Probeset	Coefficient	Probeset	Coefficient	Signature parameter						
208892 s at	0.084441	209435 s at	0.011602	Intercept: -10.669325						
208891 at	0.078566	203367 at	0.011552	1						
204011 at	0.057058	201195 s at	-0.01144	Draw in frank MCMC: 1000						
201631 s at	0.04849	209317 at	0.011036	Burn-in for MCMC: 1000						
208893 s at	0.047839	209433 s at	0.010878							
210073 at	0.045858	209434 s at	0.010827	Iterations for MCMC: 5000						
204014 at	0.040523	211686 s at	0.010775							
203348 s at	0.040421	218239 s at	0.01068							
221911 at	0.039717	221931 s at	0.010668							
203349 s at	0.038708	212672 at	0.010613							
221489 s at	0.036407	211584 s at	0.010553							
208712 at	0.035906	203612 at	0.010425							
209803 s at	0.032737	203480 s at	0.010233							
44783 s at	0.032667	204159 at	-0.01021							
202431 s at	0.03235	214805 at	0.010196							
203320 at	0.032343	206501 x at	0.009985							
218839 at	0.031885	221020 s at	0.009683							
204015 s at	0.029972	209704 at	0.009606							
203394 s at	0.029056	218047 at	-0.00959							
205193 at	0.027913	202332 at	0.009459							
206233 at	0.026701	207667 s at	0.009346							
212558 at	0.024504	214427 at	0.009252							
216375 s at	0.024259	210279 at	0.009011							
203395 s at	0.023353	201437 s at	0.008808							
201694 s at	0.023318	218590 at	0.00878							
209884 s at	0.021045	217053 x at	0.008315							
202081 at	0.020672	203580 s at	0.00829							
214721 x at	-0.01948	217061 s at	0.008279							
218247 s at	0.018082	204067 at	-0.00786							
202695 s at	0.017669	205698 s at	-0.00776							
204973 at	0.0172	207515 s at	0.006941							
210117 at	0.017127	212569 at	0.006585							
202770 s at	-0.01701	222303 at	0.006281							
212501 at	0.016887	221221 s at	-0.00564							
<u>218062 x at</u>	-0.01664	218104 at	0.005571							
221986 s at	-0.01633	<u>222127 s at</u>	-0.00525							
20/604 s at	0.016288	218581 at	-0.00523							
211559 s at	-0.01583	201394 s at	-0.00515							
219177 at	0.015027	48825 at	-0.00489							
208152 s at	0.014654	213137 s at	0.004503							
201661 s at	0.014517	205982 x at	-0.00415							
201328 at	0.014317	218630 at	-0.00397							
219031 s at	0.012506	2195/5 s at	0.003866							
2180/0 at	0.013596	2040/8 s at	-0.00365							
201062 s at	0.01338/	205/25 at	-0.00323							
201642 at	0.013219	207525 = 207525	-0.00307							
201042 at 216249 a at	0.01262	207323 S at	-0.003							
210248 S at	0.01201	222330 at	-0.00288							
201000 at	-0.01219	220070 at	-0.00223							

Supplementary Table 1. Signature conditions for BRAF pathway activity prediction*

Supplementary Fig. S1. Generation and validation of gene signatures for the BRAF pathway. RMA normalized data was used for the signature generation and activity prediction for BRAF pathway. To generate the BRAF pathway signature, the gene expression data of five cancer cell lines (GSE10086) with wildtype BRAF was used as training set. Cells treated with or without MEK inhibitor were set as BRAF pathway 'off' and 'on', respectively. The gene expression data of mammary epithelial cell line MCF10a with forced expression of *HRAS* or *MEK1* (GSSE12764), and breast cancer cell line MCF-7 with forced expression of active MEK (GSE3542), were used to as test sets to validate the BRAF pathway signature. Each point in the plot represent one sample.

Supplementary Fig. S2. Cox regression analysis of the associations of the STAT3 pathway with recurrence risk in different subtypes of breast cancers. The three BC cohorts annotated with patient's survival information were analyzed here. The pathway activity was used as continuous variables. The recurrence risk with the increase of the pathway activity was indicated by HR (presented per one-SD increment) as shown in forest plot. The overall effect of HR was calculated using a random-effects model, and the significance of the overall effects across multiple cohorts was estimated by Z test.

Supplementary Fig. S3. Multivariate Cox regression analysis of the associations of the IFN α , IFN γ , TNF α and TGF β pathways with recurrence risk in basal-like breast cancer. Cox regression analysis was performed in patient cohort 2 (A-D), cohort 3 (E-H) and cohort 4 (I-L) for pathways IFN α (A, E, I), IFN γ (B, F, J), TNF α (C, G, K) and TGF β (D, H, L), respectively. The pathway activities were used as continuous variables. All the other covariates, including age ($\leq 50 \text{ vs} > 50$), grade (grade 1&2 vs 3), size ($\leq 2\text{cm vs} > 2\text{cm}$), ER (negative vs positive), PR (negative vs positive) and HER2 (negative vs positive) were used as categorical variable. The recurrence risk with the increase of the pathway activity in the three patient cohorts was indicated by HR (presented per one-SD increment) as shown in forest plot.

Supplementary Fig. S4. Survival curves for the five PAM50-based intrinsic subtypes in the BC cohorts used in this study. A) Cohort 2. B) Cohort 3. C) Cohort 4.

Supplementary Fig. S5. Kaplan-Meier analysis of the synergistic effects of pathway combination on prognosis prediction of BLBC. A-C) TGF β and TNF α pathway combination. D-F) TGF β and IFN α pathway combination. G-I) TGF β and IFN γ pathway combination. Three BC cohorts with survival information were analyzed, including cohort 2 (A, D, J), cohort 3 (B, E, H) and cohort 4 (C, G, K). The patients were stratified into three subgroups based on tertile splits of the scores of corresponding pathway combination. The Kaplan-Meier analysis data for subgroups stratified based on individual pathways are shown in Fig.2.

Supplementary Fig. S6. Kaplan-Meier analysis of the synergistic effects of pathway combination on prognosis prediction of BLBC. A-C) Subgroups stratified into based on IFN α pathway activity. D-F) Subgroups stratified into based on TGF β and IFN α pathway combination scores. G-I) Subgroups stratified into based on IFN γ pathway activity. J-L) Subgroups stratified into based on TGF β and IFN α pathway combination scores. G-I) Subgroups stratified into based on IFN α pathway combination scores. Three BC cohorts with survival information were analyzed, including cohort 2 (A, D, G, J), cohort 3 (B, E, H, K) and cohort 4 (C, F, I, L). The patients were

stratified into two subgroups based on median splits of the corresponding pathway activities or pathway combination scores. The Kaplan-Meier analysis data for two subgroups stratified based on TGFβ pathway activity alone are shown in **Fig.5**.

Supplementary Fig. S7. Associations of IFN α , IFN γ , TNF α and TGF β pathways with prognostic prediction for BLBC treated with chemotherapy. A) Comparison of response rate of five PAM50-based intrinsic subtypes to neoadjuvant chemotherapy. BC cohort 1 (*n*=2093) was analyzed here as it is annotated with patient's neoadjuvant response information. Luminal A BC was used as reference and its OR set as 1. B) Associations of IFN α , IFN γ , TNF α and TGF β pathways, alone or in combination, with response rate of BLBC to neoadjuvant chemotherapy in cohort 1 (*n*=584). C) Associations of IFN α , IFN γ , TNF α and TGF β pathways, alone or in combination, with BLBC recurrence risk after adjuvant chemotherapy. Only BLBC from cohorts 2 (*n*=150) and 4 (*n*=84) were tested here since there are only 21 basal-like samples in cohort 3 annotated chemotherapy information. Lum A: luminal A; Lum B: luminal B; Normal: Normal-like; Her2: HER2-enriched; Basal: basal-like; IFN α : IFN α ; IFN β : IFN γ ; TNF α : TNF α ; TGFb: TGF β .

Supplementary Fig. S8. Synergistic effects of TNF α and TGF β pathways on prediction of recurrence risk for BLBC after adjuvant chemotherapy. Only cohort 2 (A-C) and cohort 4 (D-F) were tested with Kaplan-Meier plot since there are only 21 basal-like samples in cohort 3 annotated chemotherapy information. The patients were stratified into two groups based on median splits of predicted pathway activities or pathway combination scores in each cohort. A, D) Stratification based on TNF α pathway activity. **B**, **E**) Stratification based on TGF β pathway activity. **C**, **G**) Stratification based on the combination scores of TNF α and TGF β pathway.

Supplementary Fig. S9. Synergistic effects of combination of TGF β with IFN α or IFN γ on prediction of recurrence risk for BLBC after adjuvant chemotherapy. A, B) Subgroups stratified into based on IFN α pathway activity. C, D) Subgroups stratified into based on TGF β and IFN α pathway combination scores. E, F) Subgroups stratified into based on TGF β and IFN α pathway activity. G, H) Subgroups stratified into based on TGF β and IFN α pathway activity. G, H) Subgroups stratified into based on TGF β and IFN α pathway activity. G, H) Subgroups stratified into based on TGF β and IFN α pathway combination scores. Two BC cohorts with survival information were analyzed, including cohort 2 (A, C, E, G) and cohort 4 (B, D, F, H). The patients were stratified into two subgroups based on median splits of the corresponding pathway activities or pathway combination scores. The Kaplan-Meier analysis data for two subgroups stratified based on TGF β pathway activity alone are shown in Supplementary Fig. S8.

Supplementary Fig.S10. Associations of TNF α and TGF β pathway status with different immune cell subsets in BLBC. BLBC from four BC patient cohorts were tested. A) Cohort 1. B) Cohort 2. C) Cohort 3. D) Cohort 4. Four BLBC subgroups, including high-TNF α /low-TGF β , low-TNF α /high-TGF β , high-TNF α /high-TGF β and low-TNF α /low-TGF β as indicated, were stratified from each cohort based on median values of the TNF α and TGF β pathway activities, the heatmap was used to depict relative immune cell subset levels across the four BLBC subgroups. Each row represents one immune cell subset. Each column represents one BLBC sample. The fractions of 22 immune cell subsets were predicted based on gene expression data. Four of subsets that correlated with TNF α and TGF β pathway status were shown in **Fig.6**. Data for the remaining subsets are presented here. 1: T cells CD4 naive; 2: B cells naive; 3: B cells memory; 4: Plasma cells; 5: T cells CD8; 6: T cells CD4 memory resting; 7: T cells follicular helper; 8: T cells regulatory (Tregs); 9: T cells gamma delta; 10: NK cells resting; 11: NK cells activated; 12: Monocytes; 13: Dendritic cells resting; 14: Dendritic cells activated; 15: Mast cells resting; 16: Mast cells activated; 17: Eosinophils; 18: Neutrophils.

Supplementary Fig.S11. Comparison of levels of activated memory CD4 T cells among BLBCs with different status of high TNF α and low TGF β pathway activities. Each dot represents one sample and the red point represents mean value of activated memory CD4 T cells in one subgroup.



Supplementary Fig.S1

Subgroup	n	STAT3	p-value	HR[95%CI]
All patient	ts			
cohort2	2904	j ⊢≣ -(0.02	1.09 [1.01, 1.16]
cohort3	957	⊢∔⊣	0.99	1.00 [0.89, 1.12]
cohort4	817	I <u>-</u> ∎I	0.18	1.11 [0.95, 1.28]
Overall		•	0.02	1.07 [1.01, 1.13]
Luminal A	l			
cohort2	1003	⊦÷∎−−1	0.28	1.09 [0.93, 1.26]
cohort3	271	⊢ → − → 1	0.71	1.06 [0.77, 1.47]
cohort4	240 H		0.24	0.79 [0.53, 1.17]
Overall		•	0.50	1.05 [0.92, 1.19]
Luminal B	3			
cohort2	1044	⊢-•	0.95	1.00 [0.89, 1.14]
cohort3	330	⊢ ∎1	0.56	0.94 [0.76, 1.16]
cohort4	216	⊢ − − − −	0.13	1.30 [0.93, 1.82]
Overall		•	0.81	1.01 [0.91, 1.12]
Normal-lik	re			
cohort2	135	⊢I	0.97	0.99 [0.63, 1.57]
cohort3	38 🕂	1	0.22	0.56 [0.22, 1.43]
cohort4	33 🔶		2.72e-03	0.33 [0.16, 0.68]
Overa ll			0.14	0.59 [0.30, 1.19]
HER2-enr	iched			
cohort2	309	⊦∔∎−−1	0.38	1.08 [0.91, 1.29]
cohort3	105	⊢ ∎i	0.14	0.81 [0.61, 1.07]
cohort4	77	⊢	0.95	1.01 [0.72, 1.42]
Overall			0.83	0.98 [0.82, 1.18]
Basal-like				
cohort2	413	⊢ -∎1	0.22	1.11 [0.94, 1.31]
cohort3	213	⊢ ∎	0.59	1.06 [0.86, 1.30]
cohort4	251	H 	0.12	1.21 [0.95, 1.53]
Overall		•	0.06	1.11 [0.99, 1.25]
	[7	
	0.5	07 1 13	2	
	0.0	0.7 1 1.0	2	

Hazard Ratio

A)	Covariates	n		p-valu	e HR[95%CI]	E) Covariates	n			p-value	HR[95%CI]	I)	Covariates	n		p-value	HR[95%CI]
-	IFNa + Age	317	.	0.02	0.79 [0.65, 0.96]	IFNa + Age	140	.		8 64e-03	0.69 (0.53, 0.91)		IFNa + Age	251		0.30	0.88 (0.70, 1.12)
	IFNa + Grade	270		0.03	0.81 [0.66, 0.98]	IFNa + Grade	155			0.02	0.73 [0.57, 0.95]		IFNa + Grade	234		0.39	0.90 [0.70, 1.15]
	IFNa + Node	322		0.04	0.81 [0.66, 0.99]	IFNa + Node	176	.		6.22e-03	0.71 [0.55, 0.91]		IFNa + Node	251		0.19	0.85 [0.67, 1.08]
	IFNa + Size	240		- 0.14	0.84 [0.66, 1.06]	IFNa + Size	132			3.73e-03	0.66 [0.50, 0.87]		IFNa + Size	250		0.43	0.91 [0.72, 1.15]
	IFNa + ER	369		. 0.16	0.89 [0.76, 1.05]	IFNa + ER	211		-	0.08	0.82 [0.66, 1.02]		IFNa + ER	251		0.25	0.87 [0.69, 1.10]
	IFNa + PR	260		- 0.65	0.96 [0.80, 1.15]	IFNa + PR	149		<	0.03	0.75 [0.57, 0.98]		IFNa + PR	201		0.47	0.91 [0.70, 1.17]
	IFNa + HER2	245		- 0.50	0.94 [0.77, 1.13]	IFNa + HER2	147		4	0.05	0.76 [0.58, 1.00]		IFNa + HER2	231		0.37	0.89 [0.70, 1.14]
									-								
			0.5	2				0.5	1 2						0.5 1	2	
			HR (Lo	g scale)				HR (Lo	g scale)						HR (Log	scale)	
B)	Covariates	n		p-valu	e HR[95%CI]	F) _{Covariates}	n			p-value	HR[95%CI]	J)	Covariates	n		p-value	HR[95%CI]
-						151					0.05.10.10.0.053						
	IFNg + Age	317		8.48e-0	0.72 [0.60, 0.88]	IFNg + Age	140			1.70e-03	0.65 [0.49, 0.85]		IFNg + Age	251		0.03	0.78 [0.62, 0.98]
	IFNg + Grade	270		6.12e-0	14 0.72 [0.60, 0.87]	IFINg + Grade	155			3.936-03	0.69 [0.54, 0.69]		IFING + Grade	234	-	0.05	0.79 [0.62, 1.00]
	IFNg + Node	322		1.08e-0	0.73 [0.60, 0.88]	IFINg + Node	1/6			1.87e-04	0.66 [0.52, 0.64]		IFING + Node	251	_	0.02	0.75 [0.60, 0.95]
	IFNg + Size	240		5.57e-0	0.73 [0.58, 0.91]	IFNg + Size	132	••		1.89e-04	0.61 [0.47, 0.81]		IFNg + Size	250		0.06	0.80 [0.63, 1.01]
	IFNg + ER	369		0.02	0.83 [0.71, 0.97]	IFNg + ER	211			9.34e-03	0.75 [0.61, 0.93]		IFNg + ER	251		0.02	0.76 [0.61, 0.96]
	IFNg + PR	260		• 0.17	0.88 [0.73, 1.05]	IFNg + PK	149			9.386-03	0.71 [0.54, 0.92]		IFNg + PR	201	-	0.13	0.83 [0.64, 1.06]
	IFNg + HER2	245		0.10	0.86 [0.71, 1.03]	IFNg + HER2	147			0.03	0.74 [0.56, 0.96]		IFNg + HER2	231		0.08	0.81 [0.64, 1.03]
								0.5							0.5 1		
			0.5 1	2				0.5	1 2						0.5 1	2	
			HR (Loç	g scale)				HR (Lo	g scale)						HK (Log	scale)	
C)	Covariates	n		p-valu	e HR[95%CI]	G) _{Covariates}	n			p-value	HR[95%CI]	К)	Covariates	n		p-value	HR[95%CI]
	TNFa + Age	317		0.01	0.79 [0.65, 0.95]	TNFa + Age	140			0.05	0.76 [0.58, 1.00]		TNFa + Age	251		0.07	0.81 [0.65, 1.02]
	TNFa + Grade	270		1.22e-0	3 0.73 [0.60, 0.88]	TNFa + Grade	155		4	0.04	0.77 [0.61, 0.99]		TNFa + Grade	234		0.06	0.80 [0.63, 1.01]
	TNFa + Node	322		0.01	0.78 [0.65, 0.94]	TNFa + Node	176	- -		8.28e-03	0.72 [0.56, 0.92]		TNFa + Node	251		0.05	0.79 [0.64, 0.99]
	TNFa + Size	240		0.02	0.77 [0.62, 0.96]	TNFa + Size	132	——		0.02	0.72 [0.54, 0.95]		TNFa + Size	250		0.10	0.83 [0.66, 1.04]
	TNFa + ER	369		0.19	0.90 [0.77, 1.05]	TNFa + ER	211			0.05	0.80 [0.64, 1.00]		TNFa + ER	251		0.06	0.80 [0.64, 1.01]
	TNFa + PR	260		→ 0.34	0.92 [0.77, 1.10]	TNFa + PR	149		•	0.04	0.75 [0.57, 0.99]		TNFa + PR	201		0.09	0.81 [0.63, 1.04]
	TNFa + HER2	245		→ 0.43	0.93 [0.77, 1.12]	TNFa + HER2	147		-	0.27	0.85 [0.63, 1.14]		TNFa + HER2	231		0.08	0.81 [0.64, 1.02]
			r i						i – – i						r i		
			0.5 1	2				0.5	1 2						0.5 1	2	
			HR (Log	g scale)				HR (Lo	g scale)						HR (Log :	scale)	
D)	Covariates	n		p-valu	e HR[95%CI]	H) Covariates	n			p-value	HR[95%CI]	L)	Covariates	n		p-valu	HR[95%CI]
_	TGFb + Age	317			5 1.48 [1.23, 1.80]	TGFb + Age	140		-	0.11	1.23 [0.95, 1.60]		TGFb + Age	317			5 1.48 [1.23, 1.80]
	TGFb + Grade	270		1.96e-0	1.53 [1.26, 1.85]	TGFb + Grade	155			0.18	1.18 [0.92, 1.52]		TGFb + Grade	270			5 1.53 [1.26, 1.85]
	TGFb + Node	322		1.40e-0	4 1.45 [1.20, 1.76]	TGFb + Node	176		- -	0.11	1.21 [0.96, 1.54]		TGFb + Node	322		1.40e-0	4 1.45 [1.20, 1.76]
	TGFb + Size	240		2.07e-0	3 1.45 [1.15, 1.85]	TGFb + Size	132			0.23	1.18 [0.90, 1.54]		TGFb + Size	240			3 1.45 [1.15, 1.85]
	TGFb + ER	369		1.37e-0	5 1.42 [1.21, 1.67]	TGFb + ER	211			0.14	1.16 [0.95, 1.42]		TGFb + ER	369		1.37e-0	5 1.42 [1.21, 1.67]
	TGFb + PR	260		9.06e-0	4 1.35 [1.13, 1.61]	TGFb + PR	149	-		0.30	1.14 [0.89, 1.45]		TGFb + PR	260		9.06e-0	4 1.35 [1.13, 1.61]
	TGFb + HER2	245			4 1.36 [1.14, 1.64]	TGFb + HER2	147			0.10	1.24 [0.96, 1.60]		TGFb + HER2	245		9.05e-0	4 1.36 [1.14, 1.64]
									÷						ł		
			0.5 1	2				0.5	1 2						0.5 1	2	
			HR (Log	scale)				HR (Lo	g scale)						HR (Log	scale)	



Supplementary Fig.S4





Supplementary Fig.S6



B) Covariates		p-value	OR[95%CI]
TGFb	·	0.19	0.89 [0.75, 1.06]
IFNa	· •	0.46	0.94 [0.79, 1.11]
IFNg	·	0.68	1.04 [0.87, 1.23]
TNFa		0.45	1.07 [0.90, 1.28]
IFNa & TGFb		0.67	1.04 [0.87, 1.24]
IFNg & TGFb	· -	0.21	1.12 [0.94, 1.35]
TNFa & TGFb		0.11	1.17 [0.97, 1.41]
	0.75 1 1.2 1.	5	
	Odds Ratio		





Supplementary Fig.S8



Supplementary Fig.S9





Supplementary Fig.S11