SUMMARY

[0006a] In one aspect, the present disclosure refers to a method of determining whether a subject suffering from natural killer/T-cell lymphoma will respond to PD-1 blockade therapy, the method comprising detecting the presence or absence of at least one JAK3 activating mutation or at least one PD-L1 structural rearrangement in a sample obtained from the subject; wherein the presence of at least one JAK activating mutation or at least one PD-L1 structural rearrangement indicates that the subject will respond to PD-1 blockade therapy, wherein the PD- 1 blockade therapy is optionally pembrolizumab treatment. In another aspect, the present disclosure refers to a kit for detecting the presence or absence of at least one JAK3 activating mutation or at least one PD-L1 structural rearrangement comprising a detection agent, and at least one pair of primers; wherein the at least pair of primers are selected from the group consisting of SEQ ID NO: 1 and 2, SEQ ID NO: 3 and 4, SEQ ID NO: 5 and 6, SEQ ID NO: 7 and 8, SEQ ID NO: 9 and 10, SEQ ID NO: 11 and 12, SEQ ID NO: 13 and 14, SEQ ID NO: 15 and 16, SEQ ID NO: 17 and 18, SEQ ID NO: 19 and 20, SEQ ID NO: 21 and 22, SEQ ID NO: 23 and 24, SEQ ID NO: 25 and 26, SEQ ID NO: 27 and 28, SEQ ID NO: 29 and 30, SEQ ID NO: 31 and 32, SEQ ID NO: 33 and 34, SEQ ID NO: 35 and 36, SEQ ID NO: 37 and 38, SEQ ID NO: 39 and 40¸ SEQ ID NO: 41 and 42¸ SEQ ID NO: 43 and 44, SEQ ID NO: 45 and 46, and SEQ ID NO: 47 and 48.

[0007] In one example, the present disclosure refers to a method of treating natural killer/T-cell lymphoma in a subject, the method comprising administering to a subject a therapeutically effective amount of pembrolizumab, wherein the subject is characterised by the presence of at least one JAK3-activating mutation or at least one PD-L1 structural rearrangement.

[0008] In another example, the present disclosure refers to a method of determining response of a subject suffering from natural killer/T-cell lymphoma to pembrolizumab treatment, the method comprising obtaining a sample from the subject; detecting the presence or absence of at least one JAK3 activating mutation or at least one PD-L1 structural rearrangement; wherein the presence of at least one JAK activating mutation or at least one PD-L1 structural rearrangement indicates that the subject will respond to pembrolizumab treatment.

[0009] In yet another example, the present disclosure refers to a kit for detecting the presence or absence of at least one JAK3 activating mutation or at least one PD-L1 structural rearrangement, the kit comprising a detection agent, and at least one pair of primers; wherein the primers enrich for the genomic regions of the JAK3 and PD-L1 genes.

[0010] In a further example, the present disclosure refers to a kit for detecting the presence or absence of at least one JAK3 activating mutation or at least one PD-L1 structural rearrangement for next-generation sequencing.

[0011] In another example, the present disclosure refers to a kit as disclosed herein for use according to the method as disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

[0013] **Fig. 1** shows genomic profiles of 11 pre-treated natural-killer/T-cell lymphoma tumours from patients who were subsequently treated with pembrolizumab. **Fig. 1A** shows a staircase plot of recurrent and mutually exclusive non-silent genomic alterations found in the 11 pairs of NKTL-normal whole-genome sequencing data. The top of the staircase plot denotes the number of non-silent mutations. **Fig. 1B** shows the schematics of the *PD-L1* structural rearrangements that were validated in this study. **Fig. 1C** shows the positron emission tomography-computed tomography frontal and side scans of an NKTL1 patient, who had achieved complete response from pembrolizumab, before and after treated with pembrolizumab.

[0014] **Fig. 2** shows the timelines of treatment for the eleven extranodal natural killer/T-cell lymphoma patients, who were administered pembrolizumab, after failing multiple lines of treatment.

[0015] **Fig. 3** refers to recurrent somatic mutated genes in the 11 pembrolizumab-treated patients' initial tumours. Precedence of ordering, from top to bottom gene, is by recurrence and mutual exclusivity of

CLAIMS

1. A method of determining whether a subject suffering from natural killer/T-cell lymphoma will respond to PD-1 blockade therapy, the method comprising detecting the presence or absence of at least one JAK3 activating mutation or at least one PD-L1 structural rearrangement in a sample obtained from the subject; wherein the presence of at least one JAK activating mutation or at least one PD-L1 structural rearrangement indicates that the subject will respond to PD-1 blockade therapy, wherein the PD- 1 blockade therapy is optionally pembrolizumab treatment.

2. The method of claim 1, wherein the subject is to be administered a compound which impedes the PD-1/PD-L1 axis.

3. The method of claim 2, wherein the compound is selected from the group consisting of nivolumab (opdivo), pembrolizumab (keytruda), atezolizumab (tecentriq), avelumab (bavencio), durvalumab (imfinzi), pidilizumab, AMP-224, AMP-514, PDR001, cemiplimab, and combinations thereof.

4. The method according to any of the preceding claims, wherein the JAK3 activating mutation is selected from the group consisting of M511I, A572V, A573V, R657Q, V722I, V674A, L857P, R403H, Q501H, E958K, and combinations thereof.

5. The method according to claim 4, wherein the JAK3 activating mutation is A573V.

6. The method according to any of the preceding claims, wherein the PD-L1 structural rearrangement is a mutation in the PD-L1 gene.

7. The method according to claim 6, wherein the mutation is selected from the group consisting of insertions, deletions, substitutions, translocations, inversions, micro-inversions, duplications, tandem repeats, breakpoint(s) (mutations), and combinations thereof.

8. The method according to any one of claims 6 to 7, wherein the mutation in the PD-L1 gene disrupts the 3’ UTR of the PD-L1 gene.

9. The method of any one of the preceding claims, wherein the natural killer/T-cell lymphoma is extranodal natural killer/T-cell lymphoma.

10. The method of any one of the preceding claims, wherein the natural killer/T-cell lymphoma is relapsed and/or refractory natural killer/T-cell lymphoma.

11. A kit for detecting the presence or absence of at least one JAK3 activating mutation or at least one PD-L1 structural rearrangement comprising a detection agent, and at least one pair of primers; wherein the at least pair of primers are selected from the group consisting of SEQ ID NO: 1 and 2, SEQ ID NO: 3 and 4, SEQ ID NO: 5 and 6, SEQ ID NO: 7 and 8, SEQ ID NO: 9 and 10, SEQ ID NO: 11 and 12, SEQ ID NO: 13 and 14, SEQ ID NO: 15 and 16, SEQ ID NO: 17 and 18, SEQ ID NO: 19 and 20, SEQ ID NO: 21 and 22, SEQ ID NO: 23 and 24, SEQ ID NO: 25 and 26, SEQ ID NO: 27 and 28, SEQ ID NO: 29 and 30, SEQ ID NO: 31 and 32, SEQ ID NO: 33 and 34, SEQ ID NO: 35 and 36, SEQ ID NO: 37 and 38, SEQ ID NO: 39 and 40¸ SEQ ID NO: 41 and 42¸ SEQ ID NO: 43 and 44, SEQ ID NO: 45 and 46, and SEQ ID NO: 47 and 48.

12. The kit according to claim 11, for next-generation sequencing.

13. The kit according to claim 11 or 12 for use according to the method according to any one of claims 1 to 10.