Supplementary Tables

In vivo vectorization and delivery systems for gene therapies and RNA-based therapeutics in oncology

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***Table S1**: Selection of recent gene therapies using Adenoviral vectors*

Serotype / Modification	**Transgene**	**Administration**	**Cancer**	**Phase**	**Sponsor / Investigator**	**NCT +** ASCO
NA	HSV-tk	NA	GBM	I/II	David S Baskin, Houston Methodist Neurological Institute	NCT03596086: **Gene Therapy for High Grade Glioma: The Clinical Experience** Varela et Al. [1]
24-base pair deletion in the E1A gene (replication deficient)	OX40L	Intra-tumoral	Resectable Colorectal Liver Metastasis	I	DNAtrix, Inc.	NCT04714983: **DNX-2440 for Resectable Colorectal Liver Metastasis** Jiang et Al. [2]
		stereotactic injection	GBM	I	DNAtrix, Inc	NCT03714334: **DNX-2440 Oncolytic Adenovirus for Recurrent Glioblastoma** Jiang et Al. [2]
NA	p53	intra-tumoral	Solid Tumours	II	MultiVir, Inc.	NCT03544723: **Analysis of Adenoviral p53 Gene Therapy Clinical Trials in Recurrent Head and Neck Squamous Cell Carcinoma** Sobol et Al. [3]
Replication deficient	Interferon Alpha-2b	Intrapleural	Malignant Pleural Mesothelioma (INFINITE)	III	Trizell Ltd	NCT03710876: **Nadofaragene Firadenovec: First Approval** Lee et al. [4]
NA	TMZ-CD40L and 4-1BBL	Intra-tumoral	advanced pancreatic cancer	III	Trizell Ltd	NCT02705196**: LOAd703 Oncolytic Virus Therapy for Pancreatic Cancer** **A phase I/II study of LOAd703, a TMZ-CD40L/4-1BBL-armed oncolytic adenovirus, combined with nab-paclitaxel and gemcitabine in advanced pancreatic cancer** Musher et Al. [5] **LOAd703, an oncolytic virus-based immunost** Musher et Al. [6]

Ad5	yCD/mutTKSR39 (yeast cytidine deaminase/mutant S39R HSV-1 thymidine kinase) and human IL-12 (IL12)	Intra-tumoral	metastatic pancreatic cancer	I	Henry Ford Health System	NCT03281382: **Phase 1 Trial of Interleukin 12 Gene Therapy for Metastatic Pancreatic Cancer** Phase I trial of oncolytic adenovirus-mediated cytotoxic and interleukin-12 gene therapy for the treatment of metastatic pancreatic cancer Barton & Al. [7]
Ad-5, El-deleted Ofranergene obadenovec	Fas-chimera (Fas-c) transgene	IV	recurrent platinum resistant ovarian cancer	III	Vascular Biogenics Ltd. operating as VBL Therapeutics	NCT03398655: **Randomized controlled phase III trial of weekly paclitaxel ± ofranergene obadenovec (VB-111) for platinum-resistant ovarian cancer** (OVAL Study/GOG 3018). =>no improvement of OS or PFS Arend et Al. [8]
HER 2 CAR-T + AdV	Dual expression of IL-12 and PD-L1 blocker	Tumour site	Advanced HER2 Positive Solid Tumours (VISTA)	I	Shalini Makawita, Baylor College of Medicine	NCT03740256: **Binary oncolytic adenovirus in combination with HER2-specific autologous CAR VST for treatment of advanced HER2-positive solid tumors** (VISTA). Makawita et Al. [9]
NA	Ad-RTS-hIL-12 (RheoSwitch Therapeutic System = TF) & interleukin-12	stereotactic	Glioblastoma or Malignant Glioma	I	Alaunos Therapeutics	NCT02026271: **A Study of Ad-RTS-hIL-12 With Veledimex in Subjects With Glioblastoma or Malignant Glioma** Final results of controlled IL-12 monotherapy in adults with grade III or IV gliomas. Chiocca et al. [10]

Table S2: *Clinical developments of aglatimagene besadenovec (AglaVec) (CAN-2409): Summary of clinical trials, therapeutic indications, and outcomes using vector particles (VP).*

Cancer	Clinical Development	Dose and treatment protocol	Results	References
High grade glioma/ Glioblastoma	Phase I/II (NCT00870181)	Intra-arterial cerebral infusion (1×10^{12} viral particles of AglaVec)	**- Progression-Free Survival (PFS)**: ADV-TK treatment significantly improved PFS compared to control, with a median survival of 29.6 weeks versus 7.9 weeks (HR: 0.315, $p < 0.001$). The benefit was more pronounced in the GBM subgroup, achieving a PFS of 34.9 weeks compared to 9.0 weeks (HR: 0.157, $p < 0.001$). **- Overall Survival (OS)**: DV-TK markedly extended OS, with a median survival of 45.6 weeks versus 7.9 weeks (HR: 0.207, $p < 0.001$). The GBM subgroup showed the most significant gain, with an OS of 45.4 weeks compared to 9.6 weeks (HR: 0.125, $p < 0.001$). **- Hazard Ratio (HR)**: the lower HR values for both PFS and OS demonstrates a substantial survival advantage for ADV-TK, particularly in the GBM subgroup.	**Adenovirus-mediated delivery of herpes simplex virus thymidine kinase administration improves outcome of recurrent high-grade glioma** Ji et al. [11]
Malignant pleural effusion (Lung cancer, Mesothelioma Breast Cancer Ovarian Cancer	Phase I/II (NCT01997190)	- Cohort 1: 3 patients received 1×10^{12} vp. - Cohort 2: 3 patients received 1×10^{13} vp. - Cohort 3: 14 patients enrolled (13 treated) received 1×10^{13} vp combined with celecoxib	- Response Evaluation (RECIST): 17 patients were evaluable -Best response: Partial Response (PR) observed in 4 patients, including 3 with MM and 1 with NSCLC.	**Phase I study of gene mediated cytotoxic immunotherapy (GMCI) for patients with malignant pleural effusion (MPE)** Aggarwal et al. [12]
Malignant Glioma (Anaplastic Astrocytoma Glioblastoma Multiforme High Grade Glioma Malignant Glioma	Phase IIa (NCT00589875)	Single dose of 3×10^{11} vp administered directly to the tumour bed post-resection on day 0	PFS and OS showed moderate improvement	**Phase II multicenter study of gene-mediated cytotoxic immunotherapy as adjuvant to surgical resection for newly diagnosed malignant glioma** Wheeler et Al. [13]
Paediatric Brain Tumours (Malignant Glioma Recurrent Ependymoma	Phase I (NCT00634231)	AdV-tk at doses of 1×10^{11} and 3×10^{11} vp was administered into the tumour bed during surgery, followed by a 14-day course of valacyclovir	- Patient Enrolment: Eight patients were enrolled and completed therapy (6 glioblastoma, 1 anaplastic astrocytoma, 1 recurrent ependymoma). - Surgical Outcome: Five patients presented with multifocal or extensive tumours that were not fully resectable; three patients underwent gross total resection. - Toxicity: No dose-limiting toxicities were identified. - Adverse Events: The most common GMCI-related adverse events	**Phase I study of gene-mediated cytotoxic immunotherapy with AdV-tk as adjuvant to surgery and radiation for pediatric malignant glioma and recurrent ependymoma** Kieran et al. [14]

			were grade 1–2 fever, fatigue, and nausea/vomiting. - Long-Term Survival: Three patients on dose level 2 achieved survival beyond 24 months, with two remaining progression-free at 37.3 and 47.7 months post-AdV-tk injection.	
Pancreatic cancer	Phase II (NCT02446093) + FAST TRACK	NA	-OS Patients treated with CAN-2409 achieved a median OS of 28.8 months compared to 12.5 months in the control group. - 24-Month OS Rate: 71.4% for CAN-2409 vs 16.7% for the standard-of-care (SOC) group - 36-Month OS Rate: Estimated at 47.6% for CAN-2409 vs 16.7% for the control group	**Candel Therapeutics receives FDA fast track designation for CAN-2409 in pancreatic cancer** Ref [15]
Prostate cancer	Phase II (ULYSSES) (NCT02768363)	NA	NA	**Immunotherapy in prostate cancer: new horizon of hurdles and hopes** Tsaur et al. [16]
Stage III/IV NSCLC	Phase II (NCT04495153)	Two doses of CAN-2409 (5×10^{11} vp) were administered 5–7 weeks apart via bronchoscopic or percutaneous injection into the lung tumour, disease-positive lymph node, or peripheral metastasis. Adjuvant Therapy: Each dose was followed by oral prodrug administration.	- mOS: 20.6 months, exceeding standard chemotherapy outcomes. - 90% of patients: Stage IV disease. - Abscopal effect: >70% with at least one uninjected lesion. - 1–2 tumour injections sufficient to train immune cells. - Systemic and durable antitumor activity observed.	**Overall survival after treatment with CAN-2409 plus valacyclovir in combination with continued ICI in patients with stage III/IV NSCLC with an inadequate response to ICI.** Aggarwal et al. [17]

Table S3: *CF33 clinical developments*

Cancer	Clinical Development	Status	Dose	Results	References
Metastatic or Advanced Solid Tumours (MAST)	Phase 1 (NCT05346484)	Recruiting	CF33-hNIS administered IT or IV, alone or in combination with pembrolizumab in patients with advanced or metastatic solid tumours with ≥ 2 prior lines of therapy	NA	**Oncolytic virus CF33-hNIS monotherapy for the treatment of gastrointestinal (GI) malignancies.** Li et al. [18]
Anatomic Stage IV Breast Cancer AJCC Metastatic Triple-Negative Breast Carcinoma Prognostic Stage IV Breast Cancer AJCC	Phase I (NCT05081492)	Active not recruiting	intratumorally at one of 8 assigned dose levels (1×10^5 PFU, 3 × 105 PFU, 1×10^6 PFU, 3× 106 PFU, 1×10^7 PFU, 3 × 107 PFU, 1×10^8 PFU, 3 x 108 PFU) on Days 1 and 15 of each 28-day cycle for a total of 3 cycles of treatment.	Ongoing Trial: No results posted: but CASE REPORT with positive results	**CF33-hNIS-anti-PD-L1 oncolytic virus followed by trastuzumab-deruxtecan in a patient with metastatic triple negative breast cancer: a case study** Yuan et al. [19]
Advanced or Metastatic Solid Tumours	Phase 1 (NCT06063317)	Recruiting	3+3 dose escalation scheme independently of each route of CF33-CD19 administration (IT and IV) with dose levels of CF33-CD19 ranging from $1.0x10^7$ to $3.0x10^9$ PFU	NA	**Combination therapy with the oncolytic virus CF33-CD19 and blinatumomab for the treatment of advanced solid tumors.** Li & al. [20]

***Table S4**: Important parameters for nanoparticles formulation and characterization*

Character	Parameters	Definition	References
Morphology	**Size**	The physical dimensions of nanoparticles, typically measured in nanometres (nm), significantly influence their biological fate, including cellular uptake, biodistribution, and tissue penetration.	**Nanodelivery of nucleic acids** Mendes et Al. [21]
	Polydispersity	The variation in nanoparticle size within a formulation is quantified using the polydispersity index (PDI). A low PDI indicates uniformity, enhancing reproducibility, stability, and controlled drug release.	
	Shape	The geometric form of nanoparticles—spherical, rod-like, or irregular—impacts their biodistribution, cellular interactions, and clearance rates, influencing therapeutic efficiency and biological functionality.	
Surface charge	**Zeta potential**	The surface charge of nanoparticles, measured at the slipping plane in a colloidal system, determines their stability, aggregation behaviour, and interaction with biological membranes, affecting circulation and cellular uptake.	
	Hydrophobicity	The degree to which nanoparticle surfaces repel water influences their dispersibility, stability, and interaction with biological systems, playing a critical role in cellular uptake and protein corona formation.	
	Stability	The ability of nanoparticles to resist aggregation or degradation over time ensures consistent size distribution, biological activity, and therapeutic performance.	
Composition	**Encapsulation efficiency**	The proportion of the therapeutic agent successfully loaded into nanoparticles relative to the total input, which directly impacts drug dosage, bioavailability, and therapeutic efficacy.	
	Molecular Ratio	The ratio of nanoparticle components (e.g., drug-to-carrier or lipid-to-polymer) is critical for optimizing formulation stability, release profiles, and overall performance.	
Surface coating	**Targeting molecules**	Ligands, antibodies, or peptides conjugated to the nanoparticle surface enable selective binding to target cells or tissues, enhancing precision and minimizing off-target effects in drug delivery.	
	Stealth	Surface modifications, such as PEGylation, reduce nanoparticle recognition by the immune system, thereby extending circulation time, improving systemic stability, and enhancing therapeutic delivery to target sites.	

Table S5: *Targeting molecules and cancer targets in NP-based drug and gene delivery systems*

Ligand for functionalizing NPs	**Target (Cancer cell surface or intracellular binding site)**	**References**
Folate (small molecule)	Folate Receptor	**Promising Nanocarriers for PEDF Gene Targeting Delivery to Cervical Cancer Cells Mediated by the Over-expressing FRα** Gladkikh et al. [22]
Transferrin Receptor (scFv = single chain fragment)	Transferrin	**Brain tumor-targeted therapy by systemic delivery of siRNA with Transferrin receptor-mediated core-shell nanoparticles** Wei et al. [23]
Hyaluronic Acid (Polysaccharide)	CD44	**Recent advances in liposome-based targeted cancer therapy** Fidan et al. [24]
Trastuzumab (Anti-HER2 antibody)	HER-2 (ErbB2)	**Tumor-Directed Targeting of Liposomes** Park [25]
Fab' fragments of cetuximab (Anti-EGFR antibody)	EGFR (ErbB1)	**Epidermal Growth Factor Receptor–Targeted Immunoliposomes Significantly Enhance the Efficacy of Multiple Anticancer Drugs In vivo** Mamot et al. [26]
Anti-mesothelin antibody	Mesothelin	**Mesothelin-mediated targeting of adenoviral vectors for ovarian cancer gene therapy** Breidenbach et al. [27]
TAT (cell penetrating peptide) + MMP2 peptide sequence + Anti-HER2 antibody	MMP2 (enzyme) HER 2 (ErbB2)	**Intelligent TAT-coupled anti-HER2 immunoliposomes knock downed MDR1 to produce chemosensitize phenotype of multidrug resistant carcinoma** Gholamian Dehkordi et al. [28]
Dexamethasone	Glucocorticoid receptor	**Functionalized PDA/DEX-PEI@HA nanoparticles combined with sleeping-beauty transposons for multistage targeted delivery of CRISPR/ Cas9 gene** Ma et al. [29]
Aptamer (G-rich DNA oligonucleotide of 5-10nm)	Nucleolin	**Co-Delivery of Paclitaxel and PLK1-Targeted siRNA Using Aptamer-Functionalized Cationic Liposome for Synergistic Anti-Breast Cancer Effects *In Vivo*** Yu, et al. [30]

Table S6: *Overview of key lipid components in lipid nanoparticles (LNPs) and liposomal formulations.*

Type of lipid	Role	Name	Characteristics
Ionizable / Cationic Lipid (major component of LNP ~50%)	- Provide a positive charge to LNPs/liposomes, enabling interaction with negatively charged nucleic acids - Contribute to nanoparticle biodegradability - Ionizable lipids are critical for forming destabilizing non-bilayer structures at acidic pH, facilitating endosomal escape and efficient RNA delivery into the cytosol	DOTMA	M**onovalent cationic** Quaternary ammonium head with ether bonds Commonly used in lipoplexes (e.g., BioNTech formulations) Lipofectamine = DOTMA + DOPE, however, ether bonds contribute to cytotoxicity
		DOTAP	**Monovalent cationic** Monovalent cationic lipid with a quaternary amine and ester bonds More biodegradable than DOTMA due to its hydrolysable ester linkage
		DDAB	**Monocationic** Monocationic lipid with a quaternary ammonium head and alkyl (C–N) bonds
		DODMA	**Ionizable monovalent cationic lipidic** Tertiary amine with ester bonds Protonated at physiological pH (pKa = 6.59), offering improved biodegradability over quaternary amines
		DODAP	**Ionizable lipid** Tertiary amine with ester bond Effective for endosomal escape at acidic pH (pKa = 5,59)
		DOSPA	**Polycationic lipid** Polycationic spermine-based lipid with ether and carboxamide bonds Forms strong electrostatic interactions with nucleic acids, increasing positive charge density
		GL-67	**Polycationic lipid** Polycationic spermine-based lipid with ether bonds Simplified structure compared to DOSPA, improving ease of synthesis
		DOGS	**Polycationic lipid** Polycationic spermine-based lipid with amide bonds Amide bonds enhance stability but reduce biodegradability, leading to slower breakdown in vivo.
		Dlin-DMA	**Ionizable lipid** Tertiary amine with ester linker (pKa = 6.0) A linolyl analogue of DODMA, enhancing structural versatility Dlin-MC3-DMA is used for the approved Onpattro
		SM-102	**Ionizable lipid** Ionizable lipid (pKa = 6.68) with a tertiary amine, hydroxyalkyl group and branched 3-tail structure with ester bond Used in Moderna's mRNA-1273 vaccine
		ALC-0315	**Synthetic ionizable lipid** Ionizable lipid (pKa = 6.09) with a tertiary amine, hydroxyalkyl group, and branched four short tails with ester bonds. Used in Pfizer/BioNTech mRNA vaccines
		C14.4	**Ionizable monoationic lipid** Ionizable lipid (pKa = 6.5) with a tertiary amine and ether bonds
Ionizable	- Facilitates stable nanoparticle	DOPA	Ionizable anionic lipid with a phosphatidic acid head group and ester bonds.

anionic Lipid	formation by neutralizing excess positive charge - Enhances membrane fusion and transfection efficiency		Negatively charged at physiological pH, contributing to nanoparticle stability and transfection capabilities
Phospholipid (neutral)	- Provides structural rigidity and stability to nanoparticles. -Enhances transfection efficiency -Prevents nanoparticle aggregation, ensuring uniform dispersion and performance	DSPC	**P**hosphatidyl**c**holine based lipid
		18:1EPC	
		DOPC	
		POPC	
		HSPC	
		DSPE	**P**hosphatidyl**e**thanolamine based lipid
		DOPE	
		DPPE	
		POPE	
Cholesterol	- Enhances nanoparticle stability and facilitates membrane fusion - Provides structural rigidity and integrity to lipid nanoparticles - Reduces surface protein binding, improving circulation time and reducing immune clearance	DC-Cholesterol,	Cholesterol derivative
		Beta-Sitosterol	Plant-based cholesterol analogue
		SM-Chol	Cholesterol derivative with sphingomyeline (major component of cellular membranes). Enhances the structural integrity of lipid-based drug delivery systems, making them more stable, biocompatible, and effective in delivering therapeutic agents over longer periods.
PEGylated-Lipid (stealth lipid)	- Enhances colloidal stability of nanoparticles - Provides stealth properties by reducing opsonization, protecting nucleic acids from immune system recognition and degradation - Prolongs circulation time in the bloodstream and delays uptake by the mononuclear phagocyte system (MPS), improving therapeutic efficacy	C-DMG-PEG(2000)	PEGylated lipid Used in mRNA COVID-19 vaccine LNP (Moderna)
		ALC-0159	PEGylated lipid Used in mRNA vaccines LNP (BioNTech/Pfizer)
		DSG-PEG(2000)	PEGylated lipid with a 2000 Da PEG chain DSG (Distearoyl-glyceryl) is a glycerol-based lipid with two stearoyl chains, enhancing integration into cellular lipid bilayers. Provides improved nanoparticle stability, reduced immunogenicity, and prolonged circulation time

Information adapted from Wang et al. [31], *Cardarelli et al.* [32], *Jörgensen et al.* [33], *Funakoshi et al.* [34], *Wang et al.* [35], *Cullis & Felgner* [36]

Table S7: *Overview of ongoing clinical trials utilising liposomes for nucleic acid delivery.*

Composition	**NAs**	**Administration**	**Cancer**	**Phase**	**Sponsor**	**NCT + ASCO**
DOPC	EphA2 siRNA	IV	Solid tumours	I	M.D. Anderson Cancer Center	NCT01591356 **EphA2 gene targeting using neutral liposomal small interfering RNA (EPHARNA) delivery: A phase I clinical trial.** Naing et al. [37]
Amphoteric liposomes (SMARTICLES®)	Double stranded RNA to activate CEBPA gene	IV	Advanced liver cancer	I	Mina Alpha Limited	NCT02716012 **Phase Ib dose escalation and cohort expansion study of the novel myeloid differentiating agent MTL-CEBPA in combination with sorafenib in patients with advanced hepatocellular carcinoma (HCC).** Sarker et al. [38]
DOPC	ASO Bcl2	IV	Advanced Lymphoid Malignancies	I	Bio-Path Holdings, Inc.	NCT04072458 **Making Sense of Antisense Oligonucleotide Therapeutics Targeting Bcl-2** Gagliardi & Ashizawa [39]

Table S8: *Overview of ongoing clinical trials utilising lipoplexes for nucleic acid delivery.*

Platforms	Composition	NAs	R.A.	Cancer	Phase	Sponsor	NCT + ASCO
Individualized Neoantigen Specific Immunotherapy	DOTMA	mRNA RO7198457 (=BNT122, = RO7198457) encoding patient specific TSA	IV	Untreated Advanced Melanoma	II	BioNTech SE / Genentech, Inc.	NCT03815058: **Adoptive Cell Transfer and Vaccines in Melanoma: The Horizon Comes Into View** Betof-Warner et al. [40]
				NSCLC	II		NCT04267237 **The clinical progress of mRNA vaccines and immunotherapies** Barbier & Al. [41]
				ctDNA-positive, Resected Stage II (High Risk) and Stage III Colorectal Cancer	II		NCT04486378 **A phase 2 multicenter trial in patients with stage II/III colorectal cancer to compare efficacy of autogene cevumeran versus waiting.** Kopetz et al. [42]
				Solid tumour	I		NCT03289962
FixVac (**Fix**ed **Vac**cine)	DOTMA	mRNA encoding for TSA (BNT111)	IV	Advanced melanoma	II	BioNTech SE	NCT04526899
		mRNA encoding viral antigen (TSA) (BNT113)		HPV16-positive head and neck cancer	II		NCT04534205: **Breaking Ground in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Novel Therapies Beyond PD-L1 Immunotherapy** Rosenberg et al. [43]
		mixture of six liposomally formulated RNAs each of which encodes for a different tumour-associated antigen. (BNT116)		1st line metastatic NSCLC Advanced/metastatic NSCLC	I		NCT05142189
	DOTAP:Chol	P(plasmid)bi-shRNA™ EWS/FLI1 Type 1	IV	Advanced Ewing's Sarcoma	I	Gradalis, Inc.	NCT02736565 **Pbi-shRNA™ EWS/FLI1 Type 1 LPX in Subjects With Advanced Ewing's Sarcoma** Rao et al. [44]
SGT 53	DOTAP: DOPE	pcDNA53	IV	Metastatic Pancreatic Cancer	II > III	SynerGene Therapeutics, Inc.	NCT02340117 **A phase II trial combining tumor-targeting *TP53* gene therapy with gemcitabine/nab-paclitaxel as a second-line treatment for metastatic pancreatic cancer.** Leung et al. [45]

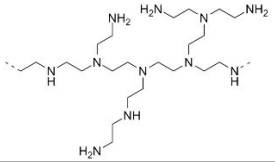
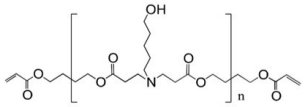
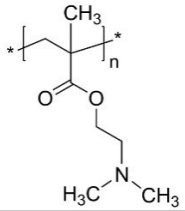
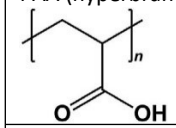
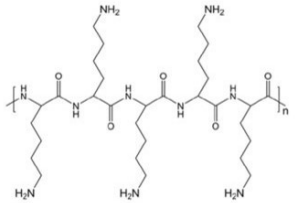
Table S9: *Overview of ongoing clinical trials utilising LNPs for nucleic acid delivery.*

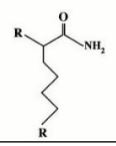
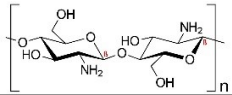
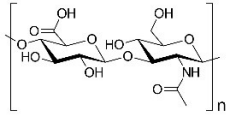
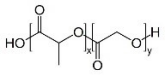
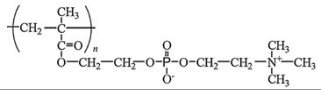
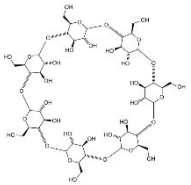
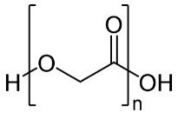
NAs	Administration	Cancer	Phase	Sponsor	NCT + ASCO
mRNA-4157: Modified to encode patient-specific tumour antigens for Individualised Neoantigen Therapy (INT). V940 (formerly mRNA-4157) encodes up to 34 tumour-derived neoantigens tailored for each patient	IV	Melanoma	II	Moderna Therapeutics Inc.	NCT03897881 (KEYNOTE-942) **Distant metastasis-free survival results from the randomized, phase 2 mRNA-4157-P201/KEYNOTE-942 trial.** Khattak et al. [46] **Personalized anti-cancer vaccine combining mRNA and immunotherapy tested in melanoma trial** Carvalho et al. [47]
	IM	Melanoma	III	Merck Sharp & Dohme LLC	NCT05933577 **INTerpath-001: Pembrolizumab with V940 (mRNA-4157) versus pembrolizumab with placebo for adjuvant treatment of high-risk stage II-IV melanoma.** Jeffrey S. Weber & Al. [48]
	IM	Non-small Cell Lung Cancer	III	Merck Sharp & Dohme LLC	NCT06077760 **The phase 3 INTerpath-002 study design: Individualized neoantigen therapy (INT) V940 (mRNA-4157) plus pembrolizumab vs placebo plus pembrolizumab for resected early-stage non–small-cell lung cancer (NSCLC).** Lee et al. [49]
mRNA encoding cytokines: Includes OX40L, IL-23, and IL-36γ to stimulate immune responses	Intratumoral	Solid tumours and lymphoma	I	ModernaTX, Inc.	NCT03739931 **A phase I study of mRNA-2752, a lipid nanoparticle encapsulating mRNAs encoding human OX40L, IL-23, and IL-36γ, for intratumoral (iTu) injection alone and in combination with durvalumab.** Patel & Al. [50]

mRNA encoding MYC: Therapeutic vaccine targeting the oncogene MYC	IV	HCC and other solid tumour types known for association with the MYC oncogene	I/II	Omega Therapeutics	NCT05497453 **A phase 1/2 open-label study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of OTX-2002 as a single agent and in combination with standard of care in patients with hepatocellular carcinoma and other solid tumor types known for association with the MYC oncogene (MYCHELANGELO I).** Rodriguez-Rivera et al. [51]
mRNA-4359: Encodes PD-L1 and IDO1 antigens for immunotherapeutic vaccination	IM	Advanced Solid Tumours	I/II	ModernaTX, Inc.	NCT05533697 **Phase 1/2 study of mRNA-4359 administered alone and in combination with immune checkpoint blockade in adult participants with advanced solid tumors.** Powderly & Al. [52]
BNT142: Encodes a bispecific antibody targeting CLDN6 (an oncofoetal antigen) and CD3 for T-cell engagement.	IV	Claudin 6 (CLDN6)-positive advanced tumours.	I/II	BioNTech SE	NCT05262530 **A phase I/II dose escalation trial with expansion cohorts to evaluate safety and preliminary efficacy of BNT142 in patients with prospectively confirmed claudin 6-positive solid tumors.** Yap et al. [53]
BNT152/153: Encodes IL-7 (BNT152) or other cytokine-modulating mRNAs for enhanced immune function.	N/A	various solid tumour indications	I	BioNTech SE	NCT04710043 **A systematic review of interleukin-2-based immunotherapies in clinical trials for cancer and autoimmune diseases** Raeber et al. [54]

Glioblastoma-targeted mRNA: Encodes a fusion protein with eight tumour-associated epitopes relevant to glioblastoma, incorporating both HLA class I and II epitopes	IM	Resected Glioblastoma (GBM) or Astrocytoma With a Molecular Signature of Unmethylated Glioblastoma	I	CureVac SE	NCT05938387 **Phase 1 dose-finding study to evaluate safety and tolerability of CVGBM in patients with newly diagnosed and surgically resected MGMT-unmethylated glioblastoma.** Tabatabai et al. [55]
Viral antigen mRNA	IM	Epstein-Barr Virus-related Refractory Malignant Tumours	I	WestGene Biopharma	NCT05714748 **Safety, tolerability, and immunogenicity of WGc-043 in subjects with EBV-positive cancers: Results from an investigator-initiated trial.** Peng et al. [56]
Increasing doses of repeated boosts with a self-amplifying mRNA encoding a neo-antigen (after AdV injection)	IM	advanced metastatic solid tumours	I	Gritstone bio, Inc.	NCT03953235 **Personalized viral-based prime/boost immunotherapy targeting patient-specific or shared neoantigens: Immunogenicity, safety, and efficacy results from two ongoing phase I studies.** Drake et al. [57]
self-amplifying mRNA vector encoding 2 neoantigens (GRT-R902) + GRT-C901-adenoviral vector	SC	newly diagnosed metastatic colorectal cancer	II/III	Gritstone bio, Inc.	NCT0514172 **Phase 2/3, randomized, open-label study of an individualized neoantigen vaccine (self-amplifying mRNA and adenoviral vectors) plus immune checkpoint blockade as maintenance for patients with newly diagnosed metastatic colorectal cancer (GRANITE).** Hecht et al. [58]
siRNA (NBF-006): Targets GSTP (glutathione S-transferase P) to inhibit tumour proliferation	IV	advanced non-small cell lung (NSCLC), pancreatic (PANC), or colorectal cancer (CRC)	I	Nitto BioPharma, Inc.	NCT03819387 **First-in-human dose-escalation study of NBF-006, a novel investigational siRNA targeting GSTP, in patients with non-small cell lung, pancreatic, or colorectal cancer.** Tolcher et al. [59]

Table S10: *Overview of the main polymers used for nucleic acids delivery nucleic acid delivery.*

Type of polymers	Role	Synthetic Or Natural	Name / Family	Advantage	Challenges
Cationic	Gene delivery via electrostatic interactions with nucleic acids	Synthetic	Polyethyleneimine (PEI) (branched or linear) 	High transfection efficiency	Toxicity and limited biodegradability due to the presence of non-degradable vinyl (-C-C-) and amide bonds
			PBAE (linear) 	Low toxicity Enhanced transfection efficiency Proton sponge for endosomal escape	
			PDMAEMA (branched or linear) 	Chemical flexibility	
			PAA (hyperbranched) 	Low toxicity Enhanced transfection efficiency	Complex synthesis, optimization of disulphide linkages
			PLL (linear or branched: dendrimer) 	Advantages include gene delivery facilitated by hydrolysable ester bonds, high biocompatibility, and efficient nucleic acid binding	Potential toxicity associated with high molecular weight and non-biodegradability in certain formulations

			Histidine-Lysine Co-polymers (HKP) **R:** KHKHKHKHKGKHKHKHKHK (HKseries) or KHKHHKHHKHHKHHKHHKHK (HHKseries) **2 branch** 	Efficient endosomal escape, siRNA and DNA complexation	Potential cytotoxicity, Serum stability
		Natural	Chitosan (CS) (linear) 	Biocompatibility and biodegradability	Low solubility under physiological conditions
			Hyaluronic acid (HA) + cationic polymers 	Biocompatibility, CD44 receptor targeting	Must be combined with cationic polymers for gene complexation
Neutral (hydrophobic non-ionizable	Controlled drug release, structural support	Synthetic	PLGA (Copolymer) *= Poly (Lactic-co-Glycolic acid)* 	biodegradability through glycolic and lactic acids, high biocompatibility, and FDA approval for GMP manufacturing	Hydrophobicity, often requires cationic polymers for gene delivery Low nucleic acid loading,
			PMPC-25 	Anti-fouling properties High biocompatibility Minimised immune response	Limited transfection efficiency for gene delivery
		Natural	Cyclodextrin 	Biocompatible Facilitates drug solubilization and complexation Oral administration possible	Limited stability in physiological conditions
Anionic	Neutralize the positive charge of cationic polymers, enhancing nanoparticle stability and reducing the cytotoxicity associated with highly cationic polymers	Synthetic	PGA 	Can be functionalized with proteins Acts as a protective shield Reduces non-specific interactions with cells and proteins in the bloodstream	Rapid clearance by the body Limited stability in certain conditions

Information adapted from *Chen et al*. [60], *Piotrowski-Daspit et al.* [61], *Molinar et al.* [62], and *Smith et al.* [63]

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