose limiting toxicity (DLT) when the immunoconjugate is administered as a single dose, including as part of a multiple single dose regimen or exceeds the maximum tolerable dose (MTD) when the immunoconjugate is administered as a single dose, including as part of a multiple single dose regimen within said active treatment cycle.

2. The use of claim 1,
wherein the active treatment cycle is followed by a resting period,
wherein the dose of the immunoconjugate administered at least once a week is about 20mg/m^2, about 30mg/m^2, about 40mg/m^2, about 50mg/m^2, about 60mg/m^2, 70 mg/m^2, about 80mg/m^2, about 90mg/m^2, about 100mg/m^2, about 110mg/m^2, about 120mg/m^2, about 130mg/m^2, about 140mg/m^2, about 150mg/m^2 or about 160mg/m^2, about 170 mg/m^2, about 180 mg/m^2, about 190 mg/m^2, about 200 mg/m^2, about 210 mg/m^2, about 220 mg/m^2, about 230 mg/m^2, about 240 mg/m^2, about 250 mg/m^2, about 260 mg/m^2, about 270 mg/m^2 or about 280 mg/m^2,
and wherein the treating comprises administering the medicament for at least three weeks alone or in combination with a cytotoxic agent.

3. The use of claim 1 or claim 2 wherein the effector molecule is at least one maytansinoid.

4. Use of an immunoconjugate in the manufacture of a medicament for treating a disease associated with target cells expressing CD138 in a human subject, wherein the immunoconjugate comprises
at least one engineered targeting antibody targeting CD138 expressing cells, and
at least one effector molecule,
wherein said engineered targeting antibody is functionally attached to said effector molecule to form said immunoconjugate,
wherein at least a part of the engineered targeting antibody confers IgG4 isotype properties, wherein the engineered targeting antibody comprises:
(i) a heavy chain having at least 85% sequence identity with SEQ ID NO: 1, wherein the heavy chain comprises a variable region comprising amino acid residues 31 to 35 (CDR1) and 51 to 68 (CDR2) and 99 to 111 (CDR3) of SEQ ID NO: 1, and
(ii) a light chain having at least 85% sequence identity with SEQ ID NO: 2, wherein the light chain comprises a variable region comprising amino acid residues 24 to 34 (CDR1) and 50 to 56 (CDR2) and 89 to 97 (CDR3) of SEQ ID NO: 2;
wherein the effector molecule is at least one maytansinoid,
wherein the treating comprises administering the medicament in an active treatment cycle of 21 days, at least three times within said 21 days,
wherein said active treatment cycle comprises administrering at least once a week,
wherein the dose of the immunoconjugate administered at least once a week is between 80 mg/m^2 and 120 mg/m^2.

5. The use of claim 4, wherein treating comprises administering the medicament at equal doses for at least three weeks and the active treatment cycle is followed by a resting period of at least one week, which together define a treatment cycle of at least 28 days.

6. The use of any one of claims 3 to 5, wherein the least one maytansinoid is DM4.

7. The use of any one of claims 1 to 6, wherein the engineered targeting antibody comprises a light chain comprising SEQ ID NO: 2 and a heavy chain comprising SEQ ID NO:1.