Claims

1. RNA containing composition comprising at least one RNA for use in the treatment or prophylaxis of tumor and/or cancer diseases.

2. The RNA containing composition of claim 1, wherein the RNA containing composition is to be applied intratumorally, especially by injection into tumor tissue.

3. The RNA containing composition of claim 1 or 2, wherein the at least one RNA is selected from the group consisting of coding RNA and non-coding RNA.

4. The RNA containing composition of claim 3, wherein the coding RNA comprises at least one coding region encoding at least one peptide or protein and is preferably selected from the group consisting of mRNA, viral RNA, retroviral RNA, and replicon RNA.

5. The RNA containing composition of claim 4, wherein the coding RNA is mRNA.

6. The RNA containing composition of claim 4 or 5, 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), IDO pathway inhibitors, and proteins or peptides that bind inhibitors of apoptosis.

7. The RNA containing composition of claim 6, wherein the cytokine is an interleukin, preferably 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-12, IL-13, IL14, 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, IL-35.

8. The RNA containing composition of claim 6 or 7, wherein the interleukin is interleukin-12 (IL-12).

9. The RNA containing composition of claim 6, wherein the cytokine is a member of the TNF family, preferably chosen from the following list: TNF, especially TNFα, LTα, LTβ, LIGHT, TWEAK, APRIL, BAFF, TL1A, GITRL, OX40L, CD40L, FASL, CD27L, CD30L, 4-1BBL, TRAIL, RANK ligand.

10. The RNA containing composition of claim 6, 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.

11. The RNA containing composition of claim 6, 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.

12. The RNA containing composition of claim 6, wherein the suicide gene product is a suicide enzyme, preferably a nucleotide metabolizing enzyme.

13. The RNA containing composition of claim 12, wherein the nucleotide metabolizing enzyme is chosen from the following list: thymidine kinase, preferably Herpes simplex virus thymidine kinase, cytosine deaminase, preferably bacterial cytosine deaminase or Yeast cytosine deaminase, deoxynucleoside kinase, preferably *Drosophila melanogaster* deoxynucleoside kinase, deoxycytidine kinase, preferably a mammalian deoxycytidine kinase, purine nucleoside phosphorylase, preferably a bacterial purine nucleoside phosphorylase.

14. The RNA containing composition of one of claims 6, 12 or 13, wherein the at least one RNA encoding at least one suicide gene product is used in combination with a prodrug which is a substrate of the suicide gene product.

15. The RNA containing composition of one of claims 6, 12 to 14, wherein the at least one RNA codes for at least one connexin and at least one suicide gene product.

16. The RNA containing composition of one of claims 6, 12 to 14, 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.

17. The RNA containing composition of claim 6, wherein the immunogenic protein or peptide is a protein or peptide of a pathogen, more preferably of a viral or bacterial pathogen.

18. The RNA containing composition of claim 17, 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, preferably CMVpp65, 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.

19. The RNA containing composition of claim 17 or 18, wherein the immunogenic peptide or protein is derived from influenza nucleoprotein.

20. The RNA containing composition of claim 6, 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.

21. The RNA containing composition of claim 6 or 20, 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.

22. The RNA containing composition of claim 6, 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.

23. The RNA containing composition of claim 6, 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.

24. The RNA containing composition of claim 6, 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.

25. The RNA containing composition of claim 6, 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.

26. The RNA containing composition of claim 6, wherein the activator of the STING (stimulator of interferon genes) pathway is an activating protein or a constitutively active protein of the STING pathway, preferably of DDX41, STING, cGAS, IRF3, TBK1, or STAT6.

27. The RNA containing composition of claim 6, 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.

28. The RNA containing composition of claim 6 or 27, 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.

29. The RNA containing composition of claim 28, wherein the antagonistic antibody is directed against PD-1, PD-L1 or CTLA-4.

30. The RNA containing composition of claim 28, wherein the agonistic antibody is directed against OX-40.

31. The RNA containing composition of claim 28, wherein the decoy receptor is a soluble PD-1 receptor.

32. The RNA containing composition of claim 6, wherein the antibody, is an agonistic antibody, an antagonistic antibody, or a neutralizing antibody.

33. The RNA containing composition of claim 6 or 32, wherein the antibody is directed against a tumor antigen or a tumor associated antigen.

34. The RNA containing composition of one of claims 3-33, wherein the G/C content of the coding region of the coding RNA, preferably mRNA is increased compared with the G/C content of the coding region of the wild type RNA, and wherein the coded amino acid sequence of said G/C-enriched RNA is preferably not being modified compared with the encoded amino acid sequence of the wild type RNA.

35. The RNA containing composition of one of claims 3-34, wherein the coding RNA, preferably mRNA comprises additionally a 5'-UTR element and/or a 3'-UTR element.

36. The RNA containing composition of one of claims 3-35, wherein the coding RNA, preferably mRNA comprises additionally at least one histone stem-loop.

37. The RNA containing composition of one of claims 3-36, wherein the coding RNA, preferably mRNA comprises additionally a 5'-CAP structure and/or a poly(A) sequence and/or a poly(C) sequence.

38. The RNA containing composition of claim 3, wherein the non-coding RNA is selected from the group consisting of small interfering RNA (siRNA), antisense RNA (asRNA), circular RNA (circRNA), ribozymes, aptamers, riboswitches, immunostimulating RNA, transfer RNA (tRNA), ribosomal RNA (rRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), microRNA (miRNA), and Piwi-interacting RNA (piRNA).

39. The RNA containing composition of claim 38, wherein the immunostimulating RNA comprises at least one RNA sequence according to formula (III) (GlXmGn), formula (IV) (ClXmCn), formula (V) (NuGlXmGnNv)a, and/or formula (VI) (NuClXmCnNv)a).

40. The RNA containing composition of claim 38 or 39, wherein the immunostimulating RNA comprises at least one RNA sequence according to SEQ ID NO. 5, 394 and 10072.

41. The RNA containing composition of any of the preceding claims, wherein the at least one RNA is complexed with one or more cationic or polycationic compounds, preferably with cationic or polycationic polymers, cationic or polycationic peptides or proteins, e.g. protamine, cationic or polycationic polysaccharides and/or cationic or polycationic lipids.

42. The RNA containing composition of claim 41, wherein the cationic or polycationic compound is a polymeric carrier.

43. The RNA containing composition of claim 42, wherein the polymeric carrier is formed by disulfide-crosslinked cationic components, preferably disulfide-crosslinked cationic peptides, preferably comprising peptides according to formula VII, VIIa and/or VIIb and/or a compound according to formula (VIII) (L-P1-S-[S-P2-S]n-S-P3-L).

44. The RNA containing composition of claims 41-43, wherein the N/P ratio of the at least one RNA to the one or more cationic or polycationic compounds, preferably cationic or polycationic peptides or proteins is in the range of about 0.1 to 10, including a range of about 0.3 to 4, of about 0.5 to 2, of about 0.7 to 2 and of about 0.7 to 1.5.

45. The RNA containing composition of any of the preceding claims wherein the RNA containing composition comprises at least one RNA, which is complexed with one or more cationic or polycationic compounds, and at least one free RNA, preferably coding RNA, more preferably mRNA.

46. The RNA containing composition of any of the preceding claims, wherein the at least one mRNA is complexed with one or more lipids and thereby forming liposomes, lipid nanoparticles and/or lipoplexes.

47. The RNA containing composition of any of the preceding claims, wherein the RNA containing composition comprises a polymeric carrier cargo complex, formed by a polymeric carrier, preferably comprising disulfide-crosslinked cationic peptides, preferably Cys-Arg_{12}, and/or Cys-Arg_{12}-Cys, and an immunostimulating RNA, preferably the RNA sequence according to SEQ ID NO: 5, 394 or 10072.

48. Pharmaceutical composition comprising the RNA containing composition as defined according to claims 1 to 47 and a pharmaceutically acceptable carrier and/or vehicle.

49. The pharmaceutical composition of claim 48, prepared for injection into tumor tissue.

50. Kit or kit of parts comprising the RNA containing composition as defined according to claims 1 to 47, or the pharmaceutical composition as defined according to claim 48 or 49, and optionally technical instructions with information on the administration and dosage for administration.

51. The RNA containing composition as defined according to one of claims 1 to 47, or the pharmaceutical composition as defined according to claim 48 or 49, or the kit or kit of parts as defined according to claim 50 for use as a medicament.

52. The RNA containing composition as defined according to claims 1 to 47, or the pharmaceutical composition as defined according to claim 48 or 49, or the kit or kit of parts as defined according to claim 50 for use in the treatment or prophylaxis of tumor and/or cancer diseases preferably by intratumoral application, especially by injection into tumor tissue.

53. Use of the RNA containing composition as defined according to claims 1 to 47, or the pharmaceutical composition as defined according to claim 48 or 49, or the kit or kit of parts as defined according to claim 50 for the treatment or prophylaxis of tumor and/or cancer diseases, preferably by intratumoral application, especially by injection into tumor tissue.

54. The use of claim 53, wherein the treatment or prophylaxis comprises the administration of at least one additional pharmaceutically active compound.

55. The use of claim 54, wherein the at least one additonal pharmaceutically active compound is selected 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), IDO pathway inhibitors, proteins or peptides that bind inhibitors of apoptosis, anti-bacterial agents, anti-viral agents, drugs, adjuvants, chemotherapeutic agents and kinase inhibitors.

56. The use of claim 54 or 55, wherein the treatment further comprises radiation therapy and/or surgery.

57. The use of claim 55, wherein the checkpoint modulator is selected from a modulator as defined in claim 27.

58. The use of claim 57, wherein the checkpoint modulator is selected from a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIM3 inhibitor, an OX-40 stimulator, a 4-1BB stimulator, a CD40L stimulator, a CD28 stimulator, a GITR stimulator.

59. The use of claim 58, wherein the PD-1 inhibitor is an antagonistic antibody directed against PD-1 and the PD-L1 inhibitor is an antagonistic antibody directed against PD-L1.

60. The use of claim 54, wherein the antibody is selected from an antibody directed against CD73 and/or CD137.

61. Use of the RNA containing composition as defined according to one of claims 1 to 47, or the pharmaceutical composition as defined according to claim 48 or 49, or the kit or kit of parts as defined according to claim 50 for preparation of a medicament for treatment of tumor and/or cancer diseases, preferably by intratumoral application, especially by injection into tumor tissue.

62. Method of treatment of tumor and/or cancer diseases with the RNA containing composition as defined according to one of claims 1 to 47, or the pharmaceutical composition as defined according to claim 48 or 49, or the kit or kit of parts as defined

according to claim 50, preferably by intratumoral application, especially by injection into tumor tissue.