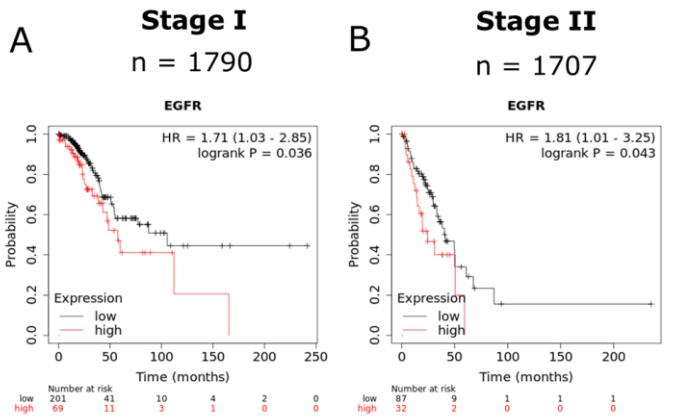
SUPPLEMENTARY DATA

Peptide-Conjugated Vascular Endothelial Extracellular Vesicles Encapsulating Vinorelbine for Lung Cancer Targeted Therapeutics

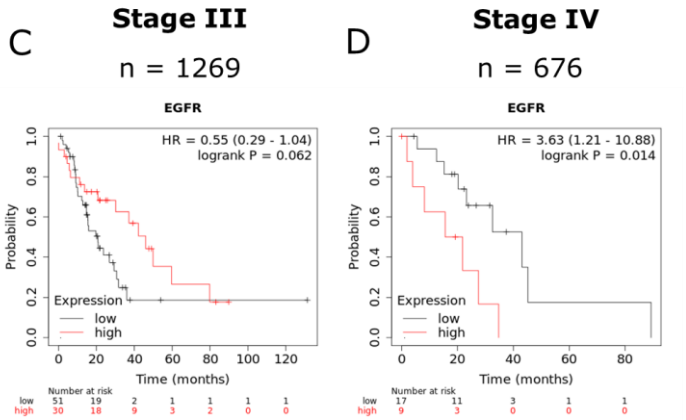
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Low expression cohort (months)	High expression cohort (months)
105.63	57.5

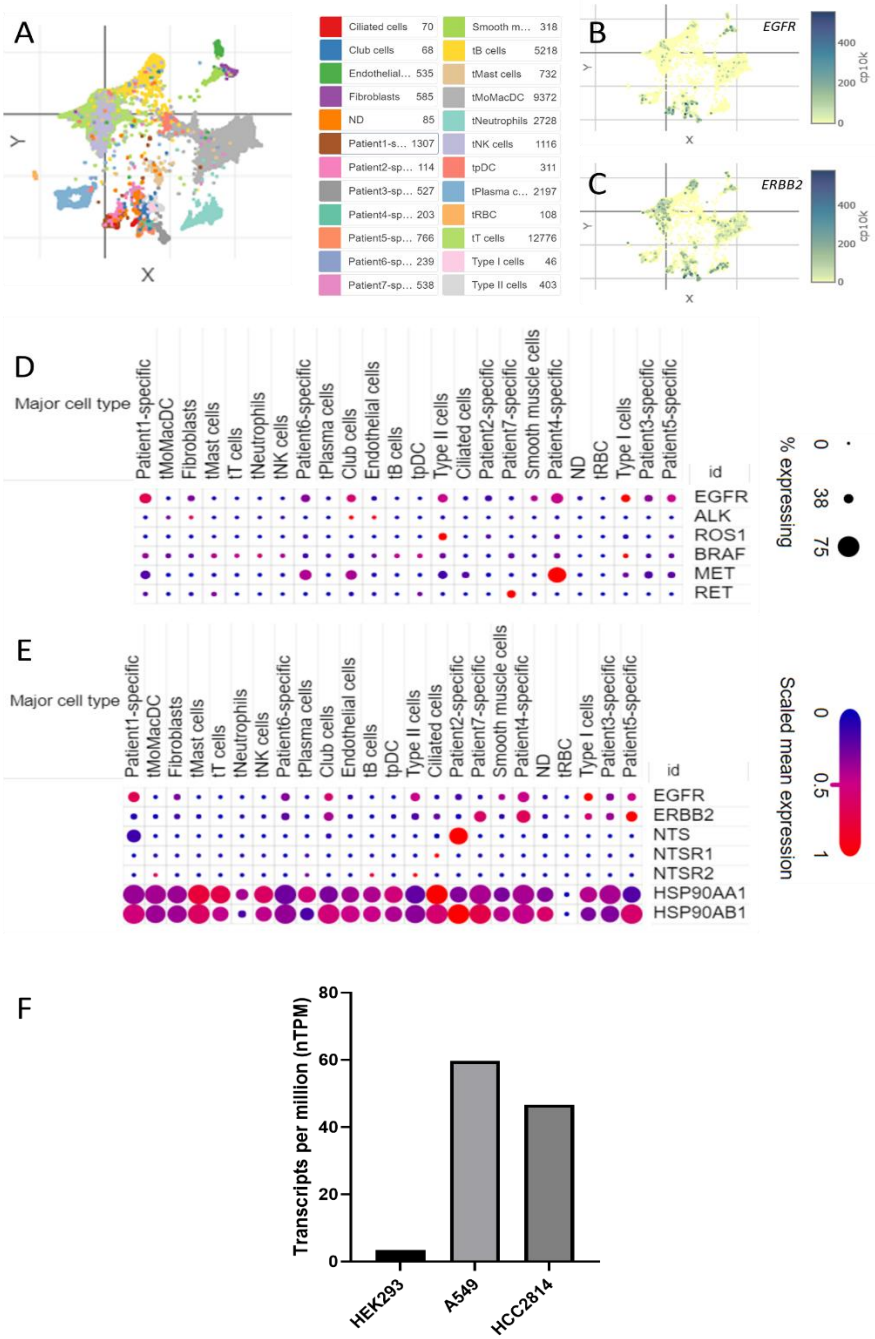
Low expression cohort (months)	High expression cohort (months)
41.17	24.57



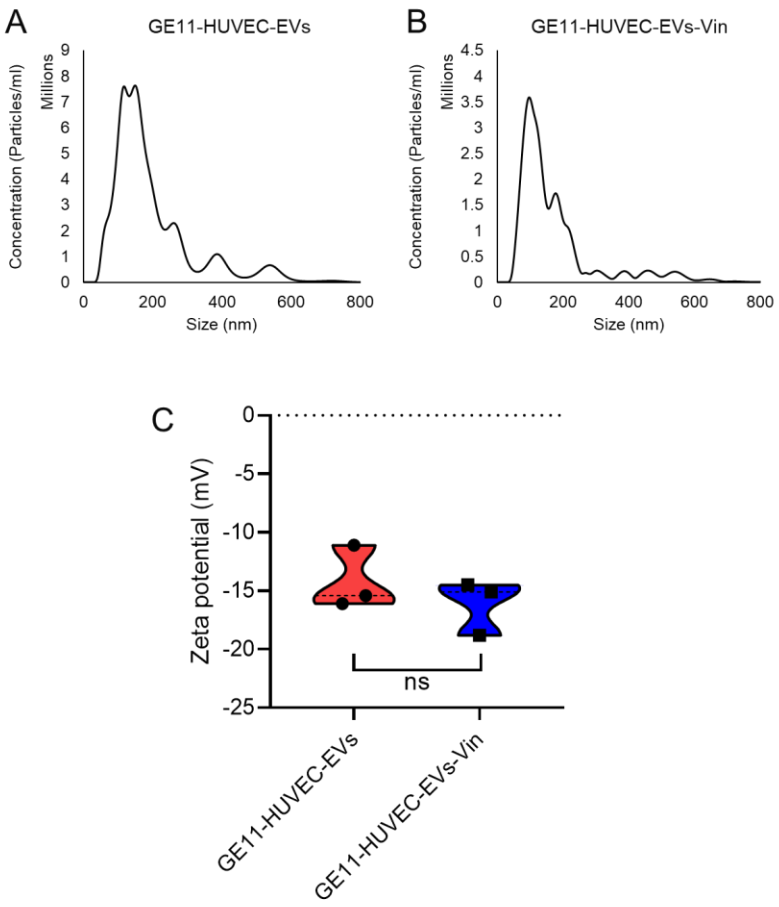
Low expression cohort (months)	High expression cohort (months)
20.8	45.97

Low expression cohort (months)	High expression cohort (months)
43.1	21.87

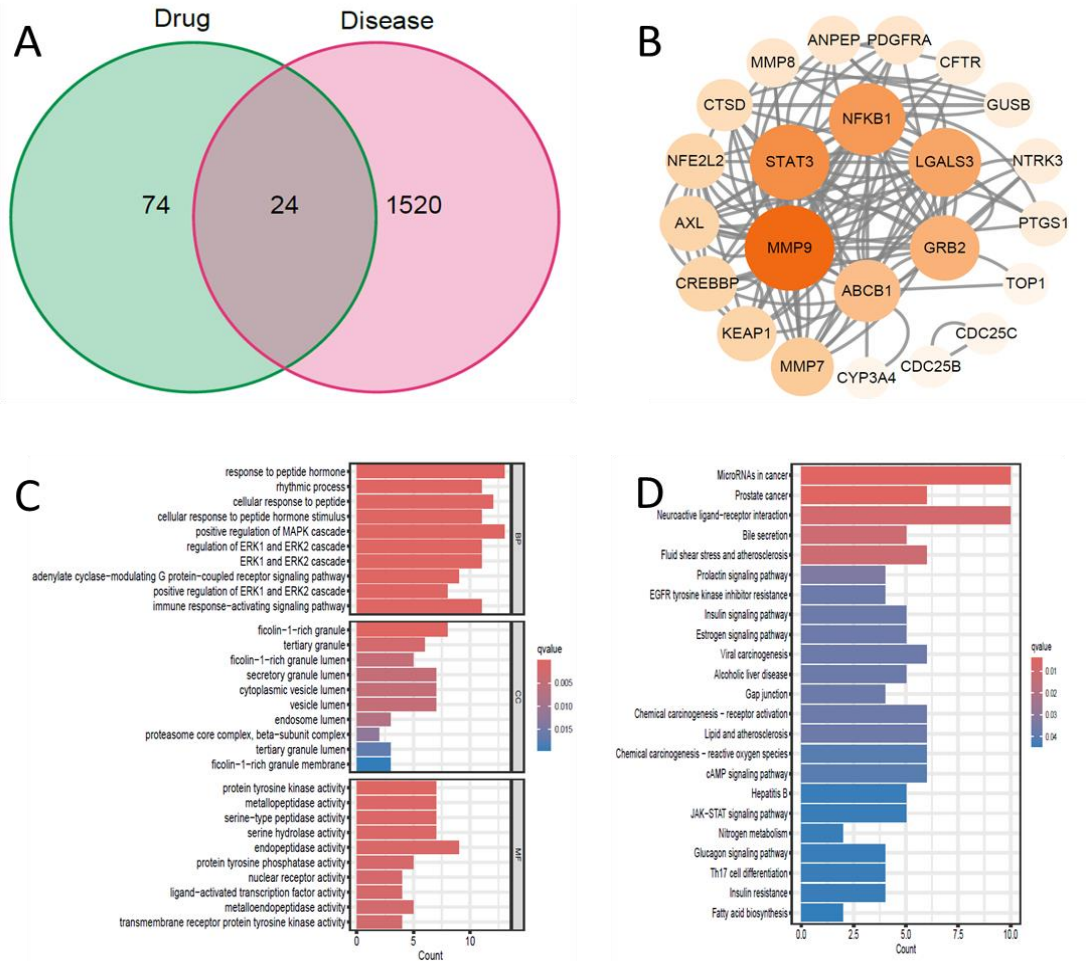
Supplementary Figure S1. Stage-dependent survival of lung cancer patients with the corresponding expression level of *EGFR*. Survival curves of patients with lung cancer with the expression of *EGFR* in **(A)** stage I, **(B)** stage II, **(C)** stage III, and **(D)** stage IV.



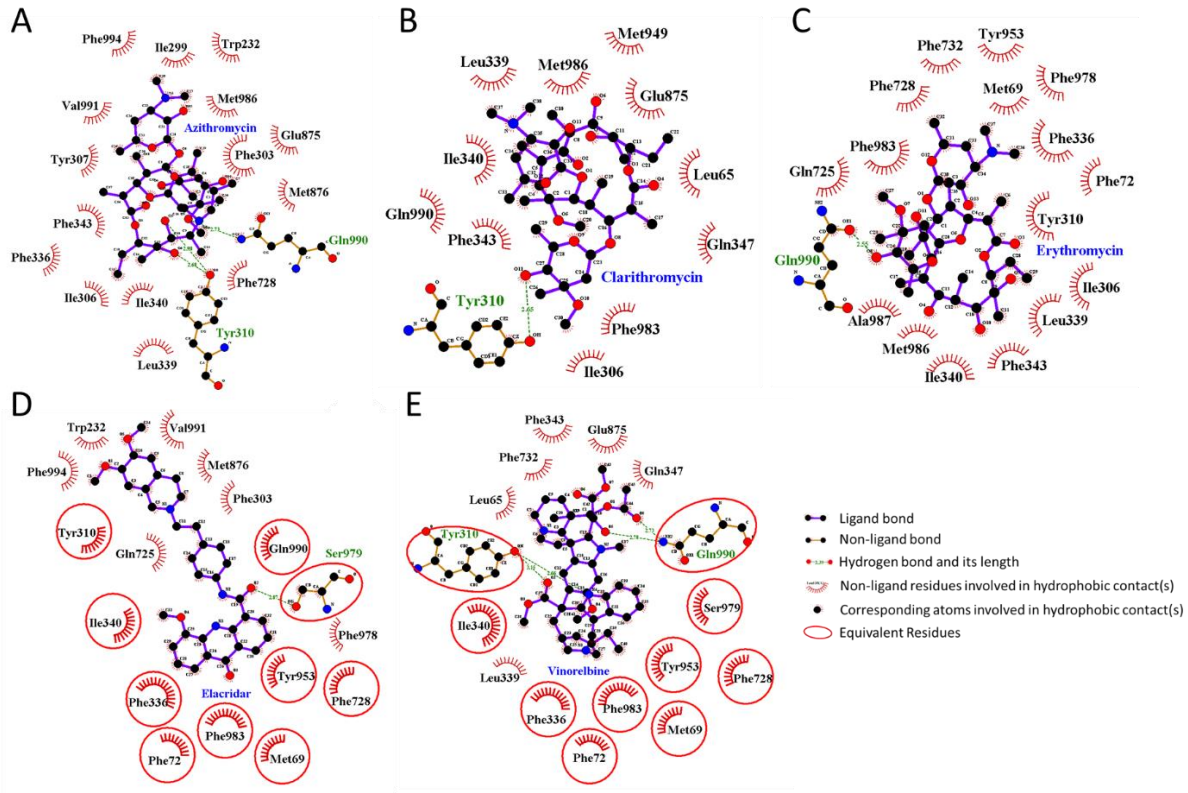
Supplementary Figure S2. Single-cell RNA-seq analysis of tumor microenvironments (TMEs) in lung cancer patients. (A) UMAP depicting the different cell types in the TME of human non-small cell lung cancer compared to control group (based on GEO: GSE127465). **(B, C)** UMAPs showing the expressions of (B) *EGFR* and (C) *ERBB2* in the clusters, representing cancer cell types. **(D, E)** Dot plots showing the cell type-specific expression of major cancer markers including *EGFR* and *ERBB2*. The figures are based on the analysis of single cell RNA-seq data publicly available (GSE127465). **(F)** Expression level of EGFR in HEK293, A549, and HCC2814 cell lines, as analyzed using protein atlas.



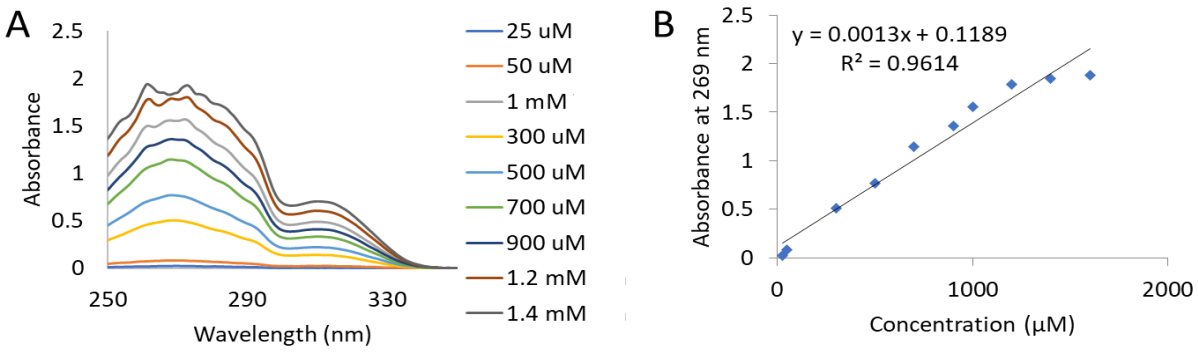
Supplementary Figure S3. Size distribution and zeta potential of GE11-HUVEC-EVs, without and with loading of vinorelbine. (A, B) The graph showing the size dependent concentration of GE11-HUVEC-EVs and GE11-HUVEC-EVs-Vin. (C) Violin plot showing the zeta potential of GE11-HUVEC-EVs and GE11-HUVEC-EVs-Vin.



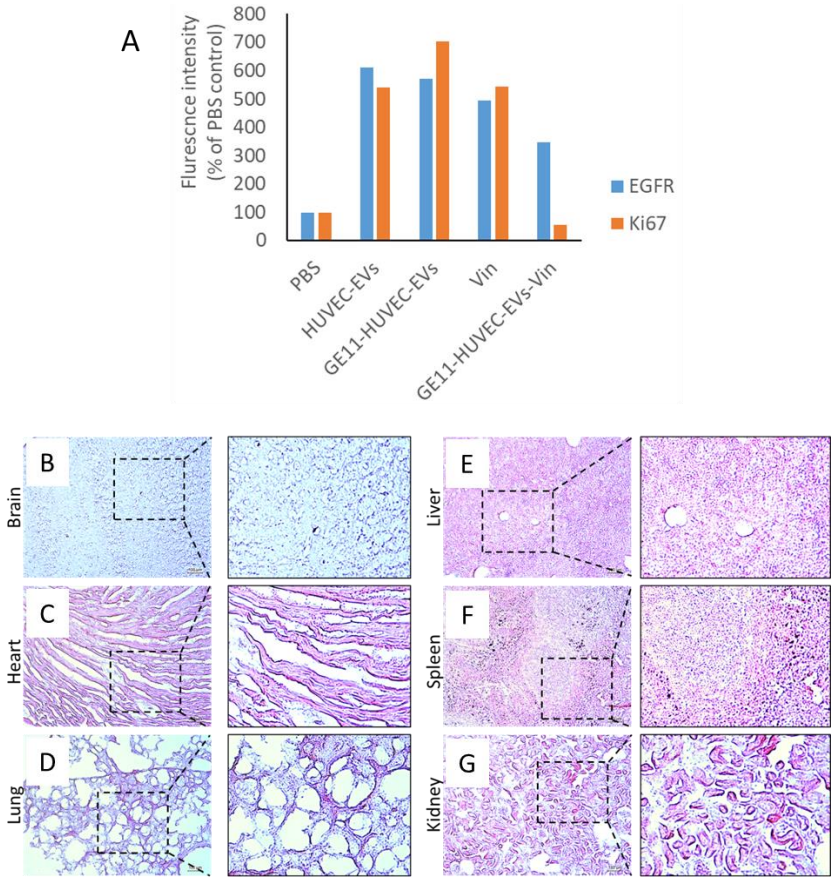
Supplementary Figure S4. Identification of potential lung cancer targets via *in silico* analysis. (A) The intersection of compound target proteins and lung cancer treatment targets resulted in 44 intersecting targets. **(B)** These 24 potential targets were imported into the STRING (https://cn.string-db.org/) online website to obtain a PPI network, which contains 24 nodes and 110 edges. The depth of color and circle size represent the corresponding size of the degree. **(C)** GO enrichment analysis was conducted on these 24 potential targets, and the top 10 enrichment results were displayed. **(D)** KEGG enrichment analysis was performed on these 24 potential targets, and the top 30 enrichment results were displayed.



Supplementary Figure S5. Molecular docking of vinorelbine with ABCB1 protein. Depiction of H-bonding and hydrophobic interaction pattern of control drugs (azithromycin, clarithromycin, erythromycin, and elacridar) and vinorelbine with ABCB1.



Supplementary Figure S6. Evaluation of vinorelbine encapsulation in GE11-HUVEC-EVs. (A) UV-visible spectra of difference concentrations of vinorelbine standard solutions. **(B)** Calibration standard graph showing the linear regression between concentration of vinorelbine standard solutions and the corresponding absorbance at the wavelength of 269 nm (λ_{max}).



Supplementary Figure S7. Evaluation of in vivo toxicity of GE11-HUVEC-EVs in major organs of mice. (A) Bar graph showing the fluorescence intensity depicting the expression level of EGFR and Ki67. **(B-G)** H&E-stained images of major organs of lung cancer xenograft mice: (B) brain, (C) heart, (D) lung, (E) liver, (F) spleen, and (G) kidney.

Supplementary Table S1. Docking of different ligands with ABCB1

Compound name	Binding Energy	Ki	H-bonding with ABCB1
Azithromycin	-9.80 kcal/mol	65.09 nM	Gln990, Tyr310
Clarithromycin	-8.05 kcal/mol	1.25 uM	Tyr310
Erythromycin	-9.98 kcal/mol	48.71 nM	Gln990
Elacridar	-11.86 kcal/mol	2.03 nM	Ser979
Vinorelbine	-11.31 kcal/mol	5.09 nM	Tyr310, Gln990

Supplementary Table S2. Calculation of efficiency of vinorelbine encapsulation in GE11-HUVEC-EVs.

Components	Absorbance	Conc. (μM)
Initial drug	0.272	200.084615 (A)
Conditioned medium after centrifugation	0.187	134.7 (B)
Drug loading efficiency	= ((A-B)/A) x 100	32.6784194 %