CLAIMS

1. A therapeutic nanoparticle comprising 55 to 85 weight percent of diblock poly(lactic)acid-poly(ethylene)glycol copolymer, wherein the therapeutic nanoparticle comprises 10 to 30 weight percent poly(ethylene)glycol, 5 to 20 weight percent of pamoic acid and 10 to 25 weight percent of 2-(3-((7-(3-(ethyl(2-hydroxyethyl)amino)propoxy)quinazolin4-yl)amino)-1H-pyrazol-5-yl)-N-(3-fluorophenyl)acetamide ("AZD1152 hqpa").

2. The therapeutic nanoparticle as claimed in claim 1, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a number average molecular weight of 15kDa to 20kDa poly(lactic acid) and a number average molecular weight of 4kDa to 6kDa poly(ethylene)glycol.

3. The therapeutic nanoparticle of claim 2, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a number average molecular weight of 16kDa poly(lactic acid) and a number average molecular weight of 5kDa poly(ethylene)glycol.

4. The therapeutic nanoparticle of any one of claims 1-3, comprising 15 to 22 weight percent of AZD1152 hqpa.

5. A therapeutic nanoparticle as claimed in claim 1 comprising 15 to 25 weight percent of AZD 1152 hqpa, 7 to 15 weight percent of pamoic acid, and a diblock poly(lactic) acid-poly(ethylene)glycol copolymer, wherein the therapeutic nanoparticle comprises 10 to 30 weight percent poly(ethylene)glycol) and the poly(lactic) acid-poly(ethylene)glycol copolymer has a number average molecular weight of 16kDa poly(lactic acid) and a number average molecular weight of 5kDa poly(ethylene)glycol.

6. A therapeutic nanoparticle as claimed in claim 1 comprising 15 to 22 weight percent of AZD 1152 hqpa, 7 to 10 weight percent of pamoic acid, and a diblock poly(lactic) acid-poly(ethylene)glycol copolymer, wherein the therapeutic nanoparticle comprises 10 to 30 weight percent poly(ethylene)glycol, and the poly(lactic) acid-poly(ethylene)glycol copolymer has a number average molecular weight of 16kDa poly(lactic acid) and a number average molecular weight of 5kDa poly(ethylene)glycol); wherein less than 20% of the AZD1152 hqpa is released from the nanoparticle after 30 hours in PBS and polysorbate20 at 37°C.

7. A therapeutic nanoparticle as claimed in claim 1 comprising 15 to 22 weight percent of AZD1152 hqpa, 7 to 10 weight percent of pamoic acid, and a diblock poly(lactic) acid-poly(ethylene)glycol copolymer, wherein the therapeutic nanoparticle comprises 10 to 30 weight percent poly(ethylene)glycol and the poly(lactic) acid-poly(ethylene)glycol copolymer has a number average molecular weight of

16kDa poly(lactic acid) and a number average molecular weight of 5kDa poly(ethylene)glycol; wherein less than 20% of the AZD1152 hqpa is released from the nanoparticle after 30 hours in PBS and polysorbate20 at 37°C, and wherein the nanoparticles are made by a process comprising the following steps:

1) combining a first organic phase which comprises a 16:5 PLA-PEG co-polymer, AZD1152 hqpa and pamoic acid in a solvent mixture comprising TFA, benzyl alcohol, DMSO and ethyl acetate such that the benzyl alcohol: ethyl acetate are present in a molar ratio of 1:3.6 and the pamoic acid and AZD1152 hqpa are added at an initial ratio of 0.8 moles pamoic acid: 1 mole AZD1152 hqpa; with a first aqueous solution comprising a polyoxyethylene (100) stearyl ether in water, DMSO and benzyl alcohol)to form a second phase, wherein the ratio of the aqueous phase to the organic phase is 5.5:1;

2) emulsifying the second phase to form a coarse emulsion;

3) holding the coarse emulsion for a hold time, such as 10 to 15 minutes, conveniently at about 0 °C for example by immersing in an ice-bath;

4) forming a nano-emulsion using a high pressure homogenizer;

5) optionally waiting for a delay time of at least 5 minutes, for example 10 minutes;

6) quenching of the emulsion phase at 0-5 °C thereby forming a quenched phase, wherein quenching of the emulsion phase comprises mixing the emulsion phase with a second aqueous solution comprising a buffer at pH 6.5, wherein the ratio of second aqueous solution to emulsion is between 2:1 and 10:1, such as 3:1;

7) adding an aqueous surfactant solution to the quench solution;

8) concentrating and isolating the resulting nanoparticles by filtration.

8. The therapeutic nanoparticle as claimed in claim 1 consisting of 15-19 wt% AZD1152 hqpa, pamoic acid in a molar ratio of 0.76 relative to the AZD1152 hqpa, and a di-block poly(lactic) acid-poly(ethylene)glycol copolymer, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a number average molecular weight of 16kDa poly(lactic acid) and a number average molecular weight of 5kDa poly(ethylene)glycol.

9. A therapeutic nanoparticle as claimed in claim 3, wherein the therapeutic nanoparticle releases less than 20% of AZD1152 hqpa after 30 hours in phosphate buffer solution and polysorbate 20 at 37°C.

10. The therapeutic nanoparticle of any one of claims 1-9 which has a hydrodynamic diameter of 70-140 nm.

11. A pharmaceutically acceptable composition comprising a plurality of therapeutic nanoparticles of any one of claims 1-10 and one or more pharmaceutically acceptable excipients, diluents and/or carriers.

12. A therapeutic nanoparticle as claimed in any one of claims 1 to 10 for use as a medicament.

13. A composition as claimed in claim 11 for use as a medicament.

14. A therapeutic nanoparticle as claimed in any one of claims 1 to 10 for use as a medicament for the treatment of cancer.

15. A composition as claimed in claim 11 for use as a medicament for the treatment of cancer.

16. A therapeutic nanoparticle for use as a medicament for the treatment of cancer as claimed in claim 14, wherein the cancer is lung cancer, colorectal cancer or a haematological cancer, such as acute myeloid leukemia (AML) or diffuse large B cell lymphoma (DLBCL).

17. A composition for use as a medicament for the treatment of cancer as claimed in claim 15, wherein the cancer is lung cancer, colorectal cancer or a haematological cancer, such as AML or DLBCL.

18. A combination suitable for use in the treatment of cancer comprising a pharmaceutically acceptable composition as claimed in claim 11 and another anti-tumour agent.

19. A combination as claimed in claim 18 wherein the other anti-tumour agent is selected from:

a) standard-of-care chemotherapy regimens including replacing or augmenting anti-mitotic chemotherapies in solid tumour and haematological cancers, such as taxeanes and vinca alkaloids;

b) therapies that target the DNA damage response, including agents that inhibit DNA damage repair and the cell cycle; and

c) immune mediated therapies, including inhibitors of the immune checkpoint blockade such as CTLA4, PD-1 and PDL-1 targeted therapies.

20. A kit of parts comprising:

a) a lyophilized pharmaceutical composition comprising nanoparticles as claimed in any one of claims 1 to 10; and

b) instructions for use.

21. A process for preparing a therapeutic nanoparticle as claimed in claim 1, said process comprising:

1) combining a first organic phase which comprises a polymer in ethyl acetate, AZD1152 hqpa in a TFA/water/benzyl alcohol solvent system and pamoic acid in DMSO; with a first aqueous solution comprising a surfactant such as sodium cholate or polyoxyethylene (100) stearyl ether, in water and benzyl alcohol to form a second phase;

2) emulsifying the second phase to form an emulsion;

3) quenching of the emulsion phase at <5 °C thereby forming a quenched phase, wherein quenching of the emulsion phase comprises mixing the emulsion phase with a second aqueous solution having a pH between 4 and 7;

4) adding an aqueous surfactant solution;

5) concentrating and isolating the resulting nanoparticles by filtration.

22. A process as claimed in claim 21, comprising

1) combining a first organic phase which comprises a polymer in ethyl acetate, AZD1152 hqpa in a TFA/water/benzyl alcohol solvent system and pamoic acid in DMSO, with a first aqueous solution comprising a surfactant such as sodium cholate or polyoxyethylene (100) stearyl ether, in water, DMSO and benzyl alcohol, to form a second phase;

2) emulsifying the second phase to form a coarse emulsion;

3) holding the coarse emulsion for a hold time;

4) forming a nano-emulsion using a high pressure homogenizer;

5) optionally waiting for a delay time of at least 5 minutes;

6) quenching of the emulsion phase at 0-5 °C thereby forming a quenched phase, wherein quenching of the emulsion phase comprises mixing the emulsion phase with a second aqueous solution comprising a buffer having a pH between 4 and 7, such as pH 6.5;

7) adding an aqueous surfactant solution;

8) concentrating and isolating the resulting nanoparticles by filtration.

23. A process as claimed in claim 22 comprising:

1) combining a first organic phase which comprises a 16/5 PLA-PEG copolymer, AZD1152 hqpa and pamoic acid in a solvent mixture comprising TFA, benzyl alcohol, DMSO and ethyl acetate such that the benzyl alcohol: ethyl acetate are present in a molar ratio of 1:3.6, with a first aqueous solution comprising a surfactant such polyoxyethylene (100) stearyl ether, in water, DMSO and benzyl alcohol, to form a second phase;

2) emulsifying the second phase to form a coarse emulsion;

3) holding the coarse emulsion for a hold time;

4) forming a nano-emulsion using a high pressure homogenizer;

5) optionally waiting for a delay time of at least 5 minutes;

6) quenching of the emulsion phase at 0-5 °C thereby forming a quenched phase, wherein quenching of the emulsion phase comprises mixing the emulsion phase with a second aqueous solution comprising buffer at pH 6.5;

7) adding an aqueous surfactant solution as a solubilizer;

8) concentrating and isolating the resulting nanoparticles by filtration.

24. A process as claimed in claim 23, wherein the pamoic acid and AZD1152 hqpa are added at an initial ratio of 0.8 moles pamoic acid: 1 mole AZD1152 hqpa.