composed of platinum and doxorubicin or taxane, and are used for the patients bearing tumors with aggressive features such as pathologically high grade, invasion into the outer myometrium, lymphovascular space or cervix, and extrauterine spread[13, 14]. As shown in Table 2, the tumor recurrence rate in the group of intermediate-risk patients was significantly diminished by adjuvant chemotherapies, while recurrence was not improved in the high-risk group receiving similar therapies. Several randomized trials have reported effectiveness of adjuvant therapies. The carboplatin-paclitaxel regimen was previously reported as a well-tolerated and active regimen that provides a median time to progression of 13 months and a median overall survival of 47 months in high-risk patients[15]. The GOG 177 trial showed that addition of paclitaxel to the doxorubicin-cisplatin regimen significantly improved the rate of objective response and overall survival of high-risk or recurrent cases[5]. These results, such as the 57% of response rate and 17.3 months of overall survival are, however, not satisfactory in terms of therapeutic effect, and so the need for improved treatment strategies is urgently required to improve therapeutic benefit for patients with high-risk or recurrent disease.

The majority of high-risk or chemo-refractory endometrial cancer cases are high grade, and the major challenge in developing more effective therapeutic strategies for these women involves confronting the heterogeneity of the disease and the distinct underlying mechanisms. The NCI60 database is comprised of more than 60 established cell lines from a diverse collection of malignant human tissues that have been tested for sensitivity to over 40,000 compounds to identify those with anticancer activity. Due to this diversity, the NCI60 is regarded as a reasonable representation of tumor heterogeneity and has been extensively utilized for discovering potent anti-cancer drugs[11, 16, 17]. Endometrial cancers are heterogeneous tumors that are classified into several types based on histological differentiation, and etiologic heterogeneity

exists as well, especially within endometrioid adenocarcinoma. Thus efforts have been made to establish molecular-based classifications which may help in understanding the differences in biology and clinical outcome among subtypes[18]. In this study, 39% of the NCI60 cell lines were refractory to cisplatin, doxorubicin, or paclitaxel, and intriguingly, this rate is quite similar to the 44% of high-risk patients who are chemo-refractory from our data. With the aim of prompt clinical translation, the GI50 values from the NCI60 data were analyzed for 24 agents already in clinical use, and the results indicated none were promising for the high-risk patient population. However, since the anti-cancer drugs and the molecular-targeting drugs exhibit distinct spectra, combined therapy using agents from each group may be a reasonable and more effective approach for use as second-line chemotherapy.

Gene expression profiling studies have been valuable tools for revealing the complex nature of cancer and for identifying new therapeutic strategies[11]. Since the NCI60 dataset includes gene expression information, a pharmacogenomics approach allows the ability to define common genetic backgrounds as "signatures" of chemo-refractory cell lines and to identify candidate drugs potentially effective against these cell lines. Using Bayesian binary regression methods, a sensitivity gene expression signature for each candidate drug, based on the results of the NCI60 analysis, can be projected onto independent microarray datasets including those from endometrial cancers to predict the probability of drug sensitivity for each sample. As expected, the sensitivity probabilities of three conventional chemotherapeutic agents were low in high-grade endometrial cancers (Fig.2A). In contrast, temsirolimus was predicted as a potentially effective agent against serous adenocarcinoma. Temsirolimus is a molecular targeting agent that functions by inhibiting mTOR pathway signaling, a pathway impaired in endometrial cancers. This agent is now being studied under a GOG clinical trial to investigate efficacy for chemo-

refractory endometrial cancers. Considering our analysis, temsirolimus may be effective in a subset analysis for histology even when the results of primary endpoint analysis for the entire population might be negative. In endometrial cancers, loss of PTEN correlates with poor outcomes[18], and cell lines with little or no PTEN are preferentially sensitive to temsirolimus as cell viability and Akt phosphorylation were regulated by temsirolimus in a dose-dependent manner.[19] There are no reports showing interaction between the mTOR pathway and p53 mutations in serous endometrial cancers, but up-regulation of mTOR is observed in invasive bladder cancer accompanied by deletion or mutation of p53 [20], which suggests that temsirolimus, as an mTOR inhibitor, might be useful in serous endometrial cancers in which p53 is frequently mutated.

By analyzing the complexity of the genomic signatures from the cell lines, fludarabine was also predicted as a potential candidate for chemo-refractory high-grade cases. Among seven endometrial cancer cell lines that were resistant to cisplatin, doxorubicin, and paclitaxel, five of these cell lines exhibited favorable probability of sensitivity to fludarabine; while only three of those seven exhibited a favorable probability score of sensitivity to temsirolimus (Suppl. Table 2). These results suggest that fludarabine is a promising alternative agent for chemo-refractory endometrial cancers.

The classes of antineoplastic drugs belonging to the group of purine nucleoside analogues (PNAs) plays an important role and have had a substantial impact on the treatment of cancer[21-23]. Fludarabine is a purine analog that has demonstrated significant activity in B-cell malignancies, including CLL and indolent non-Hodgkin's lymphoma. Fludarabine is converted intracellularly into its active metabolite F-ara- ATP, which inhibits DNA as well as RNA synthesis, resulting in induction of growth arrest and apoptosis[24]. A single case report in the 1980s failed to show

efficacy for recurrent endometrial cancers[25] , but as the number of cases was small and tumor histology was varied, it is hard to determine efficacy in high-grade tumors from this report. Our preliminary analysis for gene expression implies "purine metabolism" is augmented in G3 and serous endometrial cancers compared with G1 and G2 (data not shown), which is supportive of our prediction on fludarabine-efficacy toward G3 and serous cases.

The exact mechanism of apoptosis induction by F-ara-A in proliferative and quiescent cells has not been completely clarified although purine nucleoside analogs are reported to activate d-ATP-dependent caspase pathways[26]. In order to investigate the cytotoxic effect of fludarabine, *in vitro* proliferation assays were done on three endometrial cancer cell lines, which were chosen as representative cell lines according to their probability of sensitivity to conventional chemo-agents, as described in the methods. As shown in Fig.3, fludarabine has a cytotoxic effect on endometrial cancer, inhibiting tumor growth and inducing apoptosis in a dose-dependent manner *in vitro*, suggesting that fludarabine may inhibit the proliferation of endometrial cancer cells through induction of apoptosis, consistent with reports using Jurkat cells[24]. Caspase-3 is activated via death receptor signaling to induce chromatin condensation and DNA fragmentation, resulting in apoptosis[27, 28]. In both HEC1A cells and AN3CA cells, Caspase-3 was activated *in vitro* by fludarabine more than 5-fold higher than in the HEC50B cells that are resistant to fludarabine. On the other hand, fludarabine was not inhibitory to tumor growth in AN3CA inoculated mice, but robustly inhibited HEC1A-derived tumors. The reason for this difference is not clear, but as growth inhibition and induction of apoptosis *in vitro* was higher in HEC1A cells at a lower dose, it may be that drug delivery to the tumor tissue *in vivo* was not as effective. Furthermore, *Caspase-3* expression was increased, suggesting the possibility that this augmentation may play a role in determining susceptibility to fludarabine despite the belief that

constitutive expression of Caspase-3 is not usually considered significant in apoptosis. These results may imply the existence of an unknown mechanism(s) enhancing the efficacy of fludarabine in each tumor.

In this study, we have used a pharmacogenomics approach with drug-specific signatures as a targeted method to identify new candidate drugs with potential efficacy against chemoresistant endometrial cancers. Through array-based analysis, fludarabine as well as temsirolimus were identified as candidate chemotherapeutic agents for chemo-refractory endometrial cancers. This prediction was confirmed both *in vitro* and *in vivo*. Although further study is warranted, fludarabine may prove beneficial as an addition to the treatment strategy for managing high-risk endometrial cancers.

Tables

Table.1 *Patient characteristics*

Known risk factors are listed for the patients in this study. Recurrence/PD: the number of patients who showed recurrence or progressive disease during chemotherapy; LVSI means lymphovascular space invasion.

Table.2 *Patient chemoresponsiveness profiles*

Effectiveness of chemotherapy was evaluated in each risk group using Fisher's exact test.

Suppl. Table 1 *Normalized GI50 values of 27 drugs from 62 cancer cell lines*

GI50 values of 27 drugs from 62 cancer cell lines (source: NCI60 data) were normalized by median-centering method in Clustering 3.0 software, as described previously[11].

Suppl. Table 2 *Drug sensitivity probability scores of 20 endometrial cancer cell lines.*

Gene expression microarray analysis was performed in 20 endometrial cancer cell lines, and drug-susceptibility signatures for the conventional chemotherapeutic agents were applied to predict the probability of sensitivity of each cell line. Numbers in each box indicate the probability score of response.

Figure legends

Fig.1 *50% Growth Inhibitory Doses (GI50) of Anti-cancer Drugs in the NCI60 Dataset in Predicting Chemoresponsiveness.*

(A) NCI60 cell lines were aligned according to their normalized GI50 values for cisplatin, doxorubicin, and paclitaxel, shown in the top panel. Most (84.63%) of the normalized GI50 values ranged between 0.15 (red) and -0.15 (blue). Dark red and dark blue at the extreme ends of the color bar represent values >0.15 and <-0.15, respectively. (S: Sensitive; R: Resistant; threshold indicates the value (0.04) above which cells were considered as chemo-sensitive.)

(B) For the 24 chemoresistant cell lines in panel A, GI50 values were obtained for an additional 24 commonly-used chemotherapeutic agents. Unsupervised hierarchical clustering produced two clusters; cluster 1 contains anti-cancer drugs; cluster 2 contains molecular targeting drugs.

Fig.2 *Predicted susceptibility of chemo-agents in endometrial cancers in vivo.*

(A) Genomic signatures of susceptibility were generated using Bayesian binary regression from the NCI60 gene expression data, and applied to microarray data from endometrial cancers in GSE2109 for predicting the probability of sensitivity to cisplatin, doxorubicin, and paclitaxel.

(B) Drug susceptibility signatures were also developed for fludarabine, Ara-C, and irinotecan as representative anti-cancer drugs from cluster 1, and for temsirolimus, gefitinib, and sunitinib as representative molecular targeting drugs from cluster 2. The probability of sensitivity (y-axis on a scale of 0-1, with 0 indicating high probability of resistance and 1 indicating high probability of sensitivity) to the three conventional chemotherapeutic agents was not superior

in grade 3 endometrioid adenocarcinoma and serous papillary adenocarcinoma to those in low grade endometrioid adenocarcinoma. On the other hand, the probability of sensitivity to fludarabine was significantly higher in grade 3 and serous and for temsirolimus was significantly higher in serous ($p<0.001$ and $p<0.05$, respectively).

(C) Gene expression microarray analysis was performed in 20 endometrial cancer cell lines, and drug-susceptibility signatures for the conventional chemotherapeutic agents were applied to predict the probability of sensitivity of each cell line. Numbers in each box indicate the probability score with colors indicating probability of response.

Fig.3 *Cytotoxic activities of fludarabine.*

(A) The cytotoxicity of fludarabine was measured using WST-1 cell proliferation assays. There were growth-inhibitory responses in AN3CA (green) and HEC1A (blue) in a dose-dependent manner ($p<0.01$), while this response was not significant in HEC50B (red).

(B) Apoptosis induction following fludarabine treatment in HEC1A, AN3CA, and HEC50B cells. The apoptotic effect of fludarabine was measured using the Annexin-V/7-AAD apoptosis assay kit.

(C) Caspase 3 protein induction by fludarabine. After 24hr exposure to fludarabine, luminescence was gradually elevated in HEC1A cells in a dose-dependent manner, reflecting the activity of Caspase 3/7, and this induction was almost 6-fold higher than that in HEC50B cells ($p<0.001$).

(D) Fludarabine efficacy *in vivo*. Mice inoculated with $5x10^6$ endometrial cancer cells sub-cutaneously, were treated with fludarabine (125mg/kg), sterile distilled water, or cisplatin (1mg/kg/day). Tumor growth was completely inhibited by cisplatin for mice inoculated with

AN3CA (p<0.05). Tumor growth in HEC1A inoculated mice was significantly inhibited by fludarabine (p<0.05).

Suppl. Fig. 1 *Survival analysis of patients bearing endometrial cancer.*

Kaplan-Meyer analysis of overall survival was performed for 262 patients who were treated during 2004-2011 in Kyoto University. The survival curves were compared among low-risk (black, n=86), intermediate-risk (blue, n=92), and high-risk (red, n=94) patients.

Suppl. Fig.2 *Caspase 3 protein induction by Fludarabine treatment.*

(A) Expression of Caspase 3α and Caspase 3β mRNA level on AN3CA, HEC1A, and HEC50B cell lines treated with fludarabine. Expression is shown normalized to GAPDH as measured by RT-qPCR.

(B) Expression of Caspase 3 protein and Cleaved Caspase 3 protein in AN3CA, HEC1A, and HEC50B cell lines treated with fludarabine and examined by Western Blotting.

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Table 1. Patient Characteristics

		n	Recurrence/PD	*p*	Rate of 5 yr OS	*p*
age	≦50	57	3		93.5	
	>50	205	40	0.0083	85.4	0.174
stage	I	174	10		98.5	
	II	19	2	0.3348	100	0.6355
	III	46	13	<0.0001	68.6	<0.0001
	IV	23	18	<0.0001	28.6	<0.0001
Myometrial invasion	≦1/2	145	6		97.0	
	>1/2	109	29	<0.0001	81.1	0.0004
LVSI	-	166	8		96.2	
	+	81	26	<0.0001	77.2	<0.0001
grade	Low	160	7		97.7	
	high	102	36	<0.0001	70.2	<0.0001
risk	Low	86	0		100	
	Intermediate	82	3	0.1141	98.4	0.3293
	high	94	40	<0.0001	64.9	<0.0001

Table 2. Patient Chemoresponsiveness Profiles

	chemo	n	Recurrence/PD	*p*
Low	-	75	0	
	+	11	0	-
Intermediate	-	25	3	
	+	57	0	0.0260
high	-	8	4	
	+	86	36	0.7193

Supplementary Table 1(i) Normalized GI50 values of 27 drugs from 62 cancer cell lines

No.	NAME	P388/ADR	OVCAR-4	MDA-MB-468	SF-268	HL-60(TB)	MAXF 401	SK-BR-3	SF-295	NCI-H23	NCI-H460	MALME-3M	UACC-62	OVCAR-3	IGROV1	NCI-H522	SNB-75	HOP-92	U251	SW-620	SNB-19	NCI-H226
1	Cisplatin	0.1584	0.1963	0.2164	0.1542	0.1159	0.1306	0.1136	0.1094	0.0962	0.0942	0.0486	0.0547	0.0443	0.0504	0.0081	0.0166	-0.0322	0.0249	-0.0216	0.0123	-0.0125
2	Doxorubicin	0.0659	-0.0668	-0.0206	0.0244	0.0311	0.0025	-0.0476	0.0091	-0.0283	0.2288	0.0905	0.0009	-0.0801	0.0246	0.0616	0.0562	0.0536	0.0839	0.0761	0.1332	0.1204
3	Paclitaxel	-0.3747	-0.1424	-0.0528	0.0490	-0.0195	0.0505	-0.1060	-0.0339	0.0296	0.0030	-0.0438	-0.0008	0.0916	0.0328	0.0234	0.0845	-0.1629	0.0523	0.1038	0.0390	-0.0332
4	Gemcitabine		-0.0594		-0.0043	0.1860			-0.0389	0.1639	0.0946	-0.1143	0.0088	-0.1335	-0.0375	-0.0556	0.1252	-0.0677	0.0214	-0.1124	0.1168	-0.0901
5	Fludarabine	0.1625	-0.0473		-0.0389	0.1185			-0.2063	0.0286	-0.1491	0.0503	-0.0836	-0.0447	-0.1605	-0.0256	-0.1215	0.1707	-0.1747	-0.0126	0.0922	-0.0364
6	Ara-C	0.1320	-0.0378		0.0327	0.0722		0.1138	-0.0366	0.0887	0.0913	-0.0190	0.0199	-0.1115	-0.1170	-0.0511	-0.1164	0.0071	0.0029	-0.0315	0.0319	-0.0886
7	Topotecan	-0.1299	-0.0588		0.1115	0.0470			0.0929	0.0378	0.0198	-0.1253	0.0433	-0.0898	-0.0716	0.0660	0.0863	0.0408	0.0887	0.0433	0.1508	0.1140
8	Mitomycin C	-0.1145	-0.0305	-0.0148	0.0301	0.0224	0.0630	0.0447	0.0993	0.1024	0.2439	-0.0191	0.0839	-0.1067	-0.1217	-0.0236	0.0576	-0.1273	0.0578	0.0465	0.1194	0.0303
9	Irinotecan	-0.1562	-0.0110		0.1295	-0.0561			0.0385	0.0119	-0.0122	-0.0558	0.0884	-0.0383	-0.0890	0.0057	-0.0064	0.0529	0.1131	0.0259	-0.0398	0.0872
10	Etoposide	-0.2186	-0.1473		-0.0154	0.1046			-0.0144	-0.0402	0.1282	-0.0431	-0.0465	-0.1296	-0.1323	-0.0290	-0.0206	-0.0034	0.0376	0.0215	0.0315	0.1024
11	5-FUdR	0.0401	-0.0543	-0.0174	0.0868	-0.0214	-0.1593	0.0219	0.0557	0.0439	0.0036	-0.1852	0.0332	0.0596	-0.1217	0.0396	0.0521	0.0333	0.0600	-0.1510	0.0421	-0.0877
12	Methotrexate	0.0480	-0.0990	-0.1476	0.0748	0.0023	-0.1092	-0.0849	0.0527	0.0340	0.0109	-0.0917	0.0346	0.0233	0.0689	-0.0033	-0.1351	-0.1029	0.0451	0.1065	-0.0196	-0.1293
13	5-FU		0.0098	-0.1445	-0.0756	-0.0712	-0.1535	0.1351	-0.0952	0.0085	0.1736	0.0043	-0.0254	0.0298	0.0511	-0.0626	-0.1626	-0.1642	-0.0787	0.0037	-0.0899	-0.1659
14	Bleomycin	-0.1018	0.0561	-0.1389	0.0254	-0.1427	0.1301	-0.2047	0.1293	0.0101	0.1169	0.0888	0.0155	-0.0277	-0.0026	0.0438	0.0874	0.1920	0.0335	-0.0601	-0.0081	0.1684
15	Ifosfamide	0.1734	0.0551		0.0370	0.0054			-0.0213	-0.0985	-0.1094	0.0699	-0.0383	0.0641	-0.0619	0.0915	0.0093	0.0783	0.0763	0.0796	0.0811	-0.0151
16	CPA	0.0294	0.0551		-0.0632	0.2290			0.1363	-0.0303	-0.1372	-0.0538	-0.1172	0.0125	-0.0417	-0.0748	-0.0408	-0.0264	-0.0762	-0.0302	-0.0074	-0.0162
17	Sorafenib		-0.0286	-0.0184	-0.1087	0.0939			0.0915	0.0651	-0.1144	-0.1315	0.1027	-0.1098	-0.0992	-0.0258	-0.0622	0.1757	-0.0040	-0.0596	-0.0931	0.2047
18	Tegafur	0.4691	0.0261		-0.0888	-0.1114			-0.0911	-0.0899	0.1337	0.0308	-0.0326	-0.0132	-0.0655	-0.0543	0.0513	-0.0722	-0.0958	-0.0318	-0.0364	-0.0051
19	Imatinib		0.0745		-0.0776	-0.0613			-0.0630	-0.0437	-0.0932	-0.0089	-0.0912	-0.0661	-0.0291	-0.0304	-0.0228	0.0270	-0.0433	-0.0302	-0.0693	0.0158
20	Bortezomib		0.0317	-0.1552	-0.0115	-0.1488			-0.0883	-0.0221	-0.2886	0.1472	-0.0268	0.1516	-0.0874	-0.0518	-0.0712	0.0332	-0.0650	0.1363	-0.0388	0.1813
21	Sunitinib		0.0873	-0.0567	-0.1214	0.0650			-0.2485	-0.0604	-0.0817	0.0677	-0.1317	-0.0245	0.0282	-0.0766	-0.0819	0.2055	-0.0421	0.0756	-0.1804	-0.1564
22	Vincristine	-0.0482	0.0512		0.0105	-0.0246			0.0213	0.0059	-0.0338	-0.0291	-0.0221	0.0864	0.0638	0.0306	-0.0267	0.0485	0.0189	0.0752	0.0927	0.0892
23	Vinblastine	-0.3122	-0.1674	-0.0252	0.0088	-0.0072	0.0453	0.0142	0.0246	-0.0124	-0.0538	0.0480	0.0169	0.1204	0.0166	0.0700	0.0829	-0.0148	0.0076	0.0657	0.0404	0.0407
24	Gefitinib		0.0279	0.3455	-0.0741	-0.1201			0.0069	-0.1790	-0.1440	0.0035	-0.1079	0.0022	0.2411	-0.0810	-0.0328	-0.0572	-0.1212	-0.0498	-0.0668	-0.0890
25	Erlotinib		0.0854	0.1639	-0.0626	-0.1673			-0.0926	-0.1435	-0.0702	0.1080	-0.0098	0.0839	0.2444	0.1244	-0.0231	0.0486	-0.1097	-0.1425	0.0065	-0.0896
26	Rapamycin		0.2848		-0.2372	-0.2294			0.0405	-0.0800	-0.1600	0.0942	0.1125	-0.0356	0.1880	-0.0960	0.1091	-0.0427	-0.0261	-0.1875	0.0463	-0.0556
27	Temsirolimus		0.1673		0.0204	-0.2508			0.1335	-0.0345	-0.2366	0.2994	-0.0666	0.1261	0.1997	-0.2159	0.0034	0.1823	-0.1755	-0.1092	-0.0034	0.0448

Supplementary Table 1(ii) Normalized GI50 values of 27 drugs from 62 cancer cell lines

No.	NAME	MCF7	T-47D	K-562	RPMI-8226	SK-OV-3	SK-MEL-5	PC-3	HCT-116	RXF 393	MDA-MB-231/ATCC	HCC-2998	MDA-N	BT-549	HT29	HS 578T	COLO 205	MDA-MB-435	SF-539	MOLT-4	SK-MEL-2	HOP-62
1	Cisplatin	-0.0556	-0.1457	-0.1338	-0.0791	-0.0297	-0.0226	-0.0865	-0.0837	-0.0077	-0.2133	-0.0805	-0.1378	0.0001	-0.1022	-0.0500	-0.1329	-0.0864	0.0170	-0.0332	0.0186	-0.0345
2	Doxorubicin	0.1744	0.1361	0.2306	0.2248	-0.0225	0.0378	-0.0603	0.0259	-0.0183	-0.0335	-0.0476	-0.0816	-0.0277	-0.0241	-0.0064	0.0019	-0.0757	-0.0051	-0.0142	-0.1229	-0.0069
3	Paclitaxel	0.0476	-0.0088	0.0335	0.0609	0.0506	0.0413	0.0877	0.0605	0.0549	0.1260	0.0728	0.1132	0.1090	0.1126	0.1223	0.1268	0.0652	-0.0753	-0.0200	-0.3271	-0.0610
4	Gemcitabine	0.0754	0.0439	-0.0619	-0.0513	-0.0754	-0.0956	-0.1300	0.1293	0.0299	-0.0491	-0.1383	0.0138	0.0008	-0.0667	-0.1296	-0.1026	-0.0447	0.0313	-0.0522	-0.0164	-0.1277
5	Fludarabine	-0.0923	0.0673	-0.1167	-0.1268	0.0873	-0.0691	0.1182	-0.0129	0.0136	-0.0647	-0.1341	0.0037	-0.0059	-0.1581	-0.0568	-0.0260		-0.1243	0.0813	0.1672	0.0190
6	Ara-C	0.1056	-0.0489	-0.0659	-0.1614	-0.0703	-0.0446	-0.0283	0.1099	-0.0894	-0.0351	-0.1042	0.0291	-0.0686	-0.0671	-0.1084	-0.0530	0.0515	-0.0585	0.1999	-0.1178	0.1097
7	Topotecan	0.0583	0.2248	-0.0505	-0.1804	0.1027	0.0250	-0.0233	-0.0305	0.0297	-0.2614	-0.1434	0.0258		-0.0690		-0.0348		0.0438	-0.0008	-0.2173	-0.0678
8	Mitomycin C	0.0728	-0.0266	-0.1370	-0.1458	0.0095	0.0359	-0.1087	-0.0407	-0.0785	-0.1397	-0.0034	-0.0821	-0.0486	0.0040	-0.1009	0.0122	-0.0790	0.0841	-0.0633	0.0552	0.0480
9	Irinotecan	0.0348	-0.0129	-0.0011	-0.0732	-0.0448	-0.0032	-0.0302	0.0425	-0.0755	-0.0115	0.0026		0.0146	0.0139	-0.1329	-0.0008	-0.0487	0.0824	0.0929	-0.0487	-0.0610
10	Etoposide	0.0593		-0.0893	0.0710	-0.0388	-0.0133	0.2071	-0.1037	-0.0611	0.1931	-0.0481	0.1684		-0.1053	0.1785	-0.1066		0.0600	0.1287	0.0201	-0.0367
11	5-FUdR	0.0530	-0.1006	0.0086	-0.0351	-0.1097	0.0717	0.0740	0.0646	-0.0030	-0.1301	0.0898	0.0255	-0.0220	0.0552	0.0340	0.0598	0.0256	0.0586	-0.0368	-0.2482	-0.0453
12	Methotrexate	0.0422	-0.1475	0.0745	0.0311	-0.1135	0.0242	0.0514	0.0617	-0.1698	-0.1747	0.0403	0.1067	-0.1410	0.1102	-0.2153	-0.0141	0.0796	0.0471	0.0025	-0.2340	-0.0378
13	5-FU	0.1698	0.0000	-0.0188	0.1008	-0.1242	0.0329	-0.0404	0.1087	-0.0475	-0.1634	0.2199	0.1035	-0.0903	0.1202	-0.1555	0.1418	0.0848	0.1981	-0.0454	-0.0916	-0.1157
14	Bleomycin	-0.0501	0.0243	-0.1049	-0.1564	-0.0356	0.0237	-0.0755	0.0573	0.1400	-0.0567	-0.1062	-0.1069	-0.0582	-0.0991	0.0406	-0.0254	-0.1323	0.2528	-0.0657	-0.0344	0.0691
15	Ifosfamide	-0.1074		-0.0166	0.0454	0.0494	-0.0503	-0.1321	-0.0658	0.0274	-0.0590	0.0308	-0.1421	-0.1165	-0.0199	-0.1175	-0.0062	-0.1442	-0.0260	-0.1488	0.1419	-0.2220
16	CPA	-0.0978		0.1022	-0.0847	-0.0082	-0.0424	-0.0297	-0.0882	-0.0355	0.0434	0.2247			0.0785		-0.0115	-0.0418	-0.0469	-0.1991	0.1392	-0.2433
17	Sorafenib	-0.0961	0.2868	-0.1018	0.2016	0.1202	0.2042	0.0434	0.0895	-0.0589	0.3738	-0.1596		-0.0979	0.0272	-0.0878	0.1511	0.1248	-0.0161	-0.2250	0.1314	-0.2222
18	Tegafur	0.0007	0.0188	-0.1007	0.0881	0.0435	-0.0853	-0.0588	0.0155	-0.0135	0.0143	0.3028	0.1855	-0.0432	0.0074	-0.0442	0.0330		0.0666	-0.2416	0.1077	-0.2331
19	Imatinib	-0.0666	0.0681	0.7803	0.0837	-0.0343	0.0038	-0.0183	-0.0109	0.0194	0.0717	-0.0486		0.0325	0.1860	0.0438	0.0240	-0.0084	0.0060	-0.0253	0.0818	-0.2047
20	Bortezomib	0.0704	0.2017	-0.0250	0.2123	-0.3292	0.0573	-0.0985	0.0650	0.0943	0.0846	0.0948		0.1544	0.0506	0.0599	0.0359	0.1626	-0.0323	-0.0671	0.1201	-0.3616
21	Sunitinib	-0.0421	-0.1708	0.0181	0.0504	-0.0064	0.0115	0.0061	0.0317	0.0582	0.0548	0.2183		-0.0196	0.0468	0.0207	0.0099	0.0233	0.0000	0.0000	0.0491	-0.2757
22	Vincristine	0.0076	-0.3930	0.0271	0.0207	0.0265	0.0274	0.0757	0.0107	0.0509	0.1488	0.0426	0.0656	0.0913	0.0706	0.0903	0.0829	0.0636	-0.0223	-0.0886	0.1162	-0.1925
23	Vinblastine	0.0280	-0.3317	0.0245	0.0033	0.0617	0.0567	0.1181	0.0253	0.0389	0.1667	-0.0104	0.1080	0.0920	0.0892	0.1327	0.1178	0.1060	-0.0360	-0.0714	0.0853	-0.1409
24	Gefitinib	-0.1406	0.0514	0.0030	0.0188	0.1797	-0.0348	0.1316	-0.0993	-0.0134	-0.0168	-0.1049		-0.0356	0.0006	-0.0470	-0.0135	0.0131	-0.1109	-0.1128	-0.0042	-0.2167
25	Erlotinib	-0.2323	0.1444	-0.1363	-0.1233	0.2333	-0.0908	-0.0918	-0.0246	0.0596	0.1062	-0.1856	-0.1104	-0.0729	-0.1419	0.0403	-0.1046	-0.0528	-0.0714	-0.1778	0.1089	-0.1655
26	Rapamycin	0.0357	0.1727	-0.1276	0.0612	0.0224	-0.1329	0.1353	-0.2341	0.0613	-0.0844	0.0315	-0.1738	0.2156	-0.1092	0.1579	-0.1898	-0.1033	0.1099	-0.0100	0.0287	0.0341
27	Temsirolimus	-0.0047	0.2845	-0.0764	0.1831	-0.1388	-0.1893	0.1293	-0.2210	0.0979	0.0237	0.1011		0.0636	-0.1065	0.0238	-0.1118	-0.0586	-0.0523	0.0222	-0.0359	-0.0073

Supplementary Table 1(iii) Normalized GI50 values of 27 drugs from 62 cancer cell lines

No.	NAME	OVCAR-5	SN12C	M14	NCI/ADR-RES	CCRF-CEM	OVCAR-8	LOX IMVI	SR	SK-MEL-28	A549/ATCC	DLD-1	CAKI-1	786-0	HCT-15	UACC-257	ACHN	EKVX	A498	DU-145	NCI-H322M
1	Cisplatin	0.0252	-0.1162	0.0121	0.0366	0.0277	-0.0845	0.0100	0.0231	0.0367	-0.0376	-0.0103	-0.0322	-0.0832	-0.0584	0.0242	0.0115	-0.0169	-0.1196	-0.0856	-0.0021
2	Doxorubicin	-0.0932	-0.0041	-0.0980	-0.4139	-0.0566	-0.0355	0.0351	-0.1842	0.0250	0.0142	-0.1647	-0.1125	-0.1239	-0.0076	0.0267	-0.0132	-0.0568	0.0307	-0.0409	-0.0138
3	Paclitaxel	0.0036	0.0259	0.0371	-0.3409	0.0251	0.0361	0.0094	-0.0677	0.0282	0.0327	-0.0502	-0.2683	0.0164	-0.1600	0.0342	-0.1257	-0.0145	-0.1069	0.0105	0.0052
4	Gemcitabine	-0.0011	-0.0213	0.2366	0.4647	0.1352	0.2611	-0.1842	-0.1725	-0.1237	0.1116		-0.1407	0.1304	-0.0315	0.1197	0.0662	-0.0165	0.0798	0.0455	-0.1841
5	Fludarabine	0.0705	0.2015	0.1450	0.3217	0.2936	0.3150	-0.1871	-0.2014	0.0114	-0.0912	-0.0712	-0.0114	-0.0136	-0.1241	0.0000	-0.1463	0.1421	-0.1148	0.0781	-0.1859
6	Ara-C	0.0067	0.0711	0.1984	0.1811	0.2438	0.1591	0.1162	0.0612	-0.0776	0.1894	-0.1734	0.0232	0.1461	-0.0824	-0.0522	0.0893	-0.0873	-0.0042	0.0813	-0.1886
7	Topotecan	0.0008	0.0929	0.1040	0.0682	0.0688	0.0447	-0.0719	-0.0468	-0.0963	-0.0861	-0.2574	-0.0609	0.0819	-0.1560	0.0649	-0.0607	-0.0239	-0.0401	0.1430	-0.1888
8	Mitomycin C	-0.0078	0.1222	0.0587	-0.1301	0.0651	-0.0028	-0.1301	0.1071	-0.0778	0.1289	0.0092	-0.1301	0.0084	0.0298	0.0733	-0.0369	-0.1022	0.0190	0.1965	-0.1076
9	Irinotecan	-0.0252	0.1373	0.1395	-0.1196	0.1125	0.0405	-0.0357	0.4145	-0.1485	-0.1861	-0.1479	-0.2123	0.1167	-0.0513	-0.0032	-0.2669	-0.0166	0.0378	0.1365	-0.1178
10	Etoposide	-0.0738	0.0331	0.1294	-0.1631	0.1429	0.0227	-0.0551	0.1546	-0.0836	-0.0097	-0.0358	-0.0991	0.0774	-0.0279	-0.0406	-0.0470	-0.0121	0.0104	0.1939	-0.2295
11	5-FUdR	-0.3407	0.0824	0.0702	0.1227	0.0148	0.1122	-0.0404	-0.0488	-0.0453	0.0193	0.1213	-0.1126	0.0374	-0.0611	0.0666	-0.0650	-0.3041	0.0373	0.0818	-0.0453
12	Methotrexate	-0.0619	0.0756	0.0584	0.1284	0.0574	0.0993	-0.0018	-0.0402	-0.1366	0.0406	0.1971	-0.0488	0.0575	0.1445	-0.0166	-0.0350	-0.1191	-0.1060	0.0192	-0.0658
13	5-FU	-0.1054	0.0071	-0.0573	-0.0105	-0.0146	0.0715	-0.0071	0.0391	-0.0270	0.1329	0.2211	-0.0182	0.0278	0.1326	0.0000	-0.0682	-0.1051	0.0759	0.0834	0.0148
14	Bleomycin	0.0203	0.0372	0.0000	0.1344	-0.0813	-0.0007	0.0292	0.1891	-0.1216	0.0173	-0.0584	0.1322	0.0000	0.0000	-0.0394	0.1937	-0.0734	-0.0191	-0.0541	-0.1493
15	Ifosfamide	0.0029	-0.0435	-0.0807	-0.1017	0.0684	0.0604	-0.1880	-0.2239	-0.0163	-0.1701	0.0336	-0.2725	-0.0869	-0.0029	0.1282	-0.3160	0.0999	-0.0424	-0.0695	-0.0292
16	CPA	0.0115	-0.0470	-0.0673	-0.0758	0.0083	0.0584	-0.2238	-0.1933	-0.0200	-0.1674	0.0358	-0.2837	-0.0887	-0.0074	0.1306	-0.2873	0.0859	-0.0301	-0.0355	-0.0320
17	Sorafenib	0.0384	-0.0367	-0.0499	0.0994	-0.0481	0.0048	-0.2002	-0.2535	0.0224	-0.1722		-0.3265	-0.1307	0.0720	0.1261	-0.3026	0.1120	-0.0089	-0.0995	-0.0859
18	Tegafur	-0.0526	-0.0806	-0.1020	-0.1896	-0.0524	0.0527	-0.2336	-0.0634	-0.0530	-0.1177	-0.0027	-0.3739	-0.1385	-0.0485	0.0639	-0.3452	0.1724	0.0078	0.0196	-0.0766
19	Imatinib	0.3911	-0.0849	-0.0508	-0.0005	-0.0183	0.0032	-0.1728	-0.0695	0.0342	-0.1389		-0.2875	-0.0508	0.0217	0.0759	-0.2431	0.0519	-0.0238	-0.0207	-0.0528
20	Bortezomib	0.0861	-0.0116	-0.0235	0.0323	0.0121	-0.0757	-0.1701	-0.1803	0.1979	-0.1675		-0.1096	-0.0923	0.1275	0.1744	-0.1714	0.0558	0.1388	-0.0454	-0.3557
21	Sunitinib	0.0021	-0.0347	0.1001	-0.0122	0.0000	-0.0753	-0.1872	-0.0324	0.0973	-0.2274		-0.1352	-0.0630	0.2084	0.0547	-0.2148	-0.0514	-0.0173	-0.0029	-0.1892
22	Vincristine	-0.3995	0.0029	-0.0074	0.0179	-0.0161	0.0576	-0.1235	-0.1166	-0.1741	-0.0360	0.2102	-0.1272	-0.0208	0.1041	0.1029	-0.1912	-0.1704	0.0439	0.0292	-0.0147
23	Vinblastine	-0.2172	-0.0493	-0.0176	-0.1544	-0.0463	-0.0294	-0.0851	-0.0736	0.0234	-0.0713	0.0552	-0.1762	-0.0332	-0.1385	0.0844	-0.2445	-0.1423	-0.0352	0.0704	-0.0455
24	Gefitinib	-0.0474	-0.0539	-0.0613	-0.0609	-0.0387	-0.0451	-0.1945	-0.1109	0.2202	-0.1294		0.0769	-0.1070	0.0132	0.0270	0.0535	0.4207	0.1773	0.0181	0.2307
25	Erlotinib	0.0466	0.1089	0.0035	0.0509	-0.1239	0.0457	-0.0894	-0.1140	-0.1003	-0.0694		0.1272	-0.0408	0.1089	-0.0919	0.1254	0.3646	0.1089	0.1089	0.2806
26	Rapamycin	-0.1501	-0.0737	-0.2645	0.0473	0.1189	0.0979	0.0499	0.0518	0.0013	-0.1501		-0.0007	-0.0629	0.0356	-0.1617	-0.1327	0.2480	0.1862	-0.0632	0.0007
27	Temsirolimus	0.1632	0.0275	-0.1427	-0.0077	0.0625	0.0839	-0.0665	0.0962	-0.0303	-0.1419		-0.1659	0.0400	0.0313	-0.0983	-0.1321	0.1121	-0.0770	-0.1069	0.0930

Supplementary Table 2 Drug sensitivity probability scores of 20 endometrial cancer cell lines

	Cisplatin	Doxorubicin	Paclitaxel	Fludarabine	Temsirolimus
AN3CA	0.9609812	0.9922923	0.9362531	0.3949139	0.0056779
JHUEM-2	0.9801558	0.9788238	0.8392539	0.3447866	0.9955872
ACC564	0.9172088	0.9794953	0.8078635	0.2239202	0.824768
JHUEM-14	0.7879796	0.9830877	0.8391634	0.2286711	0.0550549
HEC50B	0.9272133	0.7603211	0.1506094	0.9289022	0.8183438
KLE	0.6651077	0.7013829	0.4827253	0.8949722	0.99996
RL95-2	0.1103792	0.8146491	0.8126835	0.4508468	0.8254241
Ishikawa	0.2074402	0.8258797	0.6140672	0.262248	0.9309801
JHUEM-1	0.2228058	0.7396423	0.6487264	0.244423	0.9912851
HEC108	0.1498501	0.7358695	0.6044988	0.3848306	0.1470534
HEC1B	0.5591885	0.663558	0.2656748	0.9350928	0.3533132
JHUEM-7	0.5042838	0.6326798	0.2843521	0.1760799	0.5709204
HEC265	0.0711893	0.4328958	0.6106844	0.4131935	0.3652914
SNG-M	0.1050776	0.3679269	0.3386838	0.441292	0.0084241
HHUA	0.1024104	0.4000244	0.3007096	0.5254564	0.0091142
Sawano	0.0486279	0.1386172	0.3607551	0.7312948	0.050791
TEN	0.2040208	0.2347581	0.2490615	0.7770084	0.9992827
HEC1A	0.0591909	0.3127463	0.5316516	0.817848	0.4038302
ACC230	0.3255888	0.3018474	0.1755544	0.9664279	0.9999653
JHUEM-3	0.5009493	0.2468406	0.1092376	0.9695341	0.9969814

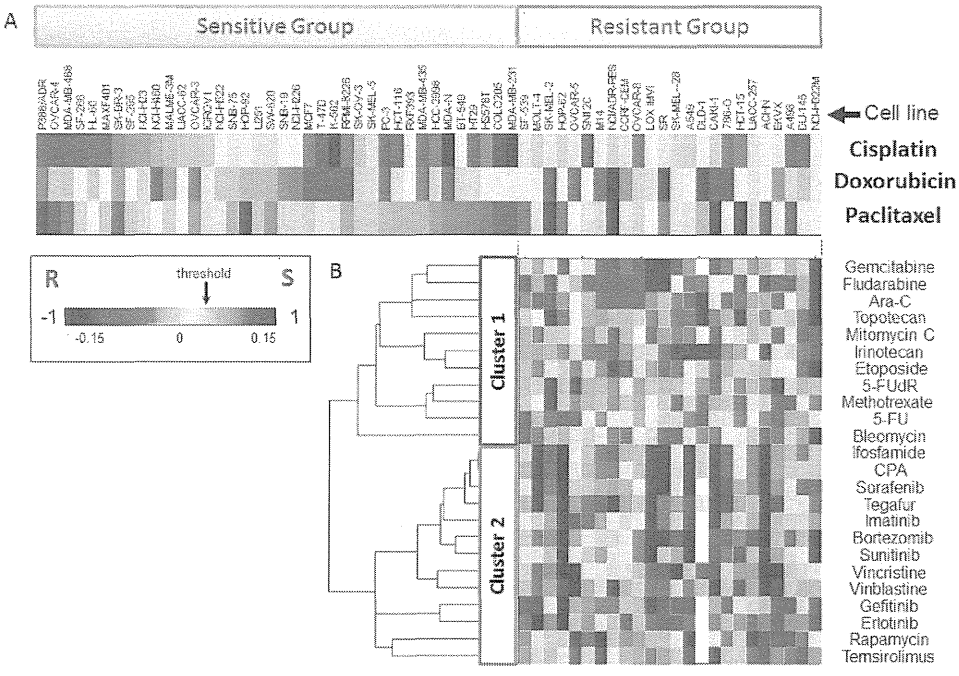
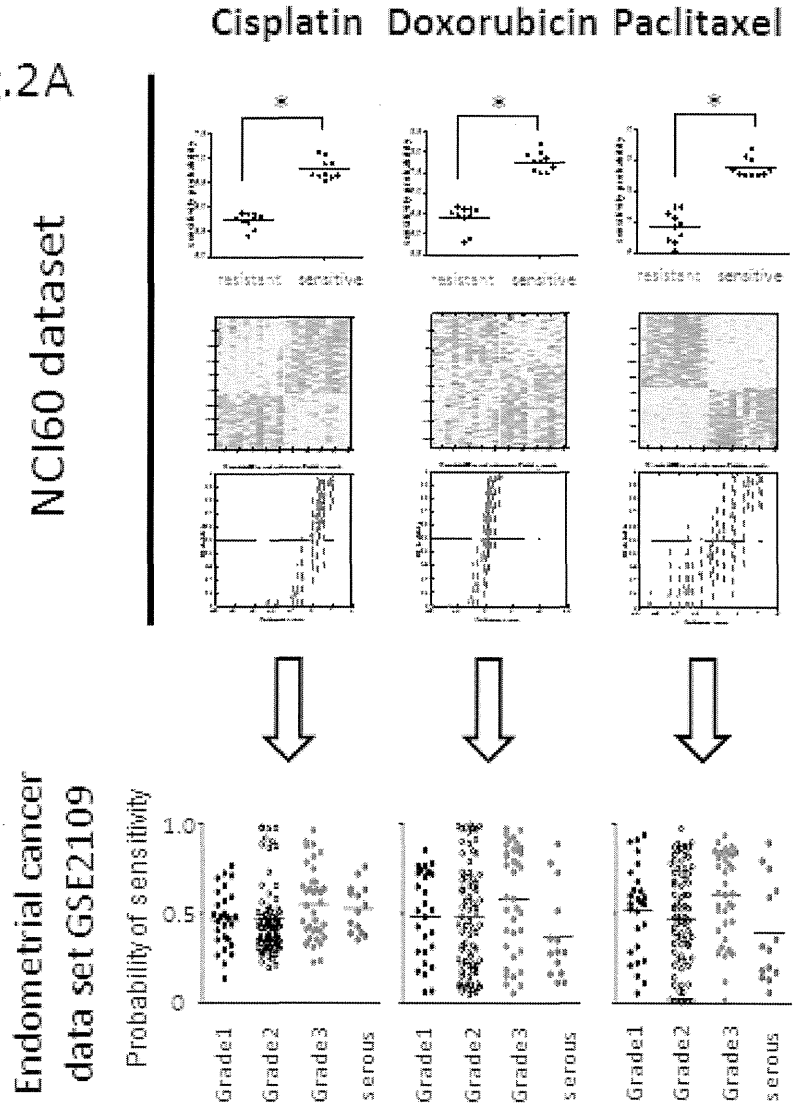


Fig.1

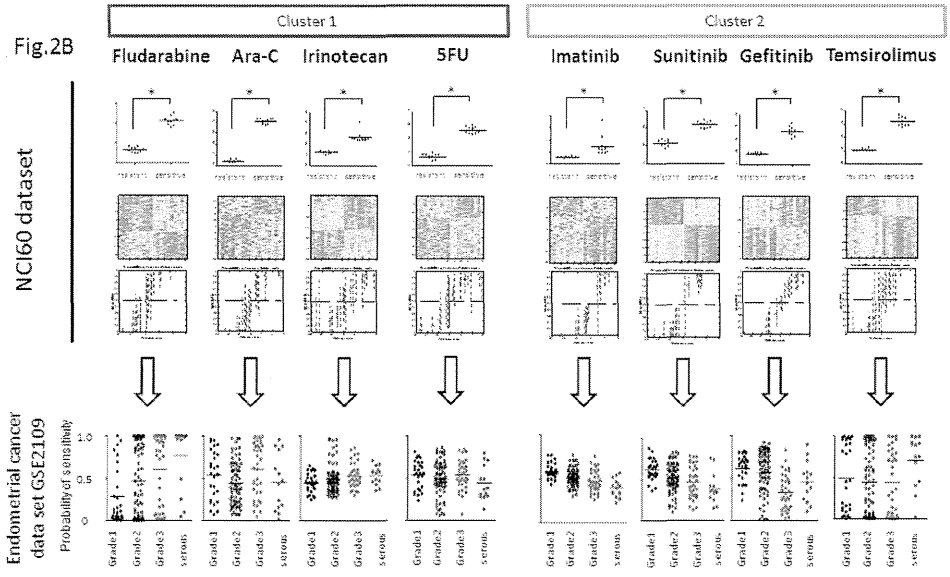
250x184mm (300 x 300 DPI)

Fig.2A



182x229mm (300 x 300 DPI)

Fig.2B



193x116mm (300 x 300 DPI)