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

In light of the prior art the technical problem underlying the present 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 examples of the present disclosure are provided by the dependent claims.

In one aspect, the disclosure relates to a method of obtaining immunoregulatory NK cells 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), wherein the irAE comprises autoimmune colitis,
- adding 8-methoxypsoralen to the sample, and
- subjecting the sample to UVA irradiation.

In one aspect, the disclosure relates to the use of immunoregulatory NK cells in the manufacture of a medicament for treatment and/or prevention of immune-related adverse events (irAE) comprising autoimmune colitis in a subject that has received a checkpoint-inhibitor therapy, wherein the immunoregulatory NK cells are obtained from a method comprising the steps of

- provision of a sample derived from an isolated blood sample of a subject,
- adding 8-methoxypsoralen to the sample, and
- subjecting the sample to UVA irradiation.

In a first example, the 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.

In a further example, the 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 example of the 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 disclosure are human. Preferably, the blood samples and cells of the disclosure are human.

In preferred examples, the blood sample used for generating the immunoregulatory NK cells of the 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 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.

A further example of the 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 examples, the photosensitizing agent is 8-methoxypsoralen. Furthermore, in examples the irradiation is UVA irradiation. In preferred examples the photosensitizing agent is 8-methoxypsoralen and the irradiation is UVA irradiation.

CLAIMS

1. A method of obtaining immunoregulatory NK cells 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), wherein the irAE comprises autoimmune colitis,
    - adding 8-methoxypsoralen to the sample, and
    - subjecting the sample to UVA 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 subject shows symptoms of or suffers from irAE.
4. 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.
5. The method according to any one of the preceding claims, wherein the subject suffers from cancer.
6. The method according to claim 5, wherein the cancer is malignant melanoma or another cancer treatable by checkpoint-inhibitor therapy.
7. The method according to any one of the preceding claims, wherein the subject is receiving an immunosuppressive drug.
8. The method of claim 7, wherein the immunosuppressive drug is a steroid, a corticosteroid, a cyclosporine and/or an anti-TNF antibody.
9. The method of claim any one of the preceding claims, wherein the subject 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. Use of immunoregulatory NK cells in the manufacture of a medicament for treatment and/or prevention of immune-related adverse events (irAE) comprising autoimmune colitis in a subject that has received a checkpoint-inhibitor therapy, wherein the immunoregulatory NK cells are obtained from a method comprising the steps of
    - provision of a sample derived from an isolated blood sample of a subject,

- adding 8-methoxypsoralen to the sample, and
- subjecting the sample to UVA irradiation.

12. The use 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 use according to any one of claims 11-12, 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.