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SUPPLEMENTARY INFORMATION

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Improving cancer immunotherapy using nanomedicines: progress, opportunities and challenges

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Improving cancer immunotherapy using nanomedicine: Progress, opportunities and challenges

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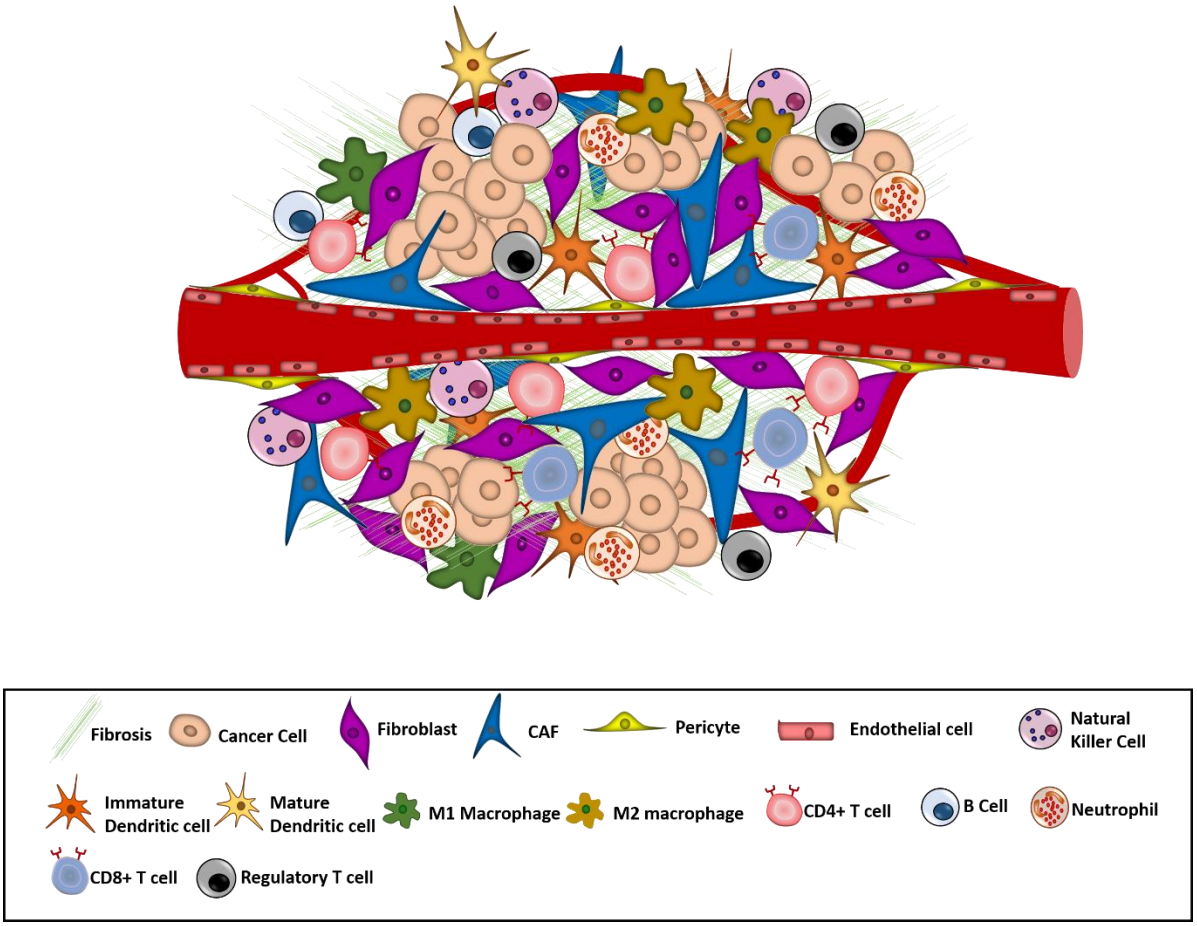

Supplementary Figure 1. Schematic representation of cancer cells and various components of the tumor microenvironment (TME). The TME includes various stromal cells and immune cells, extracellular matrix (ECM) and blood vessels. Note that tumor vessels are leaky and compressed in places with uneven diameter and abnormal pericyte and basement membrane coverage. These characteristics impair blood flow. Moreover, the ECM hinders the penetration of drugs, especially of large MW. Endothelial cells line the vessel wall. Pericytes and basement membrane surround endothelial cells and support their structure and function. Fibroblasts produce and maintain the extracellular matrix. Once activated, these carcinoma-associated fibroblasts (CAFs) produce excessive ECM and various cytokines. The myeloid compartment, including neutrophils, is responsible for antigen capture for degradation and presentation (dendritic cells), tissue repair (macrophages), and effector functions. These various phenotypes underscore the plasticity of these cells' phenotype, which can be altered by the TME. The lymphoid compartment is made of natural killer (NK) cells, NK T cells, B cells, CD8+ T cells and other T cells (not shown) including CD4+ T cells. CD8+ T cells are the major anti-tumor effector cells from which cytotoxic T lymphocytes (CTLs) arise and destroy cancer cells presenting a specific peptide-MHC complex. NK cells depend on expression of MHC class I molecules and B cells on surface proteins. Naïve CD8+ T cells become CTLs in lymphoid organs when they are presented an antigen. CD4+ cells can become anti-tumor helper cells that support CTL function or regulatory T cells that support the tumor. Tumors with more CD8+ T cells are considered hot and have better responses to immunotherapies.

Supplementary Table 1. FDA-approved intravenously administered cancer nanomedicines and their survival benefit. This table is updated from a previous review by the senior author (1).

Trade name and cancer type (patient number)	Year approved	Additional drugs in investigated regimen	Control regimen	Change in OS
PEGylated liposomal doxorubicin				
Karposi sarcoma (n = 258)(2)	1995	NA	Doxorubicin, bleomycin, and vincristine	NS
Recurrent epithelial ovarian carcinoma (n = 474) (3)	2005	NA	Topotecan	NS
Metastatic breast cancer (n = 509)(4)	NA	NA	Doxorubicin	NS
Multiple myeloma (n = 646) (4)	2008	Bortezomib	Bortezomib	Time to progression enhanced 2.8 months
Nanoparticle albumin-bound paclitaxel				
Metastatic breast cancer (n = 460)(5)	2005	NA	Paclitaxel	2.5 months
Metastatic breast cancer (n = 302) (6)	NA	NA	Docetaxel	5.4 months progression-free survival
Metastatic or locally recurrent breast cancer (n = 783) (7)	NA	NA	Paclitaxel	NS and more toxic
Neoadjuvant breast cancer (n = 1,229) (8)	NA	Epirubicin and cyclophosphamide	Paclitaxel, epirubicin and cyclo-phosphamide	9.4% increased rate of pCR
Neoadjuvant breast cancer (n = 695) (9)	NA	Anthracycline	Paclitaxel and anthracycline	NS
Advanced-stage NSCLC (n = 1,052)(10)	2012	Carboplatin	Paclitaxel, carboplatin	NS
Metastatic PDAC (n = 886) (11)	2013	Gemcitabine	Gemcitabine	1.8 months progression-free survival

Adjuvant PDAC (n = 866) (12)	NA	Gemcitabine	Gemcitabine	NS
Metastatic non-squamous NSCLC (n = 1,202) (13)	2018	Atezolizumab and/or bevacizumab with carboplatin and paclitaxel or nab-paclitaxel	Carboplatin and paclitaxel or nab-paclitaxel	Survival benefit from atezolizumab and bevacizumab. Paclitaxel equivalent to nab-paclitaxel
Advanced-stage TNBC (n = 902) (14)	2019	Atezolizumab	Nab-paclitaxel alone	Survival benefit from addition of atezolizumab
Liposomal daunorubicin				
Karposi sarcoma	1996	NA	Doxorubicin, bleomycin, and vincristine	NS
Liposomal irinotecan				
Second-line metastatic PDAC (n=266)(15)	2015	5-Fluorouracil and folinic acid	5-Fluorouracil and folinic acid	1.9 months
Liposomal vincristine				
ALL	2012	NA	NA	20% complete response
Aqueous suspension of crystalline hafnium oxide nanoparticles *				
Locally advanced soft-tissue sarcoma (n = 179) (16)	2019	Radiotherapy	Radiotherapy	Doubled rate of pathological complete response
Liposome-encapsulated combination of daunorubicin and cytarabine				
Newly-diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC) (n = 309) (17)	2017	Liposome-encapsulated combination of daunorubicin and cytarabine	Daunorubicin and cytarabine (7 + 3)	3.7 months

ALL, acute lymphocytic leukaemia; AML, Acute myeloid leukaemia; NA, not applicable; NS, not significant; NSCLC, non-small-cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.
*This formulation has received European market approval but not FDA approval

Supplementary Table 2. FDA-approved vascular normalization agents plus agents in clinical trials in combination with nanomedicines and/or immunotherapy.

Drug	Target	Approved indications	Clinical trials with ICBs	Clinical trials with nanomedicines
Axitinib	VEGFR 1–3, PDGFRβ	RCC	Approved for: first-line treatment of patients with advanced-stage renal cell carcinoma with either avelumab or pembrolizumab. NCT02684006, NCT02853331 (both RCC)	None
Bevacizumab	Anti-VEGF-A antibody	CRC, NSCLC, breast cancer, RCC	Approved for : first-line treatment of patients with metastatic non-squamous, NSCLC NCT03038100, NCT03737643, NCT02891824, NCT03642132, NCT03353831, NCT03740165, NCT03598270 (ovarian cancer); NCT03414983, NCT02997228, NCT02563002 (CRC or CRC with MMR deficiency); NCT02366143, NCT03117049 (NSCLC); NCT03635567, NCT03556839 (cervical cancer); NCT03778957, NCT03434379 (HCC); NCT02839707 (endometrial cancer); NCT02017717 (glioblastoma); NCT02420821 (RCC)	Multiple phase III trials including NCT02839707 in ovarian cancer with liposomal doxorubicin and atezolizumab and NCT00785291 with nab-paclitaxel.
Cabozantinib	VEGFR 2, Tie2	MTC, RCC	None	None
Everolimus	mTOR inhibitor	RCC, PNET, GI cancer, NSCLC	NCT01668784, NCT02811861 (RCC)	None
Lenalidomide	Chemotherapy pleiotropic	Multiple myeloma	NCT02579863	None
Levantinib	VEGFR 1–3, PDGFRα, FGFR 1–4	Thyroid cancer	None	None
Nintedanib	VEGFR 2, PDGFR-α/β, FGFR 1	NSCLC	None	None
Pazopanib	VEGFR 1–3, PDGFRβ, FGFR 1–2	RCC, soft tissue sarcoma	NCT03260894 (RCC)	None
Ramucirumab	Anti-VEGFR2 antibody	Gastric cancer, HCC NSCLC, CRC	None	None
Regorafenib	VEGFR 1–3, PDGFRβ, FGFR 1–2	CRC	None	None
Sorafenib	VEGFR 2,	RCC, HCC,	NCT03755791, NCT03434379,	None

	PDGFRβ	thyroid cancer	NCT02576509, NCT03298451 (HCC)	
Sunitinib	VEGFR 1–2, PDGFRα/β	RCC, GIST, PNET	NCT02684006, NCT03729245, NCT02231749, NCT02420821, NCT03141177, NCT02853331, NCT03260894, NCT02811861 (RCC)	None
Thalidomide	Chemotherapy pleiotropic	Multiple myeloma	NCT02576977, NCT02726581 (Multiple myeloma)	None
Vandetanib	VEGFR 2	MTC	None	None
Aflibercept	VEGF-inhibitory protein (VEGFA, VEGFB, PlGF)	CRC	None	None

CRC, colorectal cancer; GIST, gastro-intestinal stromal tumour; HCC, hepatocellular carcinoma; MTC, medullary thyroid cancer; NSCLC, non-small-cell lung cancer; PNET, primitive neuro-ectodermal tumours. On April 22, 2019 we searched clinicaltrials.gov for the [name of anti-angiogenic therapy] AND pembrolizumab OR atezolizumab OR nivolumab OR cemiplimab OR ipilimumab OR durvalumab OR avelumab OR ipilimumab AND Cancer [DISEASE] with filters for Phase III and active or recruiting. For trials in combination with NM, on April 22, 2019 we searched clinicaltrials.gov for the [name of stromal normalizing therapy] AND (nab-paclitaxel OR (liposomal AND doxorubicin)) AND Cancer [DISEASE] with filters for Phase III and active or recruiting.

Supplementary table 3. Investigational stromal normalization agents in clinical trials involving nanomedicines and/or immune-checkpoint inhibition.

Drug name/class, target	**FDA approved for cancer/other indications**	**Clinical stage for cancer with chemotherapy**	**Clinical stage with immunotherapy**	**Clinical stage with nanomedicine**
Losartan, an angiotensin system inhibitor also targeting TGFβ	No/yes	Phase II completed – historically high resection rates in patients with locally advanced PDAC(18)	NCT03563248; an ongoing phase II trial – in combination with nivolumab, radiotherapy and FOLFIRINOX in patients with PDAC	None
Paricalcitol, a vitamin D receptor agonist	No/yes	Phase II ongoing – in combination with nab-paclitaxel and gemcitabine in metastatic PDAC	NCT02930902; phase II ongoing – in combination with pembrolizumab and chemotherapy in resectable (NCT02930902, NCT03519308) or metastatic (NCT02754726) PDAC or as maintenance therapy (NCT03331562)	NCT0352079; phase II in metastatic PDAC with gemcitabine and nab-paclitaxel
Plerixafor and immunostimulant via CXCL12 and CXCR4	Yes/yes	Phase I completed – in combination with bevacizumab in GBM(19); phase II ongoing – in combination with temozolomide and radiation in GBM	Phase I and observational studies in patients with PDAC, ovarian cancer and colorectal cancer (none active or recruiting)	None
Metformin a biguanide used in diabetes that also targets TGFβ	No/yes	Phase III ongoing – in combination with paclitaxel and carboplatin in endometrial cancer	Phase II ongoing in combination with nivolumab in NSCLC (NCT03048500) and CRC (NCT03800602), pembrolizumab in melanoma (NCT03311308), durvalumab in HNSCC	Several, including NCT02488564, a phase II trial in advanced HER2+ breast cancer with doxil and NCT02336087 phase I in

			(NCT03618654), and in breast cancer (NCT01042379)	unresectable PDAC with nab-pacliatxel and gemcitabine
All-trans retinoic acid	Yes/yes	Approved for acute promyelotcytic leukaemia	Phase II ongoing in melanoma in combination with pembrolizumab (NCT03200847) and ipilimumab (NCT02403778)	NCT0330714; phase I in patients with locally advanced or metastatic PDAC
PEGPH20, a pegylated recombinant hyaluronidase*	No/no	In phase I/II, PEGPH20 associated with worse survival with FOLFIRINOX in mPDAC(20)	Early phase I trial with avelumab in chemoresistant locally advanced (NCT03481920) or metastatic PDAC (NCT03193190), with pembrolizumab in NSCLC and gastric cancer (NCT02563548, NCT03281369), with atezolizumab in cholangiocarcinoma (NCT03267940)	NCT0271580; phase III trial in stage IV PDAC first-line with gemcitabine and nab-paclitaxel in patients with high tumour hyaluronan levels, based on positive phase II results(21)
Pentoxifylline, a non-selective phosphodiesterase inhibitor	No/yes	Phase II	None	None
Pirfenidone, an anti-inflammatory agent approved for idiopathic pulmonary fibrosis that also targets TGFβ	No/yes	Phase I ongoing in NSCLC	None	None
Tranilast an anti-histamine that also targets TGFβ	No/no (approved as an anti-histamine in Japan and Korea)	None	None	None

CRC, colorectal cancer; FOLFIRINOX; folinic acid, 5-fluorouracil, irinotecan, oxaliplatin; GBM, glioblastoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung cancer; PDAC, pancreatic ductal adenocarcinoma;
*PEGPH20 does not reprogram CAFs, but rather depletes desmoplasia, which has been shown in preclinical studies to induce tumor progression. **Some studies have demonstrated a correlation between relaxin levels and tumour progression. For trials involving combination with ICI, on April 22, 2019 we searched clinicaltrials.gov for the [name of stromal normalizing therapy] AND pembrolizumab OR atezolizumab OR nivolumab OR cemiplimab OR ipilimumab OR

durvalumab OR avelumab OR ipilimumab AND Cancer [DISEASE] with filters for and active or recruiting. For trials in combination with NM, on April 22, 2019 we searched clinicaltrials.gov for the [name of stromal normalizing therapy] AND (nab-paclitaxel OR (liposomal AND doxorubicin)) AND Cancer [DISEASE] with filters for and active or recruiting.

Supplementary table 4. Retrospective studies of inhibitors of the renin—angiotensin—aldosterone (RAS) system in patients with cancer. This table is updated from a previous review of the senior author (22).

Type, population	Year	Number of patients	Combined therapies	Outcome control (months)	Outcome RAS inhibitor use (months)
NSCLC					
Stage IIIB–IV	2009(23)	287	Chemotherapy	OS 8.6	11.7
Stage IIIA–B	2015(24)	673	RT ± chemotherapy	No change in OS	
Metastatic	2015(25)	117	Chemotherapy	OS 12	17
Stage I-IIIA/Stage IIIB–IV	2016(26)	301	Surgery + Chemotherapy or TKIs	PFS 6.8	9.2
Stage IIIB–IV	2016(27)	CP: 1,465 CBP: 348	Chemotherapy ± anti-VEGF (CP± bevacizumab)	CP OS 8.4	12
Advanced-stage	2019(28)	283	Anti-PD-1/PD-L1 antibodies	PFS 3.8	2.5
Breast cancer					
Stage I–III	2011(29)	1,413	Neoadjuvant chemotherapy	No change in OS	
StageI–IIIA	2011(30)	1,779	Curative	Increased recurrence	
Stage II/III	2011(31)	703	Curative	No change in OS, reduced recurrence	
Stage I–IV	2012(32)	486	Treatment NR	No change in OS	
Early triple-negative	2013(33)	800	Resection	No change in OS	
Stage I–III	2013(34)	1,449	Neoadjuvant chemotherapy	No change in OS	
Stage I–II	2014(35)	4,216	Resected	Increased risk of second primary breast cancer	
Pathologic N3	2015(36)	218	Resected	No change in OS	
Early $ER^+/HER2^-$	2016(37)	671	NA	No change in OS	
RCC					
Metastatic	2011(38)	127	Sunitinib	PFS 6	13
Metastatic	2014(39)	278	Sunitinib	Higher PFS with RAS inhibitor use	
Metastatic	2015(40)	4,736	Systemic	OS 16.7	26.7
Metastatic	2015(41)	213	Sunitinib	Longer OS with RAS inhibitors	
Non-metastatic	2015(42)	557	Resection	Higher 5-year survival rate with RAS inhibitors	
Metastatic	2016(43)	1,545	anti-VEGF/placebo	No change in OS	

Urinary tract cancer					
Localized UTUC	2012(44)	279	Resection	5-year MFS 72.8%	93.0
NMIBC	2012(45)	330	Resection	5-year RFS 53.3%	78.4
NMIBC	2015(46)	340	Resection	5-year RFS 28.1%	45.6
Bladder cancer, T1-4, N0/≥1	2017(47)	269	Resection	5-year OS 61.4%	76.1
Prostate cancer					
Local/locally advanced	2016(48)	558	RT plus HT	Biochemical recurrence 38.3%	18.4
PDAC					
Advanced-stage	2010(49)	155	Chemotherapy	OS 9.5	15.1
Advanced-stage	2013(50)	250	Chemotherapy	Longer OS	
Advanced-stage	2015(51)	349	Chemotherapy	OS 11.2	15.6
T1-4/N0-1	2015(52)	164	Resection	No change in OS	
Resected, locally advanced, metastatic	2017(53)	794	–	OS 19.3	36.3
Oesophageal cancer					
Stage I–IV	2015(54)	1,174	CRT +/– resection	No change in OS	
Stage I–III	2015(55)	141	Resection	OS 58.3	75.3
Advanced-stage	2018(56)	375	Chemotherapy	OS 30	59
Gastric cancer					
Advanced-stage	2012(57)	63	Chemotherapy	OS 8.2	13.9
Colorectal cancer					
CRC stage II	2007(58)	55	Surgery	More distant metastasis with less RAS inhibitors	
Advanced-stage CRC	2013(59)	262	Chemotherapy or RT	OS 695 days	1,341 (when combined with β blockers)
Metastatic CRC	2015(60)	181	Chemotherapy and anti-VEGF	OS 15.2 months	26.5
Rectal cancer	2016(61)	115; 186	Neoadjuvant (C)RT	pCR 17%	52%
Hepatobiliary cancer					
HCV-related HCC without cirrhosis and	2011(62)	185; 141	Resection	5-year OS 51.6%	76.7

with cirrhosis					
HCC	2015(63)	153	RFA-treated	OS 48 months	84
Advanced-stage BTC	2016(64)	287	Chemotherapy	No change in OS	
HCC	2017(65)	156; 76	Sorafenib or experimental therapy or BSC	OS 6.8	11.9
Melanoma					
Nonmetastatic	2013(66)	741	Resection	No change in OS	
Glioblastoma					
Supratentorial GBM	2012(67)	87	RT	Steroid-sparing effect	
Supratentorial GBM	2015(68)	81	RT plus temozolomide	OS 12.9	16.7
Supratentorial GBM, newly diagnosed	2016(69)	22	–	Less oedema	
GBM	2017(70)	1,186	Chemotherapy and bevacizumab	OS 56 weeks	99
Haematological malignancies					
Multiple myeloma	2005(71)	168	PBSCT	OS 73.3	38.7
AML	2014(72)	1,043	Chemotherapy	No change in OS	
Ovarian cancer					
Stage IIIC or IV	2019(73)	222	Standard of care	OS 33 months	63
Studies including several cancer types					
Lung CRC Breast Prostate	2013(74)	4,241; 3,967; 4,019; 3,355	–	Shorter OS in breast and lung	
Breast CRC Prostate	2014(75)	9,814; 4,762; 6,339	–	No effect on OS	

AML, acute myeloid leukaemia; BSC, best-supportive care; BTC, biliary tract cancer; CP, carboplatin and paclitaxel; CBP, carboplatin, paclitaxel and bevacizumab; CRC, colorectal cancer; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NA, not applicable; NR, not reported; NSCLC, non-small-cell lung cancer; NMIBC, nonmuscle-invasive bladder cancer; OS, overall survival; PBSCT, peripheral blood stem cell transplantation; PDAC, pancreatic ductal adenocarcinoma; RAS, renin–angiotensin–aldosterone system; RCC, renal cell carcinoma; RFA, radiofrequency ablation; TKI, tyrosine-kinase inhibitor; UTUC, upper-tract urothelial carcinoma.

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