Claims

1. RNA containing composition for intratumoral use in the treatment or prophylaxis of tumor and/or cancer
diseases, wherein the RNA containing composition comprises at least one coding RNA comprising at least one coding region encoding at least one cytokine, or a fragment or variant thereof,
wherein the cytokine is interleukin-12 (IL-12),
wherein the fragment or variant has the same biological function or specific activity compared to the full-length native protein,
wherein the at least one coding RNA is an mRNA,
and wherein a patient received or receives a checkpoint modulator selected from a CTLA4 inhibitor and a PD-1 pathway inhibitor.

2. Use of an RNA containing composition in the manufacture of a medicament for the treatment or prophylaxis of tumor and/or cancer diseases, wherein the RNA containing composition comprises at least one coding RNA comprising at least one coding region encoding at least one cytokine, or a fragment or variant thereof,
wherein the cytokine is interleukin-12 (IL-12),
wherein the fragment or variant has the same biological function or specific activity compared to the full-length native protein,
wherein the at least one coding RNA is an mRNA,
wherein the RNA containing composition is to be applied intratumorally, and
wherein a patient received or receives a checkpoint modulator selected from a CTLA4 inhibitor and a PD-1 pathway inhibitor.

3. The use of claim 2, wherein the checkpoint modulator is an anti-CTLA4 antibody, an anti-PD-1 antibody or an anti-PD-L1 antibody.

4. The use of claim 2 or claim 3, wherein the medicament is to be applied by injection into tumor tissue.

5. The use of any one of claims 2-4, wherein the composition comprises at least one further RNA selected from the group consisting of coding RNA and non-coding RNA.

6. The use of claim 5, wherein the coding RNA of claim 5 comprises at least one coding region encoding at least one peptide or protein.

7. The use of claim 6, wherein the at least one coding region encoding at least one peptide or protein is selected from the group consisting of mRNA, viral RNA, retroviral RNA, and replicon RNA.

8. The use of claim 6 or claim 7, wherein the coding RNA is mRNA.

9. The use of any one of claims 6 to 8, wherein the at least one peptide or protein is selected or derived from the group consisting of cytokines, chemokines, suicide gene products, immunogenic proteins or peptides, apoptosis inducers, angiogenesis inhibitors, heat shock proteins, tumor antigens, β-catenin inhibitors, activators of the STING pathway, checkpoint modulators, innate immune activators, antibodies, dominant negative receptors and decoy receptors, inhibitors of myeloid derived suppressor cells (MDSCs), Indoleamine 2,3 dioxygenase (IDO) pathway inhibitors, and proteins or peptides that bind inhibitors of apoptosis.

10. The use of claim 9, wherein the cytokine is an interleukin.

11. The use of claim 10, wherein the interleukin is chosen from the following list:
IL-1α, IL-1β, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-13, IL-14, IL-15, IL-16, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F, IL-18, IL-19, IL- 20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-28A/B, IL-29, IL-30, IL-31, IL-32, IL-33 or IL-35

12. The use of claim 9, wherein the cytokine is a member of the TNF family.

13. The use of claim 12, wherein the TNF family, is chosen from the following list:
TNF, especially TNFα, LTα, LTβ, LIGHT, TWEAK, APRIL, BAFF, TL1A, GITRL, OX40L, CD40L, FASL, CD27L, CD30L, 4-1BBL, TRAIL, or RANK ligand.

14. The use of claim 9, wherein the cytokine is chosen from the following list:
FLT3 ligand, G-CSF, GM-CSF, IFNα/β/ω, IFNγ, LIF, M-CSF, MIF, OSM, Stem Cell Factor, TGFβ1, TGFβ2, TGFβ3, TSLP ligand.

15. The use of claim 9, wherein the chemokine is chosen from the following list:
CXCL1, CXCL2, CXCL3, CXCL4, CXCL5, CXCL6, CXCL7, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL14, CXCL15, CXCL16, CCL1, CCL2, CCL3, CCL4, CCL5, CCL6, CCL7, CCL8, CCL9/10, CCL11, CCL12, CCL13, CCL14, CCL15, CCL16, CCL17, CCL18, CCL19, CCL20, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26, CCL27, CCL28, XCL1, XCL2, CX3CL1.

16. The use of claim 9, wherein the suicide gene product is a suicide enzyme.

17. The use of claim 16, wherein the suicide enzyme is a nucleotide metabolizing enzyme.

18. The use of claim 17, wherein the nucleotide metabolizing enzyme is chosen from the following list: thymidine kinase, cytosine deaminase, deoxynucleoside kinase, deoxycytidine kinase, or purine nucleoside phosphorylase.

19. The use of claim 18, wherein:

a) the thymidine kinase is Herpes simplex virus thymidine kinase,

b) the cytosine deaminase is bacterial cytosine deaminase or Yeast cytosine deaminase,

c) the deoxynucleoside kinase is Drosophila melanogaster deoxynucleoside kinase,

d) the deoxycytidine kinase is a mammalian deoxycytidine kinase, or

e) the purine nucleoside phosphorylase is a bacterial purine nucleoside phosphorylase.

20. The use of claim 9 or any one of claims 16 to 19, wherein the at least one RNA codes for at least one connexin and at least one suicide gene product.

21. The use of claim 9 or any one of claims 16 to 19, wherein the RNA composition comprises at least one RNA encoding at least one suicide gene product and wherein the RNA composition is used in combination with a further RNA coding for at least one connexin and/or with a protein of the connexin family or parts or fragments thereof.

22. The use of claim 9, wherein the immunogenic protein or peptide is a protein or peptide of a pathogen.

23. The use of claim 22, wherein the protein or peptide of a pathogen, is a viral or bacterial pathogen.

24. The use of claim 22 or claim 23, wherein the immunogenic protein or peptide is at least one protein or peptide of one virus or bacterium of the following list: influenza virus type A or B or any other orthomyxovirus (influenza type C), picornaviruses, such as rhinovirus or hepatitis A virus, togaviruses, such as alphavirus or rubivirus, e.g. Sindbis, Semliki-Forest or rubeolavirus, rubella virus, coronaviruses, in particular subtypes HCV-229E or HCV-OC43, rhabdoviruses, such as rabies virus, paramyxoviruses, such as mumps virus, reoviruses, such as group A, B or C rotavirus, hepadnaviruses, such as hepatitis B virus, papoviruses, such as human papillomaviruses of any serotype, adenoviruses, in particular type 1 to 47, herpesviruses, such as Herpes simplex virus 1, 2 or 3, cytomegalovirus, Epstein Barr virus, vacciniaviruses, the bacterium Chlamydophila pneumoniae, Flaviviruses, such as dengue virus type 1 to 4, yellow fever virus, West Nile virus, Japanese encephalitis virus, hepatitis C virus, caliciviruses, filoviruses, such as Ebola virus, bornaviruses, bunyaviruses, such as Rift Valley fever virus, arenaviruses, such as lymphocytic choriomeningitis virus or hemorrhagic fever viruses, retroviruses, such as HIV, parvoviruses.

25. The use of claim 24, wherein the cytomegalovirus, is CMVpp65.

26. The use of any one of claims 22-24, wherein the immunogenic peptide or protein is derived from influenza nucleoprotein.

27. The use of claim 9, wherein the apoptosis inducer is chosen from the group consisting of the Bcl-2 family, tumor suppressor protein p53, ligands of transmembrane death receptors, especially the TNF receptor gene superfamily, pro-apoptic receptor agonists and Beclin-1.

28. The use of claim 9 or 27, wherein the apoptosis inducer is chosen from the following list: Bcl-10, Bax, Bak, Bid, Bad, Bim, Bik, Blk, Cytochrome c, Caspases, especially Caspase 3, Caspase 6, Caspase 7, Caspase 8, Caspase 9, Death domain, especially Fas, preferably FasL, TNFα, Apo2L/TRAIL, agonist of DR4 and/or DR5, Apo3L, DR4 agonistic antibody, DR5 agonistic antibody, protein kinase R (PKR), Granzyme B.

29. The use of claim 9, wherein the angiogenesis inhibitor is chosen from the following list: IFN-α, IFN-β, IFN-γ, CXCL9, CXCL10, IL-12, PF-4, TNF-α, sFLT-1, FLK-1, Angiostatin, Endostatin, Vasostatin, Canstatin, Tumstatin, 16 kD prolacin fragment, TIMP-1, TIMP-2, TIMP-3, TSP-1, TSP-2, Maspin, PEX, sTie1, sTie2, Angiopoietin-1, Angiopoietin-2, Anti-VEGFR2 antibody, Anti-VEGF antibody and Anti-VEGFR1 antibody.

30. The use of claim 9, wherein the heat shock protein is chosen from the following list: HSP27, HSP47, HSP60, HSP70, HSC70, GRP78, HSP90, HSP110, GRP94, GRP170, PDI/PDIA, CRT/CALR.

31. The use of claim 9, wherein the tumor antigen is chosen from the following list: 1A01_HLA-A/m; 1A02; 5T4; ACRBP; AFP; AKAP4; alpha-actinin-_4/m; alpha-methylacyl-coenzyme_A_racemase; ANDR; ART-4; ARTC1/m; AURKB; B2MG; B3GN5; B4GN1; B7H4; BAGE-1; BASI; BCL-2; bcr/abl; beta-catenin/m; BING-4; BIRC7; BRCA1/m; BY55; calreticulin; CAMEL; CASPA; Caspase_8; cathepsin_B; cathepsin_L; CD1A; CD1B; CD1C; CD1D; CD1E; CD20; CD22; CD276; CD33; CD3E; CD3Z; CD4; CD44_Isoform_1; CD44_Isoform_6; CD52; CD55; CD56; CD80; CD86; CD8A; CDC27/m; CDE30; CDK4/m; CDKN2A/m; CEA; CEAM6; CH3L2; CLCA2; CML28; CML66; COA-1/m; coactosin-like_protein; collagen_XXIII; COX-2; CP1B1; CSAG2; CT-_9/BRD6; CT45A1; CT55; CTAG2_Isoform_LAGE-1A; CTAG2_Isoform_LAGE-1B; CTCFL; Cten; cyclin_B1; cyclin_D1; cyp-B; DAM-10; DEP1A; E7; EF1A2; EFTUD2/m; EGFR; EGLN3; ELF2/m; EMMPRIN; EpCam; EphA2; EphA3; ErbB3; ERBB4; ERG; ETV6; EWS; EZH2; FABP7; FCGR3A_Version_1; FCGR3A_Version_2; FGF5; FGFR2; fibronectin; FOS; FOXP3; FUT1; G250; GAGE-1; GAGE-2; GAGE-3; GAGE-4; GAGE-5; GAGE-6; GAGE7b; GAGE-8_(GAGE-2D); GASR; GnT-V; GPC3; GPNMB/m; GRM3; HAGE; hepsin; Her2/neu; HLA-A2/m; homeobox_NKX3.1; HOM-TES-85; HPG1; HS71A; HS71B; HST-2; hTERT; iCE; IF2B3; IL-10; IL-13Ra2; IL2-RA; IL2-RB; IL2-RG; IL-5; IMP3; ITA5; ITB1; ITB6; kallikrein-2; kallikrein-4; KI20A; KIAA0205; KIF2C; KK-LC-1; LDLR;

LGMN; LIRB2; LY6K; MAGA5; MAGA8; MAGAB; MAGE-_B1; MAGE-_E1; MAGE-A1; MAGE-A10; MAGE-A12; MAGE-A2; MAGE-A3; MAGE-A4; MAGE-A6; MAGE-A9; MAGE-B10; MAGE-B16; MAGE-B17; MAGE-B2; MAGE-B3; MAGE-B4; MAGE-B5; MAGE-B6; MAGE-C1; MAGE-C2; MAGE-C3; MAGE-D1; MAGE-D2; MAGE-D4; MAGE-E1_(MAGE1); MAGE-E2; MAGE-F1; MAGE-H1; MAGEL2; mammaglobin_A; MART-1/melan-A; MART-2; MC1_R; M-CSF; mesothelin; MITF; MMP1_1; MMP7; MUC-1; MUM-1/m; MUM-2/m; MYO1A; MYO1B; MYO1C; MYO1D; MYO1E; MYO1F; MYO1G; MYO1H; NA17; NA88-A; Neo-PAP; NFYC/m; NGEP; N-myc; NPM; NRCAM; NSE; NUF2; NY-ESO-1; OA1; OGT; OS-9; osteocalcin; osteopontin; p53; PAGE-4; PAI-1; PAI-2; PAP; PATE; PAX3; PAX5; PD1L1; PDCD1; PDEF; PECA1; PGCB; PGFRB; Pim-1_-Kinase; Pin-1; PLAC1; PMEL; PML; POTE; POTEF; PRAME; PRDX5/m; PRM2; prostein; proteinase-3; PSA; PSB9; PSCA; PSGR; PSM; PTPRC; RAB8A; RAGE-1; RARA; RASH; RASK; RASN; RGS5; RHAMM/CD168; RHOC; RSSA; RU1; RU2; RUNX1; S-100; SAGE; SART-_1; SART-2; SART-3; SEPR; SERPINB5; SIA7F; SIA8A; SIAT9; SIRT2/m; SOX10; SP17; SPNXA; SPXN3; SSX-1; SSX-2; SSX3; SSX-4; ST1A1; STAG2; STAMP-1; STEAP-1; survivin; Survivin-2B; SYCP1; SYT-SSX-1; SYT-SSX-2; TARP; TCRg; TF2AA; TGFbeta1; TGFR2; TGM-4; TIE2; TKTL1; TPI/m; TRGV11; TRGV9; TRPC1; TRP-p8; TSG10; TSPY1; TVC_(TRGV3); TX101; tyrosinase; TYRP1; TYRP2; UPA; VEGFR1; WT1; XAGE1.

32. The use of claim 9, wherein the β-catenin inhibitor is chosen from the following list: TAT-NLS-BLBD-6, axin-1, TCF-4, GSK-3b, DKK-1, Dvl-1.

33. The use of claim 9, wherein the activator of the STING (stimulator of interferon genes) pathway is an activating protein or a constitutively active protein of the STING pathway.

34. The use of claim 33, wherein the activator of the STING pathway is an activating protein or the constitutively active protein of the STING pathway, is of DDX41, STING, cGAS, IRF3, TBK1, or STAT6.

35. The use of claim 9, wherein the checkpoint modulator is a modulator of B7-1/CD80, B7-2/CD86, B7-H1/PD-L1, B7-H2, B7-H3, B7-H4, B7-H6, B7-H7/HHLA2,

BTLA, CD28, CD28H/IGPR-1, CTLA-4, ICOS, PD-1, PD-L2/B7-DC, PDCD6, VISTA/B7-H5/PD-1H, BTN1A1/Butyrophilin, BTN2A1, BTN2A2/Butyrophilin 2A2, BTN3A1/2, BTN3A2, BTN3A3, BTNL2/Butyrophilin-like 2, BTNL3, BTNL4, BTNL6, BTNL8, BTNL9, BTNL10, CD277/BTN3A1, LAIR1, LAIR2, CD96, CD155/PVR, CRTAM, DNAM-1/CD226, Nectin-2/CD112, Nectin-3, TIGIT, LILRA3/CD85e, LILRA4/CD85g/ILT7, LILRB1/CD85j/ILT2, LILRB2/CD85d/ILT4, LILRB3/CD85a/ILT5, LILRB4/CD85k/ILT3, 4-1BB/TNFRSF9/CD137, 4-1BB Ligand/TNFSF9, BAFF/BLyS/TNFSF13B, BAFF R/TNFRSF13C, CD27/TNFRSF7, CD27 Ligand/TNFSF7, CD30/TNFRSF8, CD30 Ligand/TNFSF8, CD40/TNFRSF5, CD40 Ligand/TNFSF5, DR3/TNFRSF25, GITR/TNFRSF18, GITR Ligand/TNFSF18, HVEM/TNFRSF14, LIGHT/TNFSF14, Lymphotoxin-alpha/TNF-beta, OX40/TNFRSF4, OX40 Ligand/TNFSF4, RELT/TNFRSF19L, TACI/TNFRSF13B, TL1A/TNFSF15, TNF-alpha, TNF RII/TNFRSF1B, 2B4/CD244/SLAMF4, BLAME/SLAMF8, CD2, CD2F-10/SLAMF9, CD48/SLAMF2, CD58/LFA-3, CD84/SLAMF5, CD229/SLAMF3, CRACC/SLAMF7, NTB-A/SLAMF6, SLAM/CD150, TIM-1/KIM-1/HAVCR, TIM-3, TIM-4, CD7, CD96, CD160, CD200, CD300a/LMIR1, CRTAM, DAP12, Dectin-1/CLEC7A, DPPIV/CD26, EphB6, Integrin alpha 4 beta 1, Integrin alpha 4 beta 7/LPAM-1, LAG-3, TIM-1/KIM-1/HAVCR, TIM-4, TSLP R, or any combinations thereof.

36. The use of claim 9 or claim 35, wherein the checkpoint modulator is selected from the group consisting of an agonistic antibody, an antagonistic antibody, a dominant negative receptor, a decoy receptor and a ligand.

37. The use of claim 36, wherein the antagonistic antibody is directed against PD-1, PD-L1 or CTLA-4.

38. The use of claim 36, wherein the agonistic antibody is directed against OX-40.

39. The use of claim 36, wherein the decoy receptor is a soluble PD-1 receptor.

40. The use of claim 9, wherein the antibody, is an agonistic antibody, an antagonistic antibody, or a neutralizing antibody.

41. The use of claim 9 or claim 40, wherein the antibody is directed against a tumor antigen or a tumor associated antigen.