Table S4. List of anti-malarial agents that are currently being investigated in clinical trials for their effectiveness against different cancer types when alone and/or in combination with chemotherapeutic agents as well as anti-malarials that are potential new anti-cancer drugs shown to inhibit malignant cells in *vivo*/*in vitro*. The summarized data is obtained from clinicaltrials.gov, the National Institute of Health (NIH), the Drugbank, and the ReDo databank. PubMed and Google Scholar have been used to gain detailed information about the mechanism(s) of action of the potential repurposed drugs *in vitro* and *in vivo*. The keywords used for the search are "anti-cancer" and "repurposed".

Drug	**Original application / target**	**New application (anti-cancer) / Proposed Target/Mechanism of action**	**Stage of development**
Artesunate	**Anti-Malaria** Cleavage of endoperoxide bridge → ROS generation in parasite → DNA doublestrand breaks [1]	**Hepatocellular carcinoma (HCC) and Head and neck cancer (HNC):** -As single treatment Induces iron-dependent, ROS-mediated ferroptosis [2, 3] **HCC and Renal cell carcinoma (RCC):** -In combination Synergizes with Sorafenib [2, 4, 5] **Breast cancer:** **-**In combination Synergizes with DOX and PTX [6] Upregulates Beclin1 → autophagy → G2/M cell cycle arrest and chemo sensitization to Epirubicin [7] Induces ROS-dependent G2/M cell cycle arrest and apoptosis, leads to chemo sensitization to different chemotherapeutics [8] -As single treatment Disrupts endolysosomal trafficking and inhibits autophagic flux [9] **Glioblastoma:** -In combination (Supra-)additive effects with OSI-774/ sensitivity and resistance dependent on genetic alterations [10] Downregulates survivin → induces apoptosis and G2/M phase arrest, reduces DDR in combination with X-irradiation [11] -As single treatment Induces oxidative DNA stress → induces DSB and DDR → necrosis and apoptosis [12]	**Clinical trial Phase I:** -Metastatic breast cancer (NCT00764036) -Solid tumors (NCT02353026) -Cervical neoplasia intravaginally (NCT02354534) -Vulvar neoplasia: ointment (NCT03792516) -Anal neoplasia: intra-anally (NCT03100045) -HCC (NCT02304289) **Clinical trial Phase II:** -Pre-operative in stage II/III Colon (NCT02633098, NCT03093129) -Cervical neoplasia: intravaginally (NCT04098744)

Artesunate *(Continued)*		**Gastric cancer:** -As single treatment Leads to release of cytochrome c and activation of Caspase-9 via ROS production → apoptosis via COX-2 inhibition [13] Leads to oncosis-like cell death via increased cytosolic Ca2+ → calpain-2 activation and VEGF inhibition [14] **T-cell leukemia:** -In combination Synergizes with DOX [15] Leads to the release of cytochrome c and activation of Caspase-9 via ROS production → apoptosis via intrinsic pathway [15] **Lung cancer:** -As single treatment Increases radiosensitivity via increased NO production → G2/M phase arrest via reduced Cyclin B1 mRNA expression [16] Cytotoxicity is dependent on the expression of glutathione-related Enzymes [17] **T-cell leukemia:** -In combination Synergizes with DOX [15] Leads to the release of cytochrome c and activation of Caspase-9 via ROS production → apoptosis via intrinsic pathway [15] **Karposi's sarcoma:** -As single treatment Inhibits angiogenesis and tumor [18] **HCC:** -As single treatment Reduces VEGF and PlGF expression → decreases angiogenesis [4] **Lung cancer:** -As single treatment Increases radiosensitivity via increased NO production → G2/M phase arrest via reduced Cyclin B1 mRNA expression [16] Cytotoxicity is dependent on the expression of glutathione-related Enzymes [17]	***In vivo:*** -HNC cells HN9 in athymic nude BALB/c nude mice [3] -Liver cancer cells Huh7 in nude Balb/c mice [2] DEN-induced HCC model in 129S2/SvPasCrl mice [4] -Lung cancer cells A549 in nude mice [16] -Kaposi's sarcoma cells KS-IMM in C57BL/6 mice and nude (CD-1) BR mice [18] -RCC cells 786-O-Luc in nude BALB/c mice [5] -NPC cells C666-1 or CNE2 in SCID mice [19] -Gastric cancer cells BGC-823 cells in nude athymic BALB/c mice [14] -Pancreatic cancer cells Panc-1 in nude athymic BALB/c mice [14]

Artesunate *(Continued)*		**RCC:** -As single treatment Reduces cyclin D1 levels → G2/M cell cycle arrest [5] Increases calpain-1 and calpain-2 expression → oncosis-like cell death [5] Inhibits cell proliferation, migration/metastasis and angiogenesis via decreased phosphorylation of VEGFR2 [5] **Pancreatic cancer:** -As single treatment Induces Oncosis, loss of ΔΨm via mitochondrial dysfunction and ROS production [20] **Cervical and breast cancer:** -As single treatment Activates lysosomal function → increases lysosomal degradation of ferritin → necessary for ROS production and apoptosis [9, 21] **Ovarian cancer:** Sensitivity dependent on TGF/Wnt pathway genes [22] **Nasopharyngeal Carcinoma (NPC):** -As single treatment Upregulates Cyclin B1 and downregulates Rb and E2F-1 expression → G2/M cell cycle arrest [19] Induces mitochondrial-independent apoptosis, apoptosis via Akt/mTOR inhibition and ROS production [19] -In combination Synergizes with Cisplatin [19] **Non-Hodgkin lymphoma (NHL):** -As single treatment Increases Beclin-1 and LC3-I/II expression, increases Caspase-3 expression → autophagy and apoptosis simultaneously [23] **Cervical cells:** -In combination Enhances TRAIL cytotoxicity via decreased survivin, XIAP and Bcl-XL expression [24]	***In vitro:*** -HNC cells SNU, HN2-10, HN3-cisR, HN4-cisR, and HN9-cisR [3] -Liver cancer cells Huh7, HepG2 [4, 21], SNU-182 and SNU-449 [2], BWTG3 [4] -Breast cancer cells MCF-7 [6–8], MDA-MB-231 [7, 8] and T47D [9], SK-BR-3 [8] -Glioblastoma cells LN-229 [11, 12], G-211GM, G-750GM, G-1163GM, G-1187GM, G-1265GM, G-1301GM, G-1408GM, G-210GM, G-599GM, U-87MG.LUX [29], U-87MG.DK-2N, U-87MG.WT-2N, U-87MG [11] and U-87MG.ΔEGFR [10, 29] -T-cell Leukemia cells Hut78, CEM, Molt-4, Jurkat J16, J-Neo, J-Bcl-2, J-caspase-8$^{-/-}$, Jurkat A3 FADD$^{-/-}$ and Jurkat A3 [15], CCRFCEM and HL-60 [29] -Lung cancer cells A549 [16] -Kaposi's sarcoma cells Kaposi's sarcoma-IMM [18] -RCC cells Caki-1-GFP, 786-O-GFP and SN12C-GFP [5], HCT116 [29] -NPC cells C666-1, HONE-1, HK1, HNE1, CNE2 [19] -Gastric cancer cells BGC-823, HGC-27 and MGC-803 [13], SGC-7901, BGC-823, and AGS [14] -Pancreatic cancer cells Panc-1, BxPC-3 and CFPAC-1 [20] -Stem cells TSC2-WT and TSC2-KO MEFs [21] -Cervical cancer cells HeLa [21, 24] -7 different ovarian cancer cell lines [22] -NHL cells Raji [23] -MSV-HL13 and MSV-PC4 cells, panel of 55 different cell lines [17, 29–31], WEHI7.2 cells [31]

Artesunate *(Continued)*		More extensive summary is presented in the reviews of Augustin et al., Li et al., Xu et al., and Sun et al. [25–28]	
Mefloquine	**Anti-Malaria** no known mode of action, but Wong et al. showed that it target the 80S-ribosome of the parasite [32]	**Breast cancer:** -In combination Synergizes with Doxorubicin and PAX [6] Chemo sensitizes to PAX [33] -As single treatment Enhanced cleavage of caspase 7 and PARP → apoptosis induction [33] -Arrests autophagy at the stage of autophagosome formation via increased LC3 and p62 expression [33] **Osteosarcoma (OSC):** -In combination Sensitizes resistant cells to vinblastine via inhibition of P-gp and increased apoptosis [34] **Leukemia:** -In combination Sensitizes resistant cells to Doxorubicin via decreased P-gp expression and inhibited pump-efflux activity of the same [35] **Prostate cancer:** **-**As single treatment Increases ROS generation → induces apoptosis and necrosis [36] Induces G_1 cell cycle arrest via increased cyclin D1 protein expression [36] Exerts anti-clonogenic effects [37] Hyperpolarizes MMP → ROS production → decreases Akt Ser473 phosphorylation, activates ERK, JNK and AMPK signaling → decreases cell viability [37] **Gastric cancer:** -As single treatment Inhibits PI3K/Akt/mTOR phosphorylation and signaling [38] -In combination Synergizes with PAX [38]	**Clinical trial Phase I:** -Glioblastoma: in combination with Temozolomide, Memantine Hydrochloride, and Metformin Hydrochloride after surgery (NCT01430351) Results [39] ***In vivo:*** -Prostate cancer cells PC3 in C57BL/6J mice [36] -Gastric cancer cells YCC1 or SNU1 in SCID mice [38] -Cervical cancer cells HeLa in SCID mice [40] -Liver cancer cells HepG2 in nude BALB/c mice [41] -Colon cancer cells HCT116 in nude mice [42] -AML cells MDAY-D2, K562 or OCI-AML2 in NOD/SCID mice [43]

Mefloquine *(Continued)*		**Stem cells:** -As single treatment Reduces the expression levels of β-catenin and cyclin D1 → decreases self-renewal and proliferation [41] **Cervical cancer:** -As single treatment -Leads to mitochondrial dysfunction → ROS production and energy crisis, suppression of mTOR phosphorylation → inhibits proliferation and induces apoptosis [40] -In combination Synergizes with PAX [40] **Colon cancer:** -As single treatment Inhibits IKK and NF-κB activation → induces apoptosis [42] -In combination Synergizes with Doxorubicin [42] **Acute myeloid leukemia (AML):** -As single treatment Disrupts lysosomes via ROS production → permeabilizes lysosome membrane → release of cathepsins → decreases proliferation and increased death [43] **Neuroblastoma:** -As single treatment Induces autophagy in an ATG6 dependent manner via formation of autophagosomes and the conversion of LC3I into LC3II → suppression of autophagy increases Mefloquine cytotoxicity [44]	***In vitro:*** -Breast cancer cells MCF-7 [6], MDA-MB-231, MDA-MB-468 and T47D [33] -OSC cells KB and KBV20C [34] -Prostate cancer cells PC3 [36], DU145 [37] -Leukemia cells K562 and K562/DXR [35] -Gastric cancer cells SNU1, SNU16, AGS, Hs746T, NCI-N87, MKN45, MKN74, YCC1, YCC10 and YCC11 [38] -Cervical cancer cells HeLa, SiHa and C-33A [40] -Liver cancer cells HepG2 and CD133+ HepG2 [41] -Colon cancer cells HT-29, HCT116, RKO, SW620 and Lovo [42] -Kidney cancer cells HEK293T [42] -Primary AML patient cells [43] -Neuroblastoma cells SH-SY5Y, MEFS and ATG5−/− MEF [44]

Chloroquine/ hydroxychloroquine (Inhibition of Chloroquine activity under acidic stress [45])	**Anti-Malaria** Inhibition of DNA/RNA synthesis via electrostatic forces Binding of heme → toxicity against parasites [46]	**HCC:** -As single treatment Induces G0/G1 cell cycle arrest [47] Leads to loss of ΔΨm → cleavage of Caspase 3 and PARP → intrinsic apoptosis [47] Acts chemopreventive: Decreases p-AKT, AKT and NF-κB-p65 protein expression via TLR9 and TLR7 inhibition → inhibits HCC development in two HCC xenograft models [48] **Melanoma:** -As single treatment Stabilizes PUMA protein → induces apoptosis in vivo and in vitro [49] **Colon cancer:** -As single treatment Reduces phosphorylation of Akt and p44/42 MAPK → reduces proliferation and increases apoptosis in vivo and in vitro [50] Synergizes with 5-FU via enhancement of G0/G1cell cycle arrest and 5-FU induced apoptosis [51] **Melanoma and bladder cancer:** -As single treatment -Inhibits autophagic flux through inhibition of autophagosomes degradation and lysosomes fusion [52, 53] **Pancreatic cancer:** -As single treatment -Inhibits CXCL12 binding to CXCR4 and inhibits downstream signaling [54] -Inhibits autophagy → increases ROS production → increases DNA damage and alters cell metabolism [55] **Lung Cancer** -As single treatment Increases volume of lysosomes → inhibits cell proliferation [56] **Glioblastoma:** -As single treatment -Decreases invasiveness under hypoxic conditions [57] -Stabilizes p53 → tp53-depenendet apoptosis → decreased growth in vivo and in vitro [58]	**Clinical trial Phase I:** -Neoplasms (NCT02366884) -Neoplasm in combination with Carboplatin and Gemcitabine (NCT02071537) -Pancreatic in combination with Gemcitabine (NCT01777477) -Glioblastoma (NCT04772846) -Glioblastoma as radio sensitizer (NCT02378532) -Glioma, Cholangiocarcinoma, Chondrosarcoma (NCT02496741) -Carcinoma (NCT01023477) -Glioblastoma in combination with Temozolomide as chemotherapeutic agent and radio sensitizer (NCT04397679) -Results breast cancer study [59] **Clinical trial Phase II:** -Breast (NCT02333890) -Breast in combination with chemotherapy (NCT01446016) -Glioblastoma, astrocytoma (NCT02432417) -Multiple myeloma in combination with Velcade and Cyclophosphamide (NCT01438177) -Neoplasm in combination with other Anti-Protozoal Agents (NCT02366884)

Chloroquine/ hydroxychloroquine (Continued)		**Breast cancer:** **-**In combination Radio-sensitizes via increased lysosomal volume and decreased plasma membrane stability → increased necrosis [60] Synergizes with Doxorubicin [61] -As single treatment Inhibits MMP9 and MMP2, but also elevates MMP13 expression and decreases TLR9 expression (tumor-promoting and tumor-inhibiting) [62] Inhibits autophagy → decreases growth and survival in EGFR overexpressing cells [63] Leads to loss of $\Delta\Psi m$ → cleavage of caspase 3 and 9 → induces apoptosis via intrinsic pathway [64, 65] Acts anti-metastatic [64] Induces G2/M cell cycle arrest via decreased polo like kinase 1 and phosphorylated cdc25C levels [65] Breast cancer–protective effect via p53 and p21 activation: chloroquine dependent ATM phosphorylation → phosphorylation of p53 → G_1 cell cycle arrest in induced breast cancer models [66] **Stem cells:** -As single treatment Increases apoptosis and decreases clonogenic capacity [67] More extensive summary is presented in the summary of Munshin et al. [68]	**Clinical Trial Phase III:** -Glioblastoma multiforme (NCT00224978) ***In vivo:*** -Glioblastoma cells U373-EGFRwt and U373 in NMRI-nu (nu/nu) mice [63] -Glioblastoma cells U87MG in NMRI mice [58] -Liver cancer cells Huh 7 in athymic BALB/c nu/nu [67] -Liver cancer cells HepG2-GFP in nude mice [47] -Liver cancer cells HepG2 and HuH7 in NOD-SCID mice [48] -DEN-induced HCC model in Fischer F344 rats [48] -Melanoma cells SKMel23 in NOD-SCID mice [49] -NMU-induced mammary adenocarcinoma in Wistar-Furth rats [66] -Breast cancer cells MCF7 and MDA-MB-231 in athymic nude/nu Foxn1 mice [62] -Breast cancer cells 4T1 in BALB/c mice [64] -Colon cancer cells HCT116 and HT29 in nude mice -Colon cancer cells CT26 in BALB/c mice [50] -Pancreatic cancer cells 8988T and panc1 in NCr nude mice [55] -Lung cancer cells H460 in NCr nude mice [55]

Abbreviations: Acute myeloid leukemia (AML), DNA damage response (DDR), Doublestrand breaks (DSB), Doxorubicin (DOX), Head and neck cancer (HNC), Hepatocellular carcinoma (HCC), IkB Kinase (IKK), Mitochondrial membrane potential ($\Delta\Psi m$), Non-Hodgkin lymphoma (NHL), **Paclitaxel (PAX),** P-glycoprotein (P-gp), Poly (ADP-ribose)-Polymerase (PARP), Osteosarcoma (OSC), Renal cell carcinoma (RCC)

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