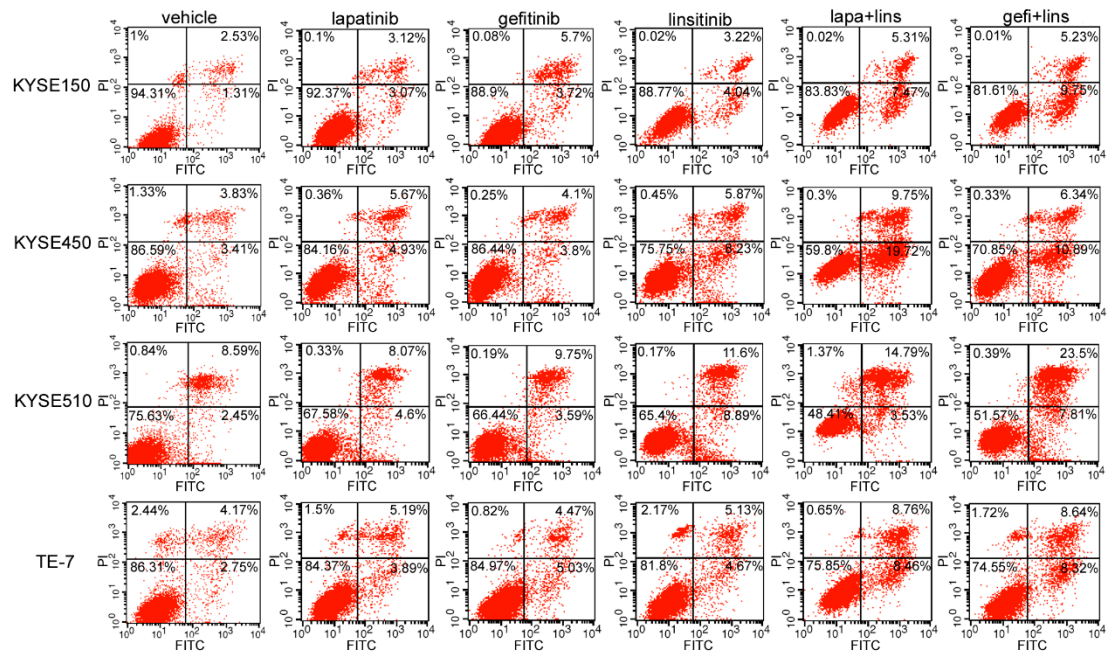
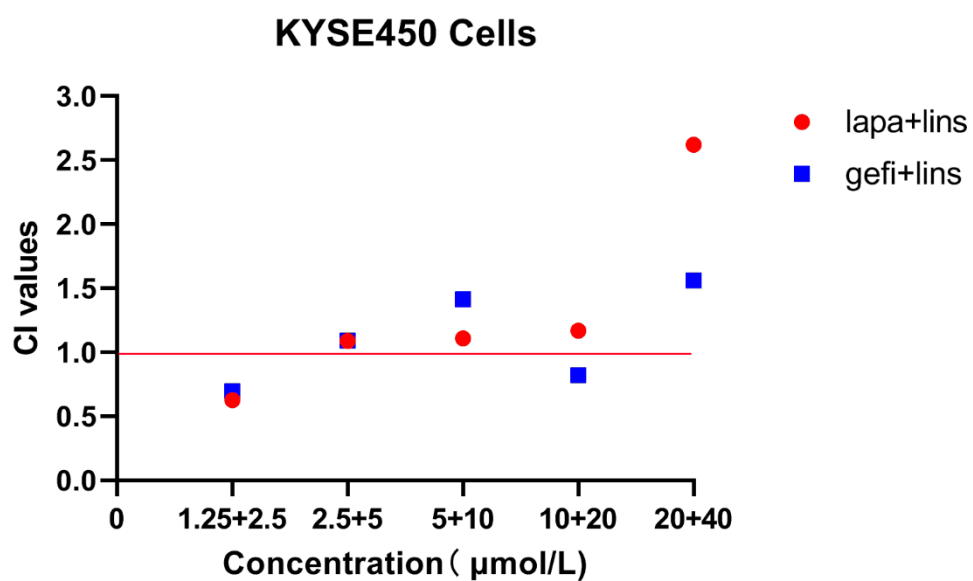


Supplementary Figure S1. The flow cytometry data of the effects of lapatinib, gefitinib, linsitinib alone or in combination on the cell cycle distribution. Four ESCC cells were stained with propidium iodide (PI) after treatment by lapatinib, gefitinib, linsitinib, lapatinib+linsitinib and gefitinib+linsitinib for 48 h. The fluorescence intensity was measured by flow cytometer and cells distributed in G1, S and G2/M phase were analyzed by ModFit software.



Supplementary Figure S2. The flow cytometry data of the effects of lapatinib, gefitinib, linsitinib alone or in combination on cell apoptosis. ESCC cells were exposed to single drugs or in combinations as indicated, and then the apoptotic cells were stained with Annexin V-FITC and PI. The fluorescence intensity was measured by flow cytometer. The lower left quadrant (FITC⁻ PI⁻) indicated the live cells, the lower right quadrant (FITC⁺ PI⁻) indicated the early apoptosis cells, the upper right quadrant (FITC⁺ PI⁺) indicated the late apoptosis cells, and the upper left quadrant (FITC⁻ PI⁺) indicated the dead cells. The ratios of cell apoptosis were calculated by the sum of early apoptosis cells and the late apoptosis cells.



Supplementary Figure S3. The CI values of lapatinib or gefitinib in combination with linsitinib at ratio of 1:2 against KYSE450 cells, calculated by using the Chou–Talalay method.

EGFR exon 19:

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Homo sapiens epidermal growth factor receptor (EGFR), RefSeqGene (LRG_304) on chromosome 7
Sequence ID: [NG_007726.3](#) Length: 244589 Number of Matches: 1

Range 1: 160691 to 160789 [GenBank](#) [Graphics](#) [▼ Next Match](#) [▲ Previous Match](#)

Score	Expect	Identities	Gaps	Strand
183 bits(99)	3e-44	99/99(100%)	0/99(0%)	Plus/Plus
Query 1		GCATCTCGATCCCAAGAGTGGAAAGCTTAAATTCCTGCTCATCAAGCAATTAAAG	60	
SubJct 160691		GCATCTCGATCCCAAGAGTGGAAAGCTTAAATTCCTGCTCATCAAGCAATTAAAG	160705	
Query 61		GAAGCAATCATCTCCGAAAGCCCAACCAAGCAATCTCCGAT	99	
SubJct 160751		GAAGCAATCATCTCCGAAAGCCCAACCAAGCAATCTCCGAT	160789	

EGFR exon 20:

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Homo sapiens epidermal growth factor receptor (EGFR), RefSeqGene (LRG_304) on chromosome 7
Sequence ID: [NG_007726.3](#) Length: 244589 Number of Matches: 1

Range 1: 167272 to 167447 [GenBank](#) [Graphics](#) [▼ Next Match](#) [▲ Previous Match](#)

Score	Spect	Identities	Gaps	Strand
326 bits (176)	9e-87	176/176 (100%)	0/176 (0%)	Plus/Minus
Query 1	TGATGGCAGCTGGACAAACCCAGCTGTGCGCGCTGCTGGGCATCTGCTCACTCCA			60
Sbj.ct 167272	TGATGGCAGCTGGACAAACCCAGCTGTGCGCGCTGCTGGGCATCTGCTCACTCCA			167331
Query 61	CGTCGACGATCATCAGGCAAGCTATGCGCTTGGCTGCTGGACATCTGGCGAAG			120
Sbj.ct 167332	CGTCGACGATCATCAGGCAAGCTATGCGCTTGGCTGCTGGACATCTGGCGAAG			167391
Query 121	ACAAAGACAAATATGCGCTCACTGCTGCTCAAGCTGTGCTGCGAGATGCCAAAG			176
Sbj.ct 167392	ACAAAGACAAATATGCGCTCACTGCTCAAGCTGTGCTGCGAGATGCCAAAG			167447

EGFR exon 21:

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Homo sapiens epidermal growth factor receptor (EGFR), RefSeqGene (LRG_304) on chromosome 7
Sequence ID: [NG_007726.3](#) Length: 244589 Number of Matches: 1

Range 1: 177688 to 177843 [GenBank](#) [Graphics](#) [▼ Next Match](#) [▲ Previous Match](#)

Score	Sequences	Identities	Gaps	Strand
289 bits(156)	le-75	156/156(100%)	0/156(0%)	Plus/Minus
Query 1	GGATGAACACTACTGAGAGAGGCTCTGGTGTGACACCGGACCTGGAGACGAGAGAGTGA	60		
Subject 177688	GGCTGCAACTACTCTGAGGAGAGGCTCTGGTGTGACACCGGACCTGGAGACGAGAGAGTGA	177747		
Query 61	CTGTGCAAAAACACCCGACGATCTGTCAGATGACAGATTTTGGCTGGCCAAACCTCTGGT	120		
Subject 177748	CTGTGCAAAAACACCCGACGATCTGTCAGATGACAGATTTTGGCTGGCCAAACCTCTGGT	177801		
Query 121	CCGCAAGCAGAAAGATGATCATCCACAGACGAGCAGAA	156		
Subject 177808	CCGCAAGCAGAAAGATGATCATCCACAGACGAGCAGAA	177843		

HER2 exon 19:

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Homo sapiens erb-b2 receptor tyrosine kinase 2 (ERBB2), RefSeqGene (LRG_724) on chromosome 17
Sequence ID: [NG_007503.1](#) Length: 47523 Number of Matches: 1

Range 1: 40773 to 40871 [GenBank](#) [Graphics](#) [▼ Next Match](#) [▲ Previous Match](#)

Score	Expect	Identities	Gaps	Strand
183 bits(99)	3e-44	99.99(100%)	0/99(0%)	Plus/Minus
Query 1		GGCATTCGATGCTTCCTGAGGCAAAATCTGAAAATTCACATGGCATCAAACTCTTTGAGG		60
ShJct 40773		GGCATTCGATGCTTCCTGAGGCAAAATCTGAAAATTCACATGGCATCAAACTCTTTGAGG		40832
Query 61		CAAAACACATCCCGCAAGCGCAACCAACAAATCTTATAG	99	
ShJct 40833		CAAAACACATCCCGCAAGCGCAACCAACAAATCTTATAG	40871	

HER2 exon 20:

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Homo sapiens erb-b2 receptor tyrosine kinase 2 (ERBB2), RefSeqGene (LRG_724) on chromosome 17
Sequence ID: [NG_007503.1](#) Length: 47523 Number of Matches: 1

Range 1: 41587 to 41772 [GenBank](#) [Graphics](#) [▼ Next Match](#) [▲ Previous Match](#)

Score	Expect	Identities	Gaps	Strand
344 bits(186)	3e-92	186/186(100%)	0/186(0%)	Plus/Minus
Query 1		GAAGCATACGCTATGCTCGCTCTGGGCTCCCATATGCTTCGGGCTCTGGGATCTTCG		60
SubJct 41587		GAAGCATACGCTATGCTCGCTCTGGGCTCCCATATGCTTCGGGCTCTGGGATCTTCG		41646
Query 61		CTGACATACACGGTGCAGCTGCTGCACACAGCTTATGCGCCTATGGCTCCTTGAACAT		120
SubJct 41647		CTGACATACACGGTGCAGCTGCTGCACACAGCTTATGCGCCTATGGCTCCTTGAACAT		41706
Query 121		CTGTGGGAAAAACCGAGGCTGTGGGCTCCAGAGAGTCTGCACTGCTATATGACGATT		180
SubJct 41707		CTGTGGGAAAAACCGAGGCTGTGGGCTCCAGAGAGTCTGCACTGCTATATGACGATT		41766
Query 181	0.000000	186		
SubJct 41767	0.000000	41772		

Supplementary Figure S4. Sequence alignment of EGFR exon 19, 20, 21 and HER2 exon 19, 20 from KYSE450 cells to the *Homo sapiens* epidermal growth factor receptor (EGFR) gene and *Homo sapiens* erb-b2 receptor tyrosine kinase 2 (ERBB2) gene, respectively, by using BLAST.