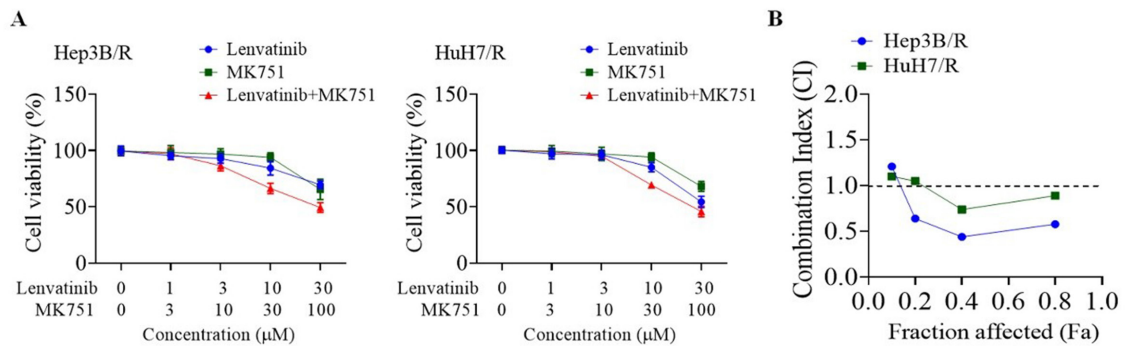


**Figure S1**  $IC_{50}$  values for HuH7/R and Hep3B/R cells after two weeks of lenvatinib withdrawal.



**Figure S2** *In vitro* combined anti-tumour effect of lenvatinib and MK751. HuH7/R and Hep3B/R cells were treated with the indicated concentrations of lenvatinib or MK751 for 48 h. (A) Cell viability was assessed using the CCK-8 assay. (B) The combination index (CI) was calculated by the Chou-Talalay method, where  $CI < 1$  indicates synergism and  $CI > 1$  indicates antagonism.

**Table S1** Gene names and primer sequences

Gene name	Primer sequence
<i>AKR1B1</i>	F: 5'-TTTTCCCATTGGATGAGTCGG-3' R: 5'-CCTGGAGATGGTTGAAGTTGG-3'
<i>AKR1B10</i>	F: 5'-CCTGTAACGTGTTGCAATCCTC-3' R: 5'-CAGCACCTCGATTCTCGTCT-3'
<i>AKR1C1</i>	F: 5'-CAGAACGTGCAGGTGTTTGA-3' R: 5'-GCTGAAATCACCAAGCAGGAG-3'
<i>AKR1C3</i>	F: 5'-GCCAGCTGAGTGACAGTGAT-3' R: 5'-TACTTCTCGGAACCTCTGGA-3'
<i>AKR1D1</i>	F: 5'-CATGGCCTTTAAGCCAGGAGA-3' R: 5'-GATGGCACTCAACCTCCCAAG-3'
<i>GAPDH</i>	F: 5'-GGACCAATACGACCAAATCCG-3' R: 5'-AGCCACATCGCTCAGACAC-3'
<i>ABCB1</i>	F: 5'-ACCTGTGAAGAGTAGAACATGAAGA-3' R: 5'-CTTCCGTTGCACCTCTCTTT-3'
<i>ABCG2</i>	F: 5'-AGAGCCTTCCAAGCAGGATA-3' R: 5'-ACGACTGTGACAATGATCTGAG-3'
<i>ABCC2</i>	F: 5'-TAGGCACATGGCTCCTGGT-3' R: 5'-ACAGGCAGGAGTAGGCTAGAT-3'

**Table S2** Antibodies used in this study

Antibody Name	Company	Cat No.	RRID	MW (kDa)	Dilution
Stat3 (79D7) Rabbit Monoclonal Antibody	Cell Signaling Technology	4904	AB_331269	86	1:2000
Phospho-Stat3 (Tyr705) (D3A7) Rabbit Monoclonal Antibody	Cell Signaling Technology	9145	AB_2491009	86	1:2000
Phospho-p38 MAPK (Thr180/Tyr182)	Cell Signaling Technology	4511	AB_2139682	43	1:1000
Phospho-JNK (Thr183/Tyr185)	Cell Signaling Technology	4668	AB_823588	46, 54	1:1000
Phospho-Akt (Ser473)	Cell Signaling Technology	4060	AB_2315049	60	1:2000
Phospho-ERK1/2 (Thr202/Tyr204)	Cell Signaling Technology	4370	AB_2315112	44, 42	1:2000
E-cadherin	Cell Signaling Technology	3195	AB_2291471	135	1:1000
Vimentin	Cell Signaling Technology	5741	AB_10695459	57	1:1000
GAPDH	Proteintech	60004-1-Ig	AB_2107436	36	1:2000
Bcl2	Proteintech	26593-1-AP	AB_2818996	26	1:2000
Bax	Proteintech	50599-2-Ig	AB_2061561	21	1:5000
Caspase 3	Proteintech	19677-1-AP	AB_10733244	32	1:1000
BCRP/ABCG2	Proteintech	27286-1-AP	AB_2880830	72	1:1000
MDR1/ABCB1	Proteintech	22336-1-AP	AB_2833023	130–150	1:1000
MRP2/ABCC2	Selleck	A5785	AB_3720819	174	1:1000
AKR1C1	GeneTex	GTX105620	AB_1949621	37	1:1000
HRP-conjugated secondary antibodies	Beyotime	A0216	AB_2860575	–	1:1000