

CLAIMS

1. A method for predicting the response of a subject diagnosed with cancer to an anti-cancer treatment that comprises the use of an agent that target the DNA damage
5 response of the cancer cells, wherein the agent that targets the DNA damage response is a PARP inhibitor, comprising:
determining the relative level of cells with RAD51 foci with respect to the number of cells in the sample that are proliferating in a sample containing tumor cells isolated from said subject wherein the subject has not received, at 24 hours
10 prior to the isolation of the sample, a chemotherapy selected from the group consisting of adriamycin/cyclophosphamide (AC), 5-fluorouracil/epirubicin/cyclophosphamide (FEC), epirubicin/cisplatin/5-fluorouracil (ECF) and navelbine/epirubicin, and wherein the sample has not
15 been treated with a method that induces DNA damage before determining the level of cells with RAD51 foci,
wherein:
 - a relative level of cells with RAD51 foci with respect to the number of cells in the sample that are proliferating lower than 20% indicates that the subject is predicted to respond to the anti-cancer treatment, or
 - 20 - a relative level of cells with RAD51 foci with respect to the number of cells in the sample that are proliferating of 20% or higher indicates that the subject is predicted not to respond to the anti-cancer treatment.
2. A method for selecting a customized therapy for a subject diagnosed with cancer,
25 comprising:
determining the relative level of cells with RAD51 foci with respect to the number of cells in the sample that are proliferating in a sample containing tumor cells isolated from said subject, wherein the subject has not received, at 24 hours
prior to the isolation of the sample, a chemotherapy selected from the group
30 consisting of AC, FEC, ECF and navelbine/epirubicin, and wherein the sample has not been treated with a method that induces DNA damage before determining the level of cells with RAD51 foci,

wherein:

- a relative level of cells with RAD51 foci with respect to the number of cells that are proliferating lower than 20% indicates that the therapy to be selected comprises the use of an agent that target the DNA damage response of the cancer cells, wherein the agent that targets the DNA damage response is a PARP inhibitor, or
- a relative level of cells with RAD51 foci with respect to the number of cells that are proliferating equal or higher than 20% indicates that the therapy to be selected does not comprise the use of an agent that target the DNA damage response of the cancer cells, wherein the agent that targets the damage response is a PARP inhibitor.

3. A method for classifying a subject diagnosed with cancer into a patient cohort, comprising:

- determining the relative level of cells with RAD51 foci with respect to the number of cells in the sample that are proliferating in a sample containing tumor cells isolated from said subject wherein the subject has not received, at 24 hours prior to the isolation of the sample, a chemotherapy selected from the group consisting of AC, FEC, ECF and navelbine/epirubicin, and wherein the sample has not been treated with a method that induces DNA damage before determining the level of cells with RAD51 foci,

wherein:

- a patient is classified into a cohort characterized by responding to an anti-cancer treatment if the relative level of cells with RAD51 foci with respect to the number of cells in the sample that are proliferating is lower than 20%, or
- a patient is classified into a cohort characterized by not responding to an anti-cancer treatment if the relative level of cells with RAD51 foci with respect to the number of cells in the sample that are proliferating is higher than 20%,

wherein the anti-cancer treatment comprises the use of an agent that targets the DNA damage response of the cancer cells, wherein the agent that targets the DNA damage response is a PARP inhibitor.

- 5 4. A method for predicting whether a tumor from a subject diagnosed with cancer is capable of DNA repair by homologous recombination:
- determining the relative level of cells with RAD51 foci with respect to the number of cells in the sample that are proliferating in a tumor sample, wherein the tumor has been isolated from a subject that has not received, at 24 hours
10 prior to the isolation of the tumor, a chemotherapy selected from the group consisting of AC, FEC, ECF and navelbine/epirubicin, and wherein the sample has not been treated with a method that induces DNA damage before determining the level of cells with RAD51 foci,
 wherein:
- 15 - a level of cells with RAD51 foci with respect to the number of cells in the sample that are proliferating lower than 20% is indicative that the tumor is capable of DNA repair by homologous recombination, or
 - a level of cells with RAD51 foci with respect to the number of cells in the sample that are proliferating equal or higher than 20% is indicative
20 that the tumor is not capable of DNA repair by homologous recombination.
5. The method according to any of claims 1 to 4 wherein the number of cells in the sample that are proliferating is determined by determining the expression of a protein
25 selected from the list consisting of Geminin, KI-67, Proliferating cell nuclear antigen, Cyclin A2.
6. The method according to claim 5 wherein the selected protein is Geminin.

7. The method according to any of the preceding claims wherein the sample is isolated from blood, saliva, cerebrospinal fluid, urine, stool, bone marrow, a nipple aspirate, or a solid tumor biopsy.
- 5 8. The method according to any of the preceding claims wherein the sample is provided as a fixed tissue, paraffin embedded tissue, histological slide, cell suspension, cell pellet, cell slide and/or frozen solid tumor biopsy.
9. The method according to any of the preceding claims wherein the determination
10 of the RAD51 foci, the determination of markers of proliferating cells and/or the determination of markers of cells that show double strand DNA breaks is determined by immunofluorescence or by immunohistochemistry.
10. The method according to any of claims 1, 2 and 5 to 9 as far as they depend from
15 claims 1 and 2, wherein the anti-cancer treatment comprises the use of surgery.
11. The method according to any of the preceding claims wherein the tumor cells are characterized by a loss of function of at least one protein involved in the DNA damage response of the cell.
20
12. The method according to claim 11 wherein at least one protein involved in the DNA damage response is selected from the group consisting of BRCA1, BRCA2 and/or PALB2.
- 25 13. The method according to any of the preceding claims, wherein the cancer diagnosed in the subject is selected from the list consisting of breast cancer, ovarian cancer, pancreatic cancer, prostate cancer, lung cancer, colorectal cancer, stomach/gastric cancer, endometrial/uterine/cervical cancer, bladder cancer, head and neck cancer, sarcoma, cholangiocarcinoma, glioblastoma, leukemia, multiple myeloma,
30 lymphoma.

14. The method according to any of the preceding claims wherein the subject from whom the sample has been isolated has not received any anti-cancer treatment before the sample is isolated.

5 15. The method according to any of claims 1 to 14 wherein the subject from whom the sample has been isolated has received an anti-cancer treatment before the isolation of the sample, wherein the anti-cancer treatment is different from a chemotherapy selected from the group consisting of AC, FEC, ECF and navelbine/epirubicin if the patient has received the anti-cancer treatment at 24 hours prior to the isolation of the
10 sample.

16. The method according to claim 15 wherein the anti-cancer treatment is the anti-cancer treatment the response to which is being determined in the method according to any of claims 1, and 5 to 15 as far as they depend from claim 1.

15

17. The use of a PARP inhibitor agent in the manufacture of a medicament for the treatment of a cancer in a subject, wherein the subject has been identified as responder to said medicament by a method as defined in any of claims 1, and 5 to 16 in as far as they depend from claim 1.

20

18. The use according to claim 17 wherein the PARP inhibitor agent is selected from the list consisting of olaparib, veliparib, talazoparib, rucaparib, niraparib, CEP-8983, E7016 and BGB-290.

25 19. The use according to claim 17 or 18, wherein the treatment, in addition to the administration of the medicament, comprises surgery, immunotherapy, chemotherapy, radiotherapy or a combination thereof and wherein the subject has been identified as responder to said medicament by a method as defined in any of claims 1, and 5 to 16 in as far as they depend from claim 1.

30

20. The use of a PARP inhibitor agent in the manufacture of a medicament for the treatment of a cancer in a subject, wherein the treatment has been selected by a method as defined in any of claims 2, and 5 to 16.
- 5 21. The use according to claim 20 wherein the PARP inhibitor agent is selected from the list consisting of olaparib, veliparib, talazoparib, rucaparib, niraparib, CEP-8983, E7016 and, BGB-290.
- 10 22. The use according to claim 20 or 21, wherein the treatment, in addition to the administration of the medicament, comprises surgery, immunotherapy, chemotherapy, radiotherapy or a combination thereof and wherein the treatment has been designed by a method as defined in any of claims 2 and 5 to 11.
- 15 23. Use of a kit in the method referred in any of claims 1 to 16, wherein the kit comprises an antibody that is capable of specifically recognizing the RAD51 protein.
- 20 24. The use according to claim 23 wherein the kit further comprises an antibody selected from the group consisting of an antibody capable of specifically recognizing the Geminin protein, and an antibody capable of specifically recognizing the γ H2AX protein or a combination thereof.