three anti-PD-L1 inhibitors, atezolizumab, avelumab, and durvalumab, for the treatments of different types of cancer.

As the use of ICIs increases, the adverse events related to this class of drugs have become an important issue. ICIs have a different toxicity profile than conventional cytotoxic chemotherapy. The side effects associated with the increased activity of the immune system by ICIs, known as immune-related adverse events (irAEs), can affect multiple organs of the body including skin, gastrointestinal tract, endocrine system, liver, lung, nervous systems, and musculoskeletal systems.

Combined immune checkpoint-inhibitor therapy, for example with anti-CTLA4 and anti-PD-1 antibodies is an efficient first-line treatment for malignant melanoma. However, approximately 50% of the patients develop serious immune-related adverse events (irAE)[1,2]. Autoimmune colitis occurs in 20% of the cases and can become corticosteroid-refractory[3].

In summary, although checkpoint-inhibitor therapy, in particular with anti-CTLA4 and anti-PD-1 antibodies, is an effective treatment for multiple forms of cancer, in particular malignantn melanoma, the treatment can be associated with substantial side effects that may result from the activation of the immune system due to checkpoint inhibitor treatment. Such side effects can result in autoimmune reactions and manifest in different clinical symptoms and may be summarized as irAE. A prominent irAE is autoimmune colitis. The side effects of the treatment, such as autoimmune reactions, in particular autoimmune colitis can persist even after the checkpoint inhibitor treatment has been stopped.

Accordingly, there is a need in the art for alternative or improved means for treating immune-related adverse events, such as autoimmune reactions and in particular autoimmune colitis in a patient that has received checkpoint-inhibitor therapy.

SUMMARY ~~OF THE INVENTION~~

In light of the prior art the technical problem underlying the present ~~invention~~ disclosure is to provide improved or alternative means for treating and/or preventing immune-related adverse events, such as autoimmune reactions and in particular autoimmune colitis in a patient that has received checkpoint-inhibitor therapy.

This problem is solved by the features of the independent claims. Preferred ~~embodiments~~ examples of the present ~~invention~~ disclosure are provided by the dependent claims.

In a first aspect, the ~~invention~~ disclosure relates to a method comprising the steps of

- provision of a sample derived from a blood sample of a subject that has received a checkpoint-inhibitor therapy and is suspected of developing or has developed symptoms of immune-related adverse events (irAE),
- adding a photosensitizing agent to the sample and
- subjecting the sample to irradiation.

The present ~~invention~~ disclosure is based on the entirely surprising finding that patients that have received a checkpoint-inhibitor therapy, for example due to a cancerous disease, which led to irAE, such as in particular autoimmune colitis, can be effectively treated by applying ECP. The ECP that was used in the examples basically corresponds to a method of adding a photosensitizing agent to a blood-derived sample of an irAE patient and subjecting the sample to irradiation. Surprisingly, it was found that preforming this method on a blood sample, such as in particular a blood sample comprising mononuclear cells (MNCs) leads to the generation of immunoregulatory NK cells in said sample. In this context, “generation of” immunoregulatory NK cells is understood as inducing or inducing the formation of such cells in the sample. In other words, cells that are comprised in the sample differentiate into or adopt a phenotype of immunoregulatory NK cells.

It was found that the sample resulting from the method of the ~~invention~~ disclosure and in particular the induced immunoregulatory NK cells comprised by the sample are useful for the treatment of irAE patients. It surprisingly could be shown that administration of such a sample or cells comprised in such a sample that underwent the method of the ~~invention~~ disclosure to a subject that has received a checkpoint-inhibitor therapy is effective in preventing the occurrence of irAE and even in the treatment of irAE that is already established in the subject. Importantly, the method of the ~~invention~~ disclosure can be performed on a sample of the same subject that has received the checkpoint inhibitor therapy. Therefore, the cells or the sample resulting from the method of the ~~invention~~ disclosure can be administered to the same subject that served as a blood donor and therefore the resulting sample can represent an autologous cell therapy.

As used herein, the term “subject that has received checkpoint-inhibitor therapy” includes subjects that are currently under ongoing checkpoint-inhibitor therapy, or subjects that have received a checkpoint-inhibitor therapy that was discontinued, for example after irAE symptoms occurred.

It was completely unexpected, that such a cell therapy using a sample or cells resulting from the method of the ~~invention~~ disclosure is even effective for irAE patients that are refractory to other immunosuppressive therapies, such as steroids or anti-TNF antibodies, and which continue to show symptoms of or still suffer from irAE after checkpoint-inhibitor treatment was discontinued.

As shown in the examples, the positive effect and the efficacy of the administration of a sample that underwent the method of the ~~invention~~ disclosure may be at least partially due to a modulation of NK cell function of the NK cells comprised in the sample, wherein said modulation is a result of the irradiation in presence of a photosensitizing agent. Therefore, the present ~~invention~~ disclosure also encompasses immunomodulatory NK cells for use in the treatment of and/or prevention of immune-related adverse events (irAE) in a subject that has received a checkpoint-inhibitor therapy. Preferably, the immunomodulatory NK cells were generated by subjecting blood or MNCs or NK cells from a person, preferably a subject that has received a checkpoint-inhibitor therapy and is suspected of developing or has developed irAE, to the method of the present ~~invention~~disclosure, and are subsequently used for treating a subject that has received a checkpoint-inhibitor therapy and is suspected of developing or has developed irAE, which is preferably the donor.

In a further aspect, the ~~invention~~ disclosure relates to immunoregulatory NK cells obtained from a method comprising the steps of

- provision of a sample derived from an isolated blood sample of a subject,
- adding a photosensitizing agent to the sample, and
- subjecting the sample to irradiation.

This aspect of the ~~invention~~ disclosure is based on the observation that NK cells comprised in a blood-derived sample that underwent irradiation after adding a photosensitizing adopt an immunoregulatory phenotype that is advantageous when using the resulting cells in the treatment and/or prevention of irAE. Such advantageous and beneficial properties have so far not been observed for any other NK cells in this context.

Preferably, the subjects of the ~~invention~~ disclosure are human. Preferably, the blood samples and cells of the ~~invention~~ disclosure are human.

In preferred ~~embodiments~~examples, the blood sample used for generating the immunoregulatory NK cells of the ~~invention~~ disclosure is from a subject that has received a checkpoint-inhibitor therapy and is suspected of developing or has developed symptoms of immune-related adverse events (irAE). This ~~embodiment~~ example is particularly advantageous, since the cells are autologous to said patient and there will be no adverse events that can occur upon transplantation of heterologous cells.

In another aspect, the disclosure relates to the immunoregulatory NK cells as described herein for use in therapy.

In a further aspect, the disclosure relates to a use of the immunoregulatory NK cells as described herein in the manufacture of a medicament for treatment and/or prevention of immune-related adverse events (irAE) in a subject that has received a checkpoint-inhibitor therapy.

A further ~~aspect~~ example of the ~~invention~~ disclosure is directed to immunoregulatory NK cells for use in the treatment and/or prevention of immune-related adverse events (irAE) in a subject that has received a checkpoint-inhibitor therapy. This includes subjects that are currently under ongoing checkpoint-inhibitor therapy, or subjects that have received a checkpoint-inhibitor therapy that was discontinued, for example after irAE symptoms occurred.

Preferably, the immunoregulatory NK cells for use in such a treatment or prevention have been generated by adding a photosensitizing agent to a sample derived from a blood sample of a human subject and subjecting the sample to irradiation.

Adding a photosensitizing agent to the blood-derived sample and subjecting the sample to irradiation generates or induces (the formation of) immunoregulatory NK cells in said sample.

In ~~embodiments~~examples, the photosensitizing agent is 8-methoxypsoralen. Furthermore, in ~~embodiments~~ examples the irradiation is UVA irradiation. In preferred ~~embodiments~~ examples the photosensitizing agent is 8-methoxypsoralen and the irradiation is UVA irradiation.

In the context of the ~~invention~~disclosure, irradiation is preferably preformed by means of an extracorporeal photopheresis (ECP) system. Irradiation of the blood sample can be performed using any suitable system or irradiation device known to the skilled person.

In ~~embodiments~~examples, the method of the ~~invention~~ disclosure is performed in vitro or ex vivo. As used herein, the terms in vivo and ex vivo are used synonymously. In the context of the present ~~invention~~disclosure, the terms relate to a method that is performed on a blood-derived sample that has been removed from the human body, wherein the method of the ~~invention~~ disclosure is performed on the blood-derived

sample outside the human body. To this end, blood of a donor subject is taken out of the body, meaning out of the physiological circulatory system. As used herein, an “isolated blood sample” is a sample of blood (meaning a certain volume of blood) that is removed from the circulatory system of the donor to a location outside the body of the person.

Such an isolated blood sample can be subjected or introduced into an extracorporeal photopheresis (ECP) system or an apheresis system for performing at least certain steps of the method of the invention. Therein, such a system can be an online system that is in a fluid connection with the blood circulatory system of the subject. In alternative ~~embodiments~~examples, the method can be performed offline, wherein the blood-derived sample that is subjected to irradiation is disconnected from the circulatory system of the donor subject.

Accordingly, in ~~embodiments~~examples, the method of the ~~invention~~ disclosure is an in vitro method. In ~~embodiments~~ examples of the method of the ~~invention~~disclosure, the blood sample is an isolated blood sample. In ~~embodiments~~examples, the method is an in vitro method and the blood sample is an isolated blood sample.

As used herein the term “blood sample” comprises all kinds of blood-derived samples, including blood-cell samples such as MNC samples that are generated from blood.

In ~~embodiments~~ examples of the ~~invention~~disclosure, the subject (the blood donor and/or recipient of cells) shows symptoms of or suffers from irAE. In further ~~embodiments~~examples, the subject has received checkpoint-inhibitor therapy, but the checkpoint-inhibitor therapy was discontinued after symptoms and/or manifestation of irAE occurred in said subject. In ~~embodiments~~examples, symptoms and/or manifestation of irAE occurred in the subject after the checkpoint-inhibitor therapy was discontinued. In ~~embodiments~~examples, symptoms and/or manifestation of irAE were maintained after the checkpoint-inhibitor therapy was discontinued.

In ~~embodiments~~ examples of the ~~invention~~disclosure, where the subject that has received a checkpoint-inhibitor therapy and is suspected of developing or has developed symptoms of irAE serves as a blood donor, provision and/or isolation of the blood sample can occur at any of the time points described in the ~~embodiments~~ examples above. For example, sample isolation can occur prior to or after development of irAE symptoms. Furthermore, sample isolation can occur during checkpoint-inhibitor therapy or after discontinuation of said therapy.

In preferred ~~embodiments~~ examples of the ~~invention~~disclosure, the sample resulting from the method of the ~~invention~~ disclosure or the NK cells for use according to the present ~~invention~~ disclosure are administered to the subject while checkpoint-inhibitor therapy is ongoing.

In preferred ~~embodiments~~examples, sample isolation occurs during ongoing checkpoint-inhibitor therapy, either before or after occurrence of irAE symptoms. The sample or cells resulting from the method of the examples can be used preventively or therapeutically by administering the sample/cells to the subject during ongoing checkpoint-inhibitor therapy. Accordingly, in preferred ~~embodiments~~ examples of the ~~invention~~disclosure, the subject that has received checkpoint-inhibitor therapy can receive immunoregulatory NK cells, which are preferably autologous and have been generated by irradiating a blood-derived sample according to a method described herein, while checkpoint-inhibitor therapy is ongoing. Such ~~embodiments~~ examples are particularly advantageous, since checkpoint-

inhibitor therapy, such as an anti-cancer checkpoint inhibitor therapy, can be maintained, while the patient receives cells of the invention and/or cells resulting from the method of the ~~invention~~disclosure.

Accordingly, in such ~~embodiments~~ examples a checkpoint-inhibitor therapy can be administered to the subject for a longer period, since the administration of the irradiated cells either prevents the occurrence of irAE or ameliorates irAE so that the checkpoint-inhibitor therapy can be continued. It could surprisingly be shown that administration of such cells resulting from a method of the disclosure~~invention~~, in particular immunomodulatory NK cells of the disclosure~~invention~~, does not interfere with the anti-cancer response of the subject to the checkpoint-inhibitor therapy. This represents an important advantage in comparison to known treatments/preventive measures of irAE, in particular administration of immunosuppressive drugs, such as corticosteroids. It surprisingly turned out that performing ECP did not notably alter the anti-cancer effect of checkpoint-inhibitor therapy, while parallel administration of glucocorticoids (specific class of corticosteroids), in particular prednisolone, resulted in a worse outcome, indicating an reduced effectivity of the checkpoint-inhibitor treatment.

Furthermore, in ~~embodiments~~ examples where a (human) blood-derived sample that underwent a method of adding a photosensitizing agent to the sample and subjecting the sample to irradiation is used in the treatment and/or prevention of irAE in a subject that has received a checkpoint-inhibitor therapy, irrespective of the source of the blood-derived sample (autologous or heterologous), the administration of the sample or cells resulting from such a method can occur, for example, prior to or after development of irAE symptoms, and/or during the checkpoint-inhibitor therapy or after discontinuation of the checkpoint-inhibitor therapy.

In ~~embodiments~~ examples of the ~~invention~~disclosure, the irAE (of a blood-donor and/or of recipient of cells) comprise symptoms of an autoimmune disease and/or is caused by an autoimmune reaction. In preferred ~~embodiments~~examples, the irAE comprise or are autoimmune colitis.

In ~~embodiments~~examples, the irAE comprise at least one irAE selected from the group comprising autoimmune colitis, autoimmune hepatitis, autoimmune thyroiditis and autoimmune dermatitis.

In ~~embodiments~~examples, the irAE comprise at least one irAE selected from the group comprising immune checkpoint inhibitor-related colitis, immune checkpoint inhibitor-related hepatitis, immune checkpoint inhibitor-related thyroiditis and immune checkpoint inhibitor-related dermatitis.

In ~~embodiments~~examples, the subject (blood-donor and/or of recipient of cells) suffers from cancer, such as malignant melanoma or another cancer treatable by checkpoint-inhibitor therapy.

In ~~embodiments~~examples, the subject is receiving immunosuppressive drugs, such as steroids, corticosteroid, cyclosporine and/or anti-TNF antibodies (for example infliximab) and/or is refractory to immunosuppressive drugs.

It was entirely surprising, that administration of cells that resulted from the methods described herein, such as immunoregulatory NK cells, have a therapeutic effect on irAE patients that are refractory to immunosuppressive drugs that have been administered for treating the irAE symptoms. For such patients, there is no effective treatment available for ameliorating irAE

symptoms and the present ~~invention~~ disclosure therefore represents a completely unexpected possibility of treating irAE in these patients.

In ~~embodiments~~examples, the checkpoint-inhibitor therapy comprises administration of at least one of anti-CTLA4 antibodies and anti-PD-1 antibodies.

In ~~embodiments~~examples, the immunoregulatory NK cells for use in the treatment and/or prevention of irAE in a subject that has received a checkpoint-inhibitor therapy are autologous with respect to said subject. In alternative ~~embodiment~~example, the NK cells may be heterologous with respect to said subject.

In ~~embodiments~~examples, the immunoregulatory NK cells for use according to the present ~~invention~~ disclosure are administered upon occurrence of irAE symptoms. In ~~embodiments~~examples, the cells are administered 1, 2, 3, 4, 5, 6 or 7 days or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 35, 40, 45 or 50 weeks after occurrence of irAE symptoms. In ~~embodiments~~examples, the immunoregulatory NK cells are administered during checkpoint-inhibitor therapy is ongoing or after the checkpoint-inhibitor therapy was discontinued.

In ~~embodiments~~examples, the immunoregulatory NK cells are administered are administered at least once to the subject, preferably at least twice, preferably on consecutive days. Accordingly, the subject may receive more than one dose of NK cells, wherein preferably not more than one dose per day is administered. In further ~~embodiments~~examples, the subject receives at least 2, 3, 4 or 5 dosages of NK cells of the invention. In embodiments, the immunoregulatory NK cells of the ~~invention~~ disclosure are administered to the subject at least every 8 weeks, preferably every 2-4 weeks.

Each optional or preferred feature of the ~~invention~~ disclosure that is disclosed or described in the context of one ~~aspect~~ example of the ~~invention~~ disclosure is herewith also disclosed in the context of the other ~~aspects~~ examples of the ~~invention~~ disclosure described herein.

Furthermore, the ~~invention~~ disclosure also relates to the following ~~embodiments~~examples:

1. An extracorporeal photopheresis (ECP) system for use in the treatment and/or prevention of immune-related adverse events (irAE) in a subject that has received a checkpoint-inhibitor therapy, wherein ECP is preferably performed with administration of 8-Methoxypsoralen.

The present ~~invention~~ disclosure is based on the entirely surprising finding that patients that have received a checkpoint-inhibitor therapy, for example due to a cancerous disease, which led to irAE, such as in particular autoimmune colitis, can be effectively treated by applying ECP. This is even true for patients that are refractory to other immunosuppressive therapies, such as steroids or anti-TNF antibodies, and which continue to show symptoms of or still suffer from irAE after checkpoint-inhibitor treatment was discontinued.

Surprisingly, it turned out that the positive effect and the efficacy of ECP treatment resulted in particular from the modulation of NK cell function after ECP. Accordingly, the present disclosure~~invention~~ in particular also relates to immunomodulatory NK cells for use in the treatment of and/or prevention of immune-related adverse events (irAE) in a subject that has received a checkpoint-inhibitor

therapy, wherein the immunomodulatory NK cells were generated by subjecting blood or MNCs or NK cells from a person, preferably the subject of the disclosure~~invention~~, to an ECP treatment.

2. ECP system for use according to the disclosure~~invention~~, wherein the ECP system is an online ECP system.

3. ECP system for use according to the disclosure~~invention~~, wherein the ECP system is an offline ECP system.

4. ECP system for use according to the disclosure~~invention~~, wherein the subject shows symptoms of or suffers from irAE.

5. ECP system for use according to the disclosure~~invention~~, wherein the checkpoint-inhibitor therapy was discontinued after symptoms and/or manifestation of irAE occurred in said subject.

6. ECP system for use according to the disclosure~~invention~~, wherein symptoms and/or manifestation of irAE occurred after the checkpoint-inhibitor therapy was discontinued.

7. ECP system for use according to the disclosure~~invention~~, wherein symptoms and/or manifestation of irAE were maintained after the checkpoint-inhibitor therapy was discontinued.

8. ECP system for use according to any the disclosure~~invention~~, wherein the ECP treatment is initiated upon occurrence of irAE symptoms.

9. ECP system for use according to the disclosure~~invention~~, wherein the ECP treatment is initiated 1, 2, 3, 4, 5, 6 or 7 days or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 35, 40, 45 or 50 weeks after occurrence of irAE symptoms.

10. ECP system for use according to any the disclosure~~invention~~, wherein ECP treatment is initiated during checkpoint-inhibitor therapy is ongoing or after the checkpoint-inhibitor therapy was discontinued.

11. ECP system for use according to the disclosure~~invention~~, wherein ECP treatment comprises at least 1, preferably at least 2 cycles of ECP preferably on consecutive days.

12. ECP system for use according to the disclosure~~invention~~, wherein ECP treatment is performed at least 2, 3, 4 or 5 times.

13. ECP system for use according to the disclosure~~invention~~, wherein ECP treatment is performed at least every 8 weeks, preferably every 2-4 weeks.

14. ECP system for use according to the disclosure~~invention~~, wherein the irAE comprise symptoms of an autoimmune disease.

15. ECP system for use according to the disclosure~~invention~~, wherein the irAE is caused by an autoimmune reaction.

16. ECP system for use according to the disclosure~~invention~~, wherein the irAE comprise at least one irAE selected from the group comprising autoimmune colitis, autoimmune hepatitis, autoimmune thyroiditis and autoimmune dermatitis.

17. ECP system for use according to the disclosure~~invention~~, wherein the irAE comprise at least one irAE selected from the group comprising immune checkpoint inhibitor-related colitis, immune checkpoint inhibitor-related hepatitis, immune checkpoint inhibitor-related thyroiditis and immune checkpoint inhibitor-related dermatitis.

18. ECP system for use according to the disclosure~~invention~~, wherein the irAE comprise autoimmune colitis.

19. ECP system for use according to the disclosure~~invention~~, wherein the irAE is autoimmune colitis.

20. ECP system for use according to the disclosure~~invention~~, wherein the subject is a human.

21. ECP system for use according to the disclosure~~invention~~, wherein the subject suffers from cancer, such as malignant melanoma or another cancer treatable by checkpoint-inhibitor therapy.

22. ECP system for use according to the disclosure~~invention~~, wherein the subject is receiving immunosuppressive drugs, such as steroids, corticosteroid, cyclosporine and/or anti-TNF antibodies (for example infliximab).

23. ECP system for use according to the disclosure~~invention~~, wherein the subject is refractory to immunosuppressive drugs, such as steroids, corticosteroid, cyclosporine and/or anti-TNF antibodies (for example infliximab).

24. ECP system for use according to the disclosure~~invention~~, wherein the checkpoint-inhibitor therapy comprises administration of at least one of anti-CTLA4 antibodies and anti-PD-1 antibodies.

25. ECP system for use according to the disclosure~~invention~~, wherein the ECP system is used for performing blood irradiation therapy.

26. ECP system for use according to the disclosure~~invention~~, wherein the ECP system comprises immunomodulatory molecules, preferably coupled to a membrane of the ECP system, wherein the immunomodulatory molecules contact immune cells of the subject.

27. In vitro method comprising the steps of

    - provision of a sample derived from an isolated blood sample of a subject that has received a checkpoint-inhibitor therapy and is suspected of developing or has developed symptoms of immune-related adverse events (irAE),

    - subjecting said sample to extracorporeal photopheresis.

28. Method of treating a subject that has received a checkpoint-inhibitor therapy and is suspected of developing or has developed symptoms of immune-related adverse events (irAE), the method comprising subjecting said subject to an extracorporeal photopheresis (ECP) therapy (ECP), such as blood irradiation therapy by means of an ECP system.

29. Immunoregulatory NK cells for use in the treatment and/or prevention of immune-related adverse events (irAE) in a subject that has received a checkpoint-inhibitor therapy.

30. Immunoregulatory NK cells for use according to the disclosure~~invention~~, wherein the immunoregulatory NK cells have been generated by subjecting a human blood sample or cells comprised in a human blood sample to extracorporeal photopheresis.

31. Immunoregulatory NK cells for use according to the disclosure~~invention~~, wherein the NK cells are autologous or heterologous with respect to said subject.

32. Immunoregulatory NK cells for use according to the disclosure~~invention~~, wherein the NK cells are administered to said subject intravenously.

33. Immunoregulatory NK cells for use according to the disclosure~~invention~~, wherein the NK cells are isolated from the human blood sample prior to or after subjection to extracorporeal photopheresis.

All features disclosed in the context of the ECP system for use in the treatment and/or prevention of immune-related adverse events (irAE) in a subject that has received a checkpoint-inhibitor therapy of the ~~invention~~ disclosure also relate to and are herewith disclosed also in the context of the in vitro method of the disclosure~~invention~~, the method of treatment of the disclosure~~invention~~ and the NK cells for use in the treatment and/or prevention of immune-related adverse events (irAE) in a subject that has received a checkpoint-inhibitor therapy of the disclosure~~invention~~, and vice versa.

DETAILED DESCRIPTION OF THE INVENTION

All cited documents of the patent and non-patent literature are hereby incorporated by reference in their entirety.

Disclosed herein are methods comprising the steps of provision of a sample derived from a blood sample of a subject, preferably a subject that has received a checkpoint-inhibitor therapy and is suspected of developing or has developed symptoms of immune-related adverse events (irAE), adding a photosensitizing agent to the sample and subjecting the sample to irradiation. Irradiation of the blood sample can be performed using any suitable system or irradiation device known to the skilled person. Preferably, irradiation is performed by means of an extracorporeal photopheresis (ECP) system.

The present invention also relates to an extracorporeal photopheresis (ECP) system for use in the treatment and/or prevention of immune-related adverse events (irAE) in a subject that has received a checkpoint-inhibitor therapy, wherein ECP is preferably performed with administration of 8-Methoxypsoralen.

Irradiation and Extracorporeal photopheresis (ECP)

Photopheresis, or extracorporeal photopheresis or ECP, is a form of apheresis and photodynamic therapy in which blood is treated with a photosensitizing agent and subsequently irradiated with specified wavelengths of light to achieve an effect. For example, buffy coat (WBC + platelets) can be separated from whole blood, chemically treated with 8-methoxypsoralen (instilled into collection bag or given per os in advance), exposed to ultraviolet light (UVA), and returned to the patient. Activated 8-methoxypsoralen crosslinks DNA in exposed cells, ultimately resulting

CLAIMS

1. A method comprising the steps of

    - provision of a sample derived from a blood sample of a subject that has received a checkpoint-inhibitor therapy and is suspected of developing or has developed symptoms of immune-related adverse events (irAE),
    - adding a photosensitizing agent to the sample and
    - subjecting the sample to irradiation.

2. The method according to claim 1, wherein adding a photosensitizing agent to the sample and subjecting the sample to irradiation generates or induces (the formation of) immunoregulatory NK cells in said sample.

3. The method according to any one of the preceding claims, wherein the photosensitizing agent is 8-methoxypsoralen and/or the irradiation is UVA irradiation.

4. The method according to any one of the preceding claims, wherein the subject shows symptoms of or suffers from irAE.

5. The method according to any one of the preceding claims, wherein the checkpoint-inhibitor therapy was discontinued after symptoms and/or manifestation of irAE occurred in said subject, or wherein symptoms and/or manifestation of irAE occurred after the checkpoint-inhibitor therapy was discontinued, and/or wherein symptoms and/or manifestation of irAE were maintained after the checkpoint-inhibitor therapy was discontinued.

6. The method according to any one of the preceding claims, wherein the irAE comprise symptoms of an autoimmune disease and/or is caused by an autoimmune reaction.

7. The method according to any one of the preceding claims, wherein the irAE comprise autoimmune colitis.

8. The method according to any one of the preceding claims, wherein the subject suffers from cancer, such as malignant melanoma or another cancer treatable by checkpoint-inhibitor therapy.

9. The method according to any one of the preceding claims, wherein the subject is receiving immunosuppressive drugs, such as steroids, corticosteroid, cyclosporine and/or anti-TNF antibodies (for example infliximab) and/or is refractory to immunosuppressive drugs.

10. The method according to any one of the preceding claims, wherein the checkpoint-inhibitor therapy comprises administration of at least one of anti-CTLA4 antibodies and anti-PD-1 antibodies.

11. Immunoregulatory NK cells obtained from a method comprising the steps of

    - provision of a sample derived from an isolated blood sample of a subject,
    - adding a photosensitizing agent to the sample, and

- subjecting the sample to irradiation.

12. Immunoregulatory NK cells according to the preceding claim, wherein the blood sample is from a subject that has received a checkpoint-inhibitor therapy and is suspected of developing or has developed symptoms of immune-related adverse events (irAE).

13. The immunoregulatory NK cells according to claim 11 or 12 for use in therapy.

~~13.~~14. Use of the ~~i~~immunoregulatory NK cells according to claim 11 or 12 ~~for use~~ in the manufacture of a medicament for treatment and/or prevention of immune-related adverse events (irAE) in a subject that has received a checkpoint-inhibitor therapy.

~~14.~~15. The ~~Immunoregulatory NK cells for~~ use according to the preceding claim, wherein the immunoregulatory NK cells have been generated by adding a photosensitizing agent to a sample derived from a blood sample of a human subject and subjecting the sample to irradiation.

~~15.~~16. The ~~Immunoregulatory NK cells for~~ use according to any of claims ~~13~~ 14 or ~~14~~15, wherein the NK cells are autologous with respect to said subject, and/or wherein the NK cells are to be administered to the subject while checkpoint-inhibitor therapy is ongoing.