

should particularly enable the effective targeting of the tissue affected by the inhibitor-induced adverse event in the GI tract, without requiring systemic application. In addition, there is also a need for a prophylactic treatment to prevent, or delay the onset of, adverse effects affecting the GI tract caused by treatment with ICP inhibitors; in particular for an early treatment to prevent serious complications like ileus and perforation as well as need for urgent endoscopies, hospital admissions and surgery.

SUMMARY DISCLOSURE

Surprisingly it has been found by the present inventors that by topically treating immune-related adverse events induced by ICP inhibitors in the GI tract, thereby removing the need for systemic immunosuppressive treatment, this overcomes the necessity to stop treatment with ICP inhibitors by allowing the concomitant topical treatment in the GI with immunosuppressive TNF α -specific antibodies or functional fragments thereof and systemic treatment with ICP inhibitors, thereby avoiding compromising the successful cancer treatment with the ICP inhibitors. Despite the fact that ICP inhibitors for treating cancer have been known for more than 15 years, it has never been suggested that TNF α -specific antibodies could be topically administered to treat or prevent the immune-related adverse effects of the ICP inhibitor therapy.

In one aspect, the present disclosure refers to a use of a pharmaceutical composition comprising an active agent selected from the group consisting of antibodies specific to tumour necrosis factor alpha (TNF α) and functional fragments and derivatives specific to TNF α which are a Fab fragment, a F(ab')₂ fragment, a Fab' fragment, a scFv, a dsFv, a diabody, a triabody, a tetrabody, an Fc fusion protein, a camelid antibody, a VHH, a vorabody, a VNAR or a minibody thereof, in the manufacture of a medicament for the treatment or prevention of at least one adverse event of the gastro-intestinal tract induced by a cancer therapy in a patient, ~~preferably~~ induced by one or more immune checkpoint (ICP) inhibitors, wherein said treatment or prevention comprises the topical administration of said composition to the affected part of the gastrointestinal tract of said patient, e.g. to the ileum and/or the large intestine of said patient, wherein said patient is a cancer patient and wherein the patient is also undergoing treatment with one or more ICP inhibitors.

The present disclosure provides a composition for use in the topical treatment in the ileum and/or the large intestine of ICP inhibitor-induced diarrhoea, colitis or enterocolitis. Moreover, the present disclosure provides a composition for use in the topical treatment in the ileum and/or the large intestine as a prophylactic therapy for ICP inhibitor-induced diarrhoea, colitis or enterocolitis. In particular, the present disclosure provides a composition for use in an early therapy for ICP inhibitor induced diarrhoea to prevent more severe adverse events affecting the gastrointestinal tract, such as colitis or enterocolitis.

The present disclosure therefore relates to the subject matter defined in the following items 1 to 69:

[1] A pharmaceutical composition comprising an active agent selected from the group consisting of antibodies specific to tumour necrosis factor alpha (TNF α) and functional fragments and derivatives thereof, for use in the treatment or prevention of at least one

Claims

1. Use of a pharmaceutical composition comprising an active agent selected from the group consisting of antibodies specific to tumour necrosis factor alpha (TNF α) and functional fragments and derivatives specific to TNF α which are a Fab fragment, a F(ab')₂ fragment, a Fab' fragment, a scFv, a dsFv, a diabody, a triabody, a tetrabody, an Fc fusion protein, a camelid antibody, a VHH, a vorabody, a VNAR or a minibody, thereof in the manufacture of a medicament for the treatment or prevention of at least one adverse event of the gastrointestinal tract induced by a cancer therapy in a patient, ~~preferably~~ induced by one or more immune checkpoint (ICP) inhibitors, wherein said treatment or prevention comprises the topical administration of said composition to the affected part of the gastrointestinal tract of said patient, e.g. to the ileum and/or the large intestine of said patient, wherein said patient is a cancer patient- and
- ~~2. The use according to claim 1,~~ wherein the patient is also undergoing treatment with one or more ICP inhibitors.
- ~~3.2.~~ The use according to claim 12, wherein treatment with one or more ICP inhibitors is interrupted for less than four weeks, preferably less than two weeks, more preferably one week, even more preferably less than five, four, three, two days or one day, and most preferably wherein treatment is not interrupted.
- ~~4.3.~~ The use according to any of the preceding claims, wherein said adverse event is selected from the group consisting of ICP inhibitor-induced diarrhoea, ICP inhibitor-induced colitis, ICP inhibitor-induced enterocolitis and combinations thereof.
- ~~5.4.~~ The use according to claim 43, wherein said ICP inhibitor-induced diarrhoea, colitis and/or enterocolitis is characterized by grade 1 toxicity or grade 2 toxicity.
- ~~6.5.~~ The use according to claim 43, wherein said treatment prevents progression of said ICP inhibitor-induced diarrhoea, colitis and/or enterocolitis to a higher grade toxicity.
- ~~7.6.~~ The use according to any one of the preceding claims, wherein said use comprises a prophylactic therapy for ICP inhibitor-induced diarrhoea, colitis and/or enterocolitis.
- ~~8.7.~~ The use according to claim 67, wherein the patient is at the same time undergoing treatment with one or more ICP inhibitors.

~~9.8.~~ The use according to any one of the preceding claims, wherein said patient is suffering from ICP inhibitor-induced diarrhoea, but not of ICP inhibitor-induced colitis or ICP inhibitor-induced enterocolitis, and wherein said composition is for use in preventing the development or onset of ICP inhibitor-induced colitis and/or ICP inhibitor-induced enterocolitis in said patient.

~~10.9.~~ The use according to claim ~~89~~, wherein said patient is suffering from ICP inhibitor-induced diarrhoea of grade 2 toxicity.

~~11.10.~~ The use according to claim ~~89~~, wherein said patient is suffering from ICP inhibitor-induced diarrhoea of grade 1 toxicity.

~~12.11.~~ The use according to any of the preceding claims, wherein the one or more ICP inhibitors are selected from the group consisting of antibodies specific to cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), antibodies specific to programmed cell death protein-1 (PD-1) and antibodies specific to programmed death-ligand 1 (PD-L1).

~~13.12.~~ The use according to claim ~~1112~~, wherein the antibodies specific to PD-1 are selected from the group consisting of pembrolizumab and nivolumab; the antibodies specific to PD-L1 are selected from the group consisting of atezolizumab, avelumab and durvalumab; or the antibodies specific to CTLA-4 are selected from the group consisting of ipilimumab and tremelimumab.

~~14.13.~~ The use according to any of the preceding claims, wherein the antibodies specific to TNF α and functional fragments thereof are selected from the group consisting of infliximab, adalimumab, etanercept, certolizumab pegol, golimumab, and functional fragments and derivatives thereof.

~~15.14.~~ The use according to any of the preceding claims, wherein the amino acid sequence of the antibodies specific to TNF α and functional fragments thereof comprise

- i) the amino acids 233P, 234V, 235A, and a deletion at amino acid position 236; and the amino acid 434A or the amino acids 252Y, 254T and 256E; and optionally the amino acids 239D, 330L and 332E or the amino acids 326A, 332E and 333A; and/or
 - ii) the amino acids 380A and 434A, and optionally the amino acid 307T; and/or
 - iii) the amino acid 434W, and optionally the amino acid 428E and/or the amino acid 311R,
- wherein the amino acid numbering refers to EU numbering.

~~16.15.~~ The use according to any one of the preceding claims, wherein said topical administration comprises or consists of oral administration of the pharmaceutical composition.

~~17.16.~~ The use according to claim ~~156~~, wherein the pharmaceutical composition is a delayed release formulation.

~~18.17.~~ The use according to claim ~~156~~ or ~~167~~, wherein the pharmaceutical composition is a solid dosage form in the form of a pellet, granule, micro particle, nano particle, mini tablet, sphere, capsule, tablet or multiparticulate drug delivery system coated with a delayed release coating, which prevents release of the active agent before entering the ileum, the ileocolonic region or the large intestine of the gastrointestinal (GI) tract.

~~19.18.~~ The use according to claim ~~178~~, wherein the delayed release coating comprises at least one component selected from the group consisting of poly vinyl acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate ~~HP-50, HP-55 or HP-55S~~, cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate ~~(HPMCAS)~~, poly(methacrylic acid, ethyl acrylate) 1:1, poly(methacrylic acid, methyl methacrylate) 1:1, poly(methacrylic acid, methyl methacrylate) 1:2, chondroitin sulfate, pectin, guar gum, chitosan, inulin, lactulose, raffinose, stachyose, alginate, dextran, xanthan gum, locust bean gum, arabinogalactan, amylose, cyclodextrin, pullulan, carrageenan, scleroglucan, chitin, curdulan, levan, amylopectin, starch, resistant starch, azo compounds being degraded by azo bonds splitting bacteria, and combinations thereof.

~~20.19.~~ The use according to any one of claims ~~1716~~ to ~~1819~~, which comprises a sustained release coating or a sustained release matrix.

~~21.20.~~ The use according to claim ~~1920~~, wherein said sustained release coating or a sustained release matrix comprises a material that disintegrates time-dependently.

~~22.21.~~ The use according to claim ~~2021~~, wherein said material that disintegrates time-dependently is selected from the group consisting of poly(ethyl acrylate, methyl methacrylate) 2 : 1 ~~(e.g. Eudragit® NM 30D, or Eudragit NE 30D)~~; poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 ~~(e.g. Eudragit® RS 30D)~~; ethylcellulose ~~(e.g. Surelease® or Aquacoat ECD)~~; poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.2 ~~(e.g. Eudragit® RL 30D)~~; polyvinyl acetate ~~(eg. Kollicoat® SR 30D)~~; and combinations thereof.

23.22. The use according to any one of claims 1516 to 2122, wherein said composition comprises a sustained release core coated with a delayed release coating.

24.23. The use according to any one of claims 1516 to 2122, wherein said composition comprises a core, a sustained release coating and a delayed release coating.

25.24. The use according to any one of claims 1 to 1415, wherein said treatment comprises the rectal administration of the composition, and wherein the composition preferably is an enema, a gel, a foam or a suppository.