

Co-stimulation or the provision of two distinct signals to T-cells is a widely accepted model of lymphocyte activation of resting T lymphocytes by antigen-presenting cells (APCs). Lafferty *et al.*, *Aust. J. Exp. Biol. Med. Sci.* 53: 27-42 (1975). The mechanism of co-stimulation is of therapeutic interest because the manipulation of co-stimulatory signals has shown to provide a means to either enhance or terminate cell-based immune response. However, as an optimal therapy co-targeting CD40 and PD-L1 has yet to be commercialized, a significant unmet medical need exists.

SUMMARY

The disclosure comprises the combination therapy of an antibody which binds to human CD40 with an antibody which binds to human PD-L1 for use in the treatment of a proliferative disease, in particular cancer.

The disclosure comprises, in one aspect, a pharmaceutical product comprising A) a first component comprising as an active ingredient an antibody or an antigen-binding portion thereof that specifically binds to and activates human CD40; and B) a second component comprising as an active ingredient a PD-L1 antibody; for the combined, sequential or simultaneous, treatment of a proliferative disease, in particular cancer.

The disclosure comprises the use of an antibody, or an antigen-binding portion thereof, that specifically binds to and activates human CD40; and a PD-L1 antibody for the manufacture of a medicament for the combined, sequential or simultaneous, treatment of a proliferative disease, such as cancer preferably solid tumors.

In another aspect, the use of an antibody, or an antigen-binding portion thereof, that specifically binds to and activates human CD40; and a PD-L1 antibody for the manufacture of a medicament for the combined, sequential or simultaneous, treatment of cancer preferably solid tumors.

The disclosure further comprises a kit comprising the pharmaceutical product as defined above. The disclosure comprises, in another aspect, a kit comprising a pharmaceutical product as defined above together with instructions how to use it.

The disclosure further comprises a method of treating a patient suffering from a proliferative disease, in particular cancer, said method comprises the combined, simultaneous or sequential administration of an anti-CD40 – and a PD-L1 antibody.

- h) a heavy chain variable domain VH of SEQ ID NO:6 and a light chain variable domain VL of SEQ ID NO:15, or
- i) a heavy chain variable domain VH of SEQ ID NO:6 and a light chain variable domain VL of SEQ ID NO:16, or
- j) a heavy chain variable domain VH of SEQ ID NO:6 and a light chain variable domain VL of SEQ ID NO:17, or
- k) a heavy chain variable domain VH of SEQ ID NO:6 and a light chain variable domain VL of SEQ ID NO:18, or
- l) a heavy chain variable domain VH of SEQ ID NO:6 and a light chain variable domain VL of SEQ ID NO:19, or
- m) a heavy chain variable domain VH of SEQ ID NO:6 and a light chain variable domain VL of SEQ ID NO:20, or
- n) a heavy chain variable domain VH of SEQ ID NO:6 and a light chain variable domain VL of SEQ ID NO:21, or
- o) a heavy chain variable domain VH of SEQ ID NO:6 and a light chain variable domain VL of SEQ ID NO:22, or
- p) a heavy chain variable domain VH of SEQ ID NO:7 and a light chain variable domain VL of SEQ ID NO:23.

3. The pharmaceutical product according to claim 1 or 2, comprising A) a first component comprising as an active ingredient an antibody comprising a VL of SEQ ID NO:3 and a VH of SEQ ID NO:4; and B) a second component comprising as an active ingredient an antibody comprising a VL of SEQ ID NO:8 and a VH of SEQ ID NO:5; for the combined, sequential or simultaneous, treatment of a proliferative disease, in particular cancer.

4. The pharmaceutical product according to claim 1 to 3, wherein components A) and B) are to be administered separately.

5. The pharmaceutical product according to claim 4, wherein component A and/or B is to be administered intravenously (i.v.) or subcutaneously (s.c.).

6. The pharmaceutical product according to claim 5, wherein component A is to be administered at fixed doses between 4 and 16mg, and component B is to be administered at a fixed dose of 1200mg.
7. The pharmaceutical product according to claim 6, wherein components A and B are to be administered separately by 1 to 42 days, preferably by 1, or 7, or 14 or 21 or 42 days.
8. The pharmaceutical product according to claim 7, wherein component A is to be administered from 1 to 4 times together with component B, and subsequently treatment continues only with component B until disease progression.
9. The pharmaceutical product according to any one of claims 1 to 8 for the treatment of cancer, preferably solid tumors.
10. The use of an antibody, or an antigen-binding portion thereof, that specifically binds to and activates human CD40; and a PD-L1 antibody for the manufacture of a medicament for the combined, sequential or simultaneous, treatment of cancer preferably solid tumors.
11. The pharmaceutical product according to claim 1, further comprising as a third component (C) a cytokine inhibitor.
12. The pharmaceutical product according to claim 11, wherein the cytokine inhibitor is an anti-TNF alpha antibody.
13. A kit comprising a pharmaceutical product according to any one of claims 1 to 12 together with instructions how to use it.
14. The use of an antibody, or an antigen-binding portion thereof, that specifically binds to and activates human CD40; and a PD-L1 antibody for the manufacture of a medicament for the combined, sequential or simultaneous, treatment of leukemia, lymphoma, myelomas, breast cancer, lung cancer, colon cancer, colorectal cancer, pancreatic cancer, gastric cancer or prostate cancer.