



Figure S1: Representative pictures of stained CTCs.

Table S1. Number of CTCs detected for each patient.

A/A	Stage	Number of CTCs			% of CTCs	
		CK+	CK+PDL1+CD45-	CK+PDL1-CD45-	%CK+PDL1+C D45-	%CK+PDL1-CD45-
1	LIMITED	5	3	2	60,00	40,00
2	EXTENSIVE	0	0	0	0,00	0,00
3	EXTENSIVE	0	0	0	0,00	0,00
4	EXTENSIVE	3	0	3	0,00	100,00
5	EXTENSIVE	0	0	0	0,00	0,00%
6	EXTENSIVE	0	0	0	0,00	0,00
7	EXTENSIVE	0	0	0	0,00	0,00
8	EXTENSIVE	0	0	0	0,00	0,00
9	EXTENSIVE	0	0	0	0,00	0,00
10	EXTENSIVE	0	0	0	0,00	0,00
11	EXTENSIVE	0	0	0	0,00	0,00
12	EXTENSIVE	1	1	0	0,00	0,00
13	LIMITED	0	0	0	0,00	0,00
14	EXTENSIVE	0	0	0	0,00	0,00
15	EXTENSIVE	0	0	0	0,00	0,00
16	EXTENSIVE	19	9	10	47,37	52,63
17	EXTENSIVE	2	1	1	50,00	50,00
18	EXTENSIVE	0	0	0	0,00	0,00
19	EXTENSIVE	0	0	0	0,00	0,00
20	EXTENSIVE	1	1	0	100,00	0,00
21	EXTENSIVE	0	0	0	0,00	0,00
22	EXTENSIVE	1	1	0	100,00	0,00
23	EXTENSIVE	0	0	0	0,00	0,00
24	EXTENSIVE	0	0	0	0,00	0,00
25	LIMITED	0	0	0	0,00	0,00
26	EXTENSIVE	1	1	0	100,00	0,00
27	EXTENSIVE	1	1	0	100,00	0,00
28	EXTENSIVE	2	2	0	100,00	0,00
29	EXTENSIVE	0	0	0	0,00	0,00
30	EXTENSIVE	1	1	0	100,00	0,00
31	EXTENSIVE	1	0	1	0,00	100,00
32	LIMITED	0	0	0	0,00	0,00
33	EXTENSIVE	0	0	0	0,00	0,00
34	EXTENSIVE	2	2	0	100,00	0,00
35	EXTENSIVE	6	5	1	83,33	16,67
36	EXTENSIVE	0	0	0	0,00	0,00
37	LIMITED	1	0	1	0,00	100,00
38	EXTENSIVE	0	0	0	0,00	0,00
39	EXTENSIVE	70	13	57	18,57	81,43
40	EXTENSIVE	0	0	0	0,00	0,00
41	LIMITED	0	0	0	0,00	0,00
42	EXTENSIVE	0	0	0	0,00	0,00
43	EXTENSIVE	23	15	8	65,22	34,78

Table S2. Associations of CTCs and clinical outcome of treatment naïve ES-SCLC patients.

CTCs	Groups	N of patients	Progresion Free Survival			Overall Survival		
			Median (days)	95% HR CI	p value	Median (days)	95% CI	p value
CK+CD45-	>1	8	176	0.303 to 1.612	0.401	260	0.277 to 2.042	0.311
	<1	29	163			232		
CK+CD45-	>3	5	167	0.586 to 6.586	0.273	180	0.534 to 5.820	0.352
	<3	32	167			261		
CK+CD45-	PD-L1+	13	172	0.355 to 1.772	0.572	271	0.213 to 1.4	0.207
	other	24	158			217		

CTC: circulating tumor cell; CK : Cytokeratin; PD-L1: programmed death ligand 1; HR: hazard ratio, CI: confidence interval estimate.

Table S3. Prognostic significance of PD-L1+ CTCs or CK+ CTCs and CD3+CD8+ PD-1+ T-cells in patients with ES-SCLC.

	Corelations	95% HR CI	p value	95% CI	p value
CK+CTCs	Group A vs Group B	0.2972 to 3.230	0.973	0.2195 to 5.599	0.900
	Group A vs Group C	0.01322 to 1.683	0.123	0.009 to 1.424	0.092
	Group A vs Group D	0.1641 to 1.299	0.143	0.8630 to 1.635	0.061
	Group B vs Group C	0.1580 to 3.667	0.733	0.07137 to 5.088	0.641
	Group B vs Group D	0.2163 to 2.231	0.540	0.1321 to 2.354	0.426
	Group C vs Group D	0.2758 to 4.800	0.847	0.1500 to 2.266	0.436
CK+CTCs	Group A vs Group B	0.3429 to 3.093	0.958	0.1755 to 3.838	0.801
	Group A vs Group D	0.1726 to 1.177	0.103	0.099 to 0.8197	<b>0.019</b>
	Group B vs Group D	0.208 to 1.614	0.297	0.1766 to 2.111	0.435

CTC: circulating tumor cell; CK : Cytokeratin; PD-1: programmed cell death receptor 1; PD-L1: programmed death ligand 1; HR: hazard ratio, CI: confidence interval estimate ; group A high CD3+CD8+PD-1+ T-cells (roc cut off) with PD-L1+CTCs (n=13) or CK+ CTCs (n= 15) , group B: high CD3+CD8+PD-1+ T-cells (roc cut off) without PD-L1+CTCs (n=12) or CK+ CTCs (n= 10) , group C: low CD3+CD8+PD-1+ T-cells (roc cut off) with PD-L1+CTCs (n=1) or or CK+ CTCs (n= 2) and group D: low CD3+CD8+PD-1+ T-cells (roc cut off) without PD-L1+CTCs (n=11) or CK+ CTCs (n= 10). Analysis of group C: low CD3+CD8+PD-1+ T-cells (roc cut off) with PD-L1+CTCs (n=1) was not performed as there was only one patient.

Table S4. Cox regression analysis.

Risk Factor	Parameter Estimate	P-Value	Hazard Ratio (HR)
			(95% CI for HR)
Age, years	0,03028	0,5925	0,9288 to 1,167
Liver Metastasis	1,457	0,1939	0,6514 to 84,70
Brain Metastasis	-0,7043	0,4463	0,06470 to 2,640
Lung Metastasis	-1,082	0,189	0,06282 to 1,754
Bone Metastasis	-1,678	0,3272	0,004018 to 6,483
Tumor diameter	-0,4144	0,7337	0,07486 to 14,32
Smoking (py)	0,4356	0,578	0,3309 to 7,781