

Updated StrataIO Model

- Discovery cohort: 610 cases → 708 cases
 - Removed cases where pembro start date was after sample collection date
- Individual PD-L1, PD-1 amplicons → average of independent PD-L1 and PD-1 amplicons
- TMB, PD-L1, PD-L2, PD-1* significant predictors → TMB, PD-L1, PD-L2, PD-1, TNFRSF9 significant predictors
- Backward selection → Backward selection, train/test subsets, search, minimize # of terms
 - TMB, PD-L2, PD-L1, GZMA*, TOP2A* → TMB, PD-L2, PD-1, ADAM12, CD4
- 8 TTNT curves to 4 IRS groups to High vs. Low → 8 TTNT curves to 3 IRS groups
 - Mirroring OncotypeDX (high and low are clear; intermediate requires additional investigation)
- Confirmed sensitivity to NSCLC vs. other, mono vs. combo, tumor content, RNA panel version

Fig. 1

Combining PD-L1 or PD-1 amplicons

Both PD-L1 and PD-1 have two amplicons targeting 3' and 5' ends of the transcripts -- these represent two independent measurements of the expression and were thus averaged together.

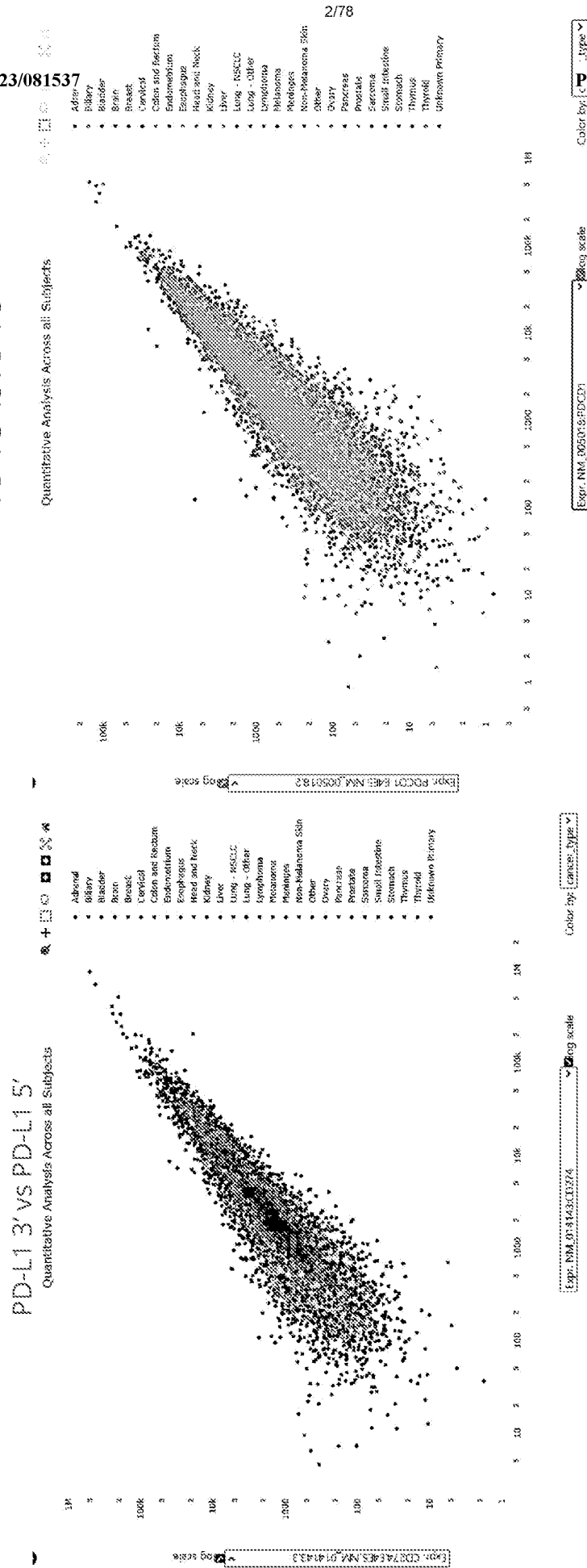


Fig. 2

Updated Model Selection

Partial-AIC/BIC for each model when trained on all 708 samples in dataset

	Model	AIC_partial	log_likelihood_partial	BIC_partial
ASCO	PD-L1 + GZM4 + TOP2A + PD-L2 + TMB	3005.16	-1497.58	3027.9722
Bare-bones	PD-L1 + PD-L2 + TMB	2998.23	-1496.12	3011.9273
Stratola	ADAM12 + CD4 + PD-1 + PD-L2 + TMB	2993.43	-1491.71	3016.2322
New "Top"	PD-L1 + ADAM12 + CD4 + PD-1 + PD-L2 + TMB	2993.80	-1490.90	3021.1747
Backward	VICN1+ IFNG + PD-L1 + ADAM12 + CD4 + PD-1 + PD-L2 + TMB	2989.73	-1486.87	3026.2396
Old "Top"	IFNG + TNFRSF9 + ADAM12 + CD4 + PD-1 + PD-L2 + TMB	2990.98	-1488.49	3022.9171

AIC = $[-2\log L + 2p]$
BIC = $[-2\log L + \ln(n)p]$

AIC is an estimate of a constant plus the relative distance between the unknown true likelihood function of the data and the fitted likelihood function of a model, so that a lower AIC means a model is considered to be closer to the truth.
BIC is an estimate of a function of the posterior probability of a model being true, under a certain Bayesian setup, so that a lower BIC means that a model is considered to be more likely to be the true model.

Fig. 3

Updated Model Selection (part II)

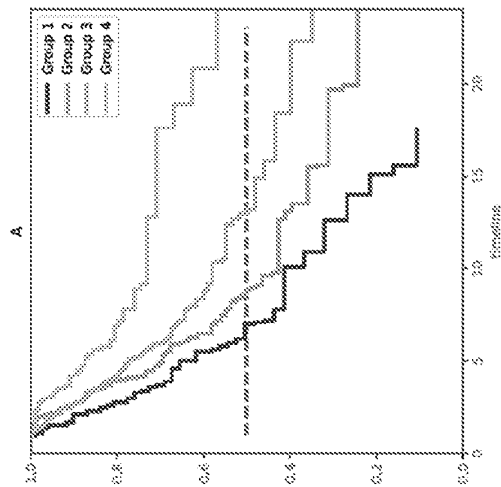
Median partial-AIC and log-likelihood for each model when trained on a random 2/3 of dataset x 100 iterations
Also shown is the median log-likelihood score of the test sets (the 1/3 left-out)

	Model	Train			Test	
		AIC_partial	Median log-likelihood_partial	Median log-likelihood_partial	Median log-likelihood_partial	Median
ASCO	PD-L1 + GZMA + TOP2A + PD-L2 + TMB	1861.020270	-925.515135	-1.724467		
Bare-bones	PD-L1 + PD-L2 + TMB	1856.877744	-925.438872	-1.718493		
StratigO	ADAM12 + CD4 + PD-1 + PD-L2 + TMB	1855.531050	-922.765525	-1.711339		
New "Top"	PD-L1 + ADAM12 + CD4 + PD-1 + PD-L2 + TMB	1855.736129	-921.868064	-1.714336		
Backward	PD-L1 + VTCN1 + ADAM12 + IFNG + CD4 + PD-1 + PD-L2 + TMB	1852.380245	-916.190122	-1.715575		
Old "Top"	TNFRSF9 + ADAM12 + IFNG + CD4 + PD-1 + PD-L2 + TMB	1854.520241	-920.260121	-1.713430		

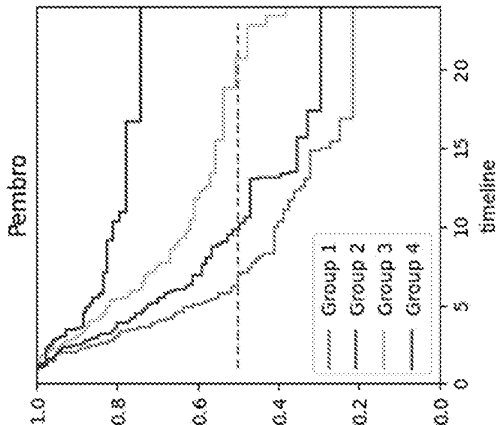
All models trained and tested on the same cuts of the data at each iteration

Fig. 4

Final Selection of 3 IRS groups



Octiles
Quartiles (1-4)
High (3&4) vs. Low (1&2)
4 vs. 3



Octiles
Stability in test sets
Quartiles
High / Inter. / Low

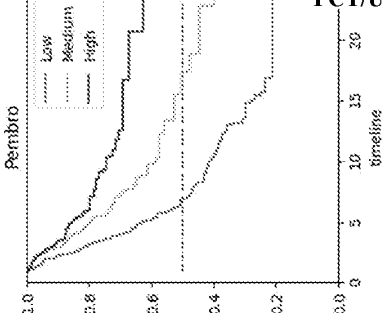
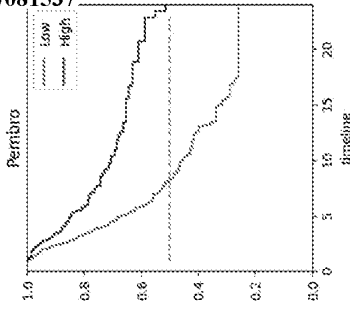


Fig. 5

708 pembrolizumab treated patients (from 24 cancer types 481 pembro+chemo; 227 pembro mono; 170 2nd line pembro mono with prior chemo) with StrataIO scores were analyzed. Aside from several outliers, pembrolizumab TNT was correlated to OS (Spearman: $n=43$ $r=0.74$, or $n=45$, $r=0.61$ with outliers).

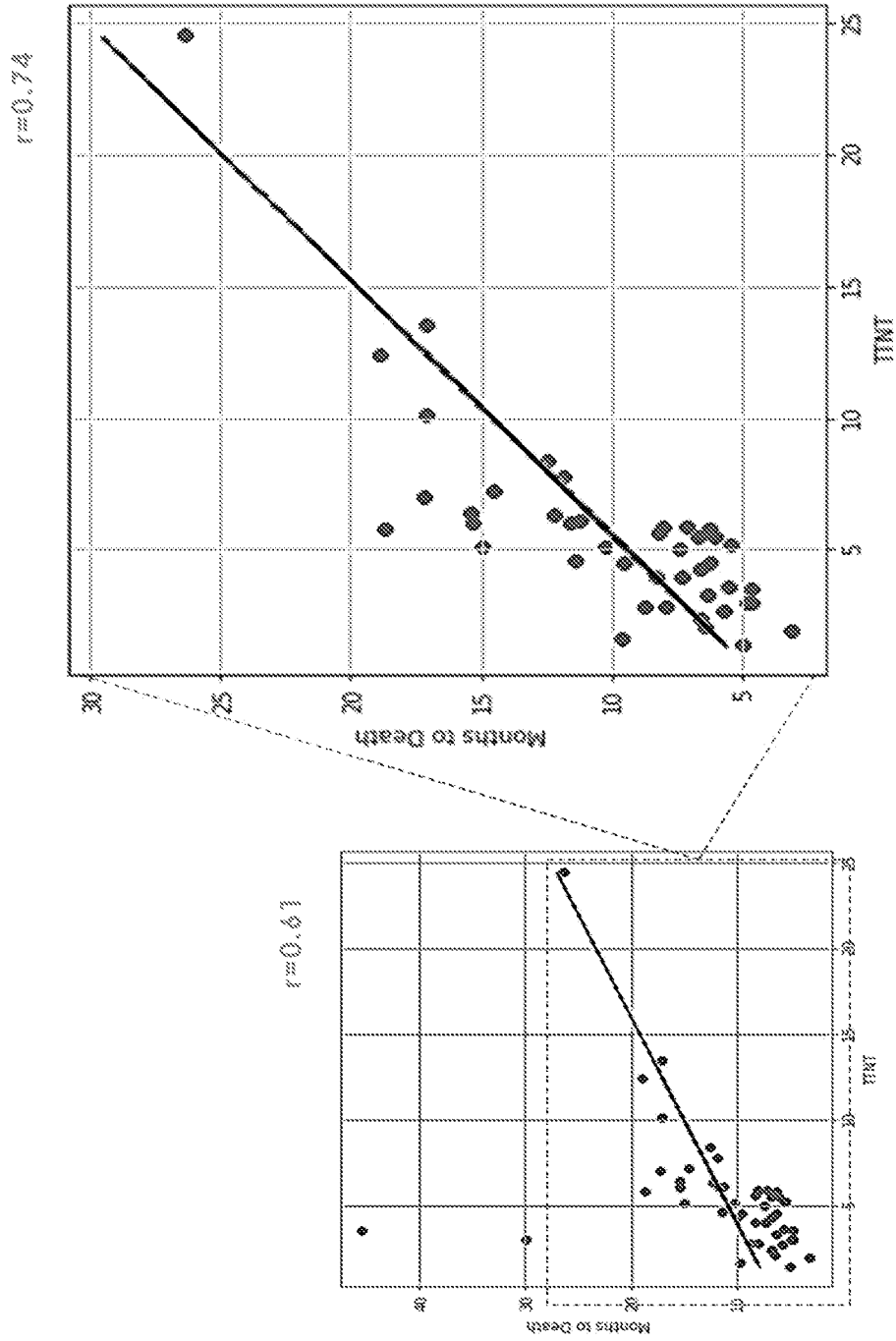


Fig. 6

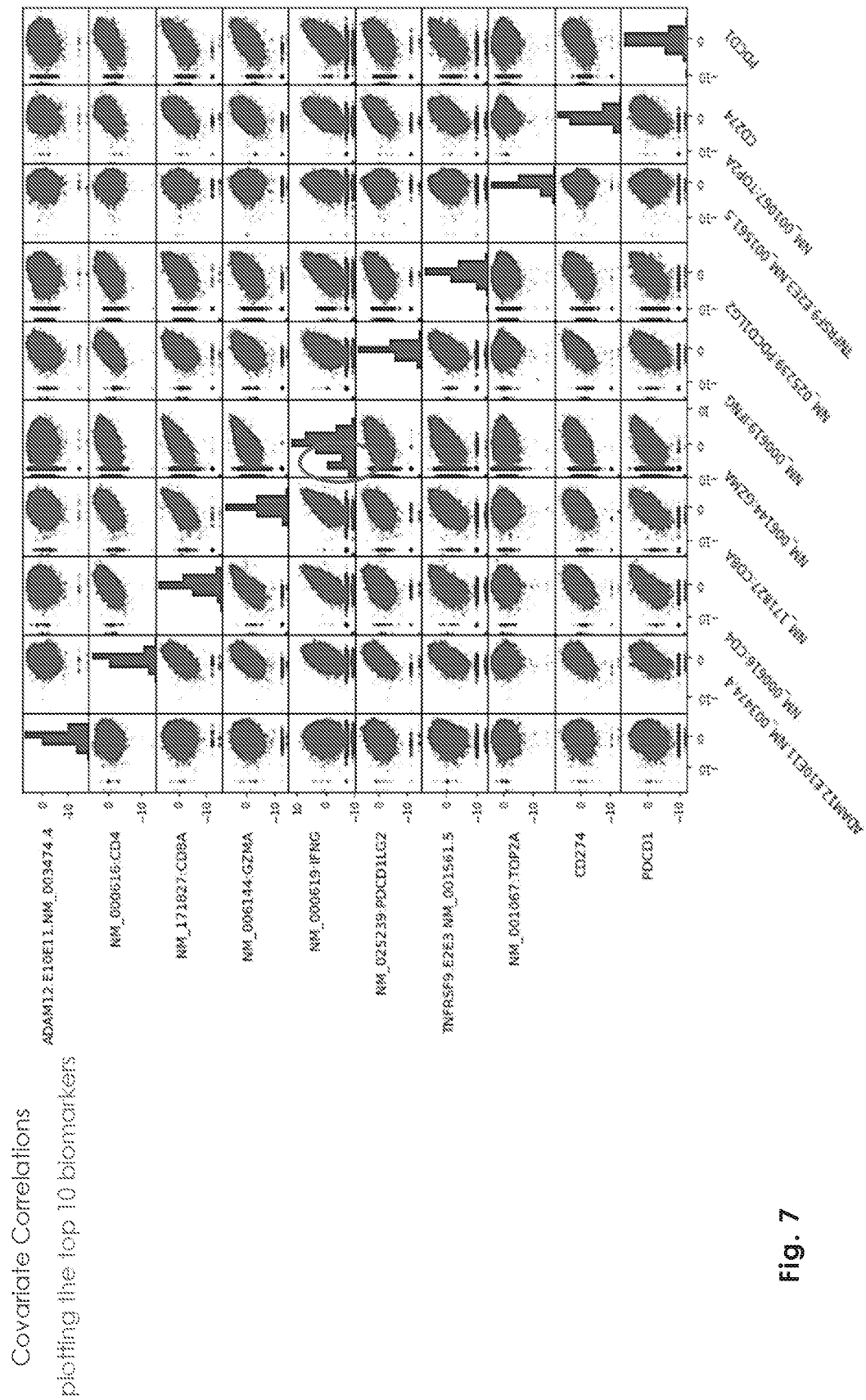


Fig. 7

Pembro and Chemo Survival by Strata: High/Medium/Low

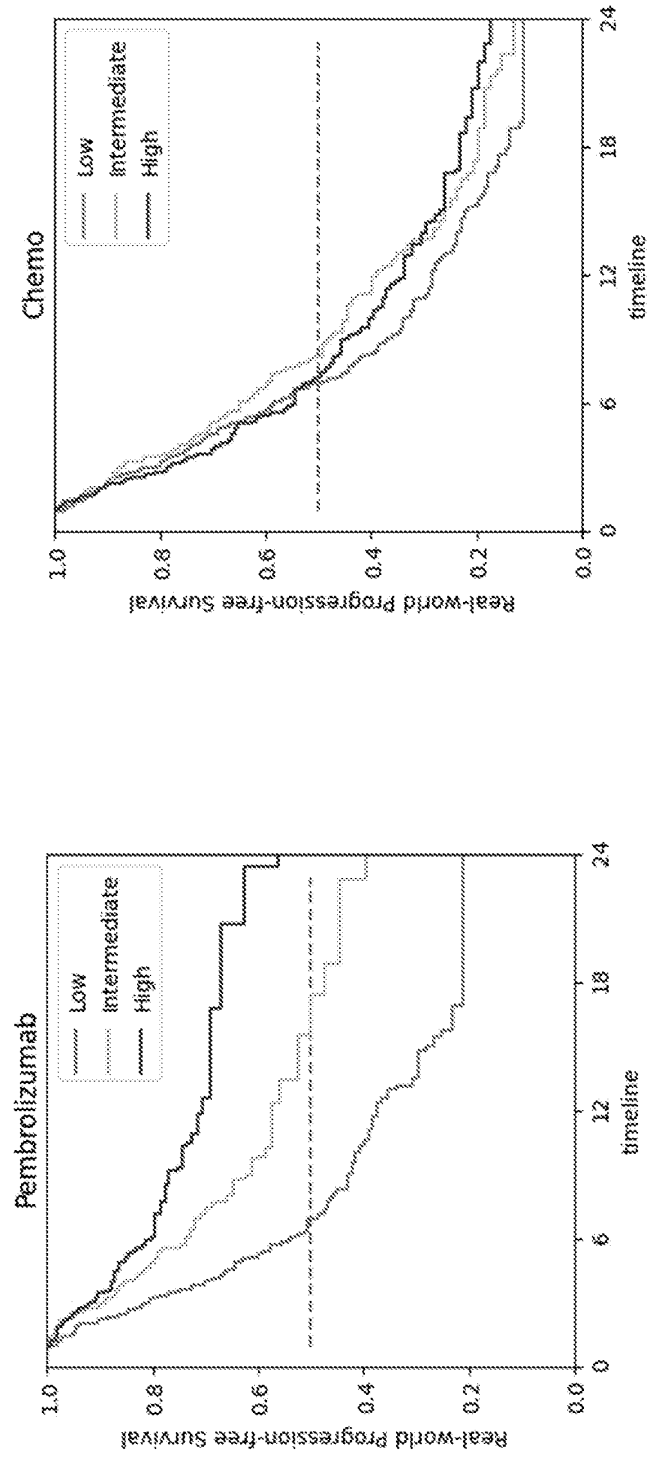
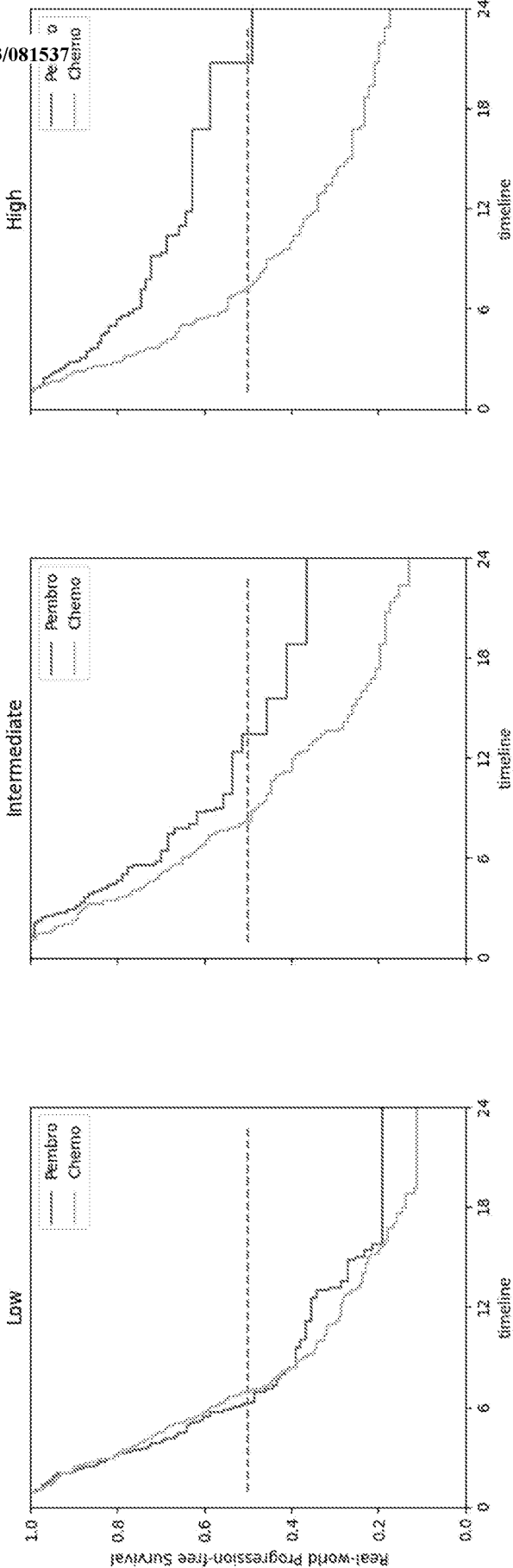


Fig. 8

Pembro vs. chemo for StratalO Low/Medium/High



	Low	Medium	High
Pembro median FPS	6.3	13.5	20.8
Chemo median FPS	7	8.2	7.3
p-value	0.69	0.13	2.4E-07

Fig. 9

Pembro NSCLC vs Other for IRS Groups

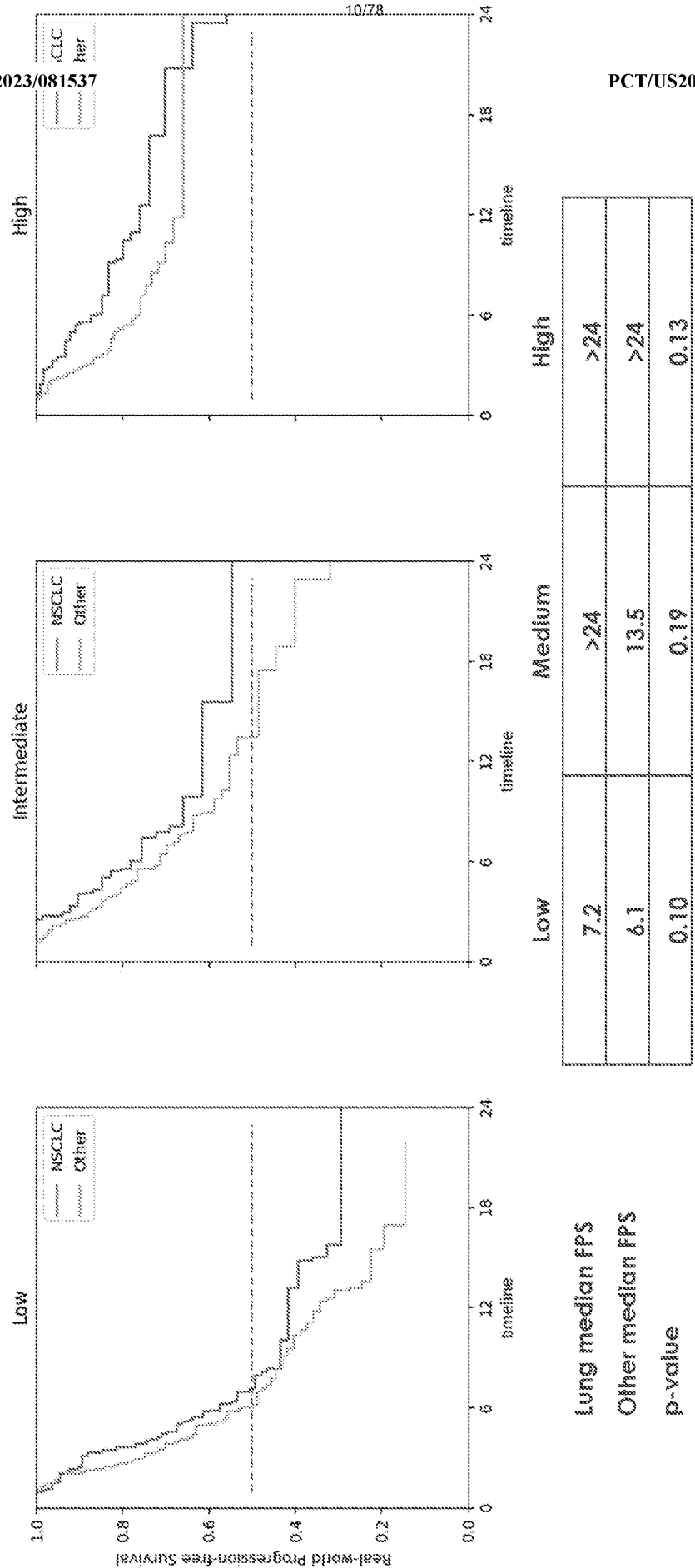


Fig. 10

IRG rates across Strata Trial cohort

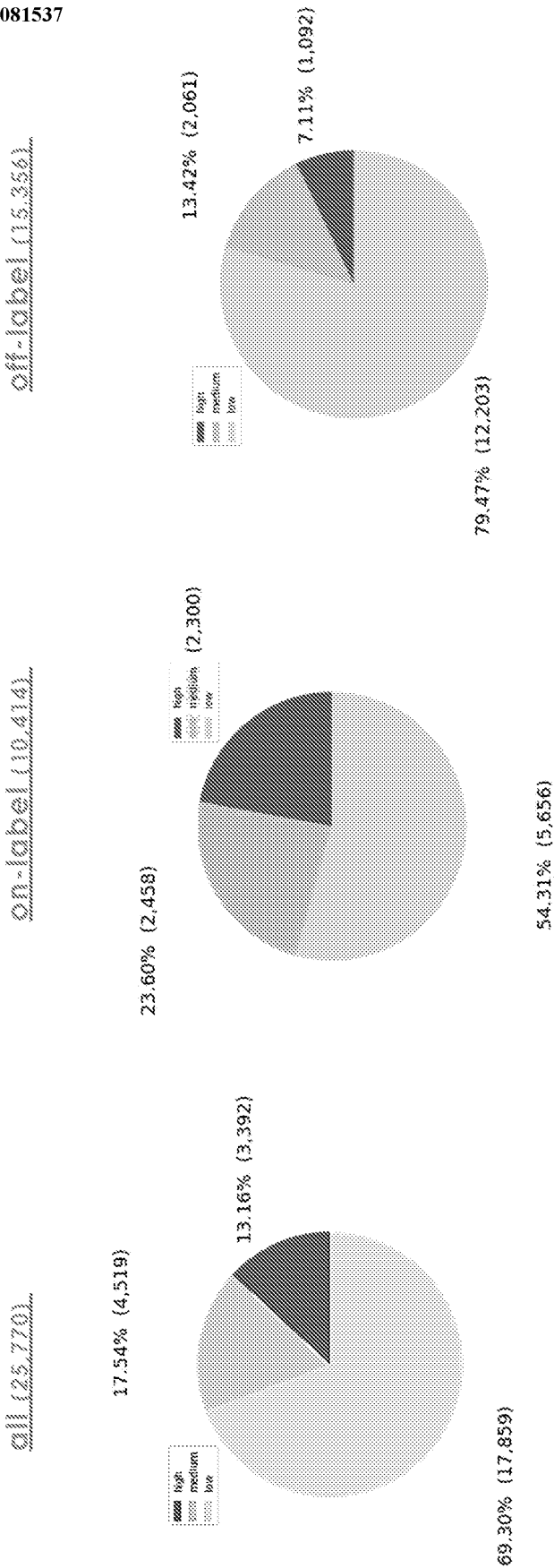


Fig. 11

IRG rates across Strata Trial cohort by Cancer Type

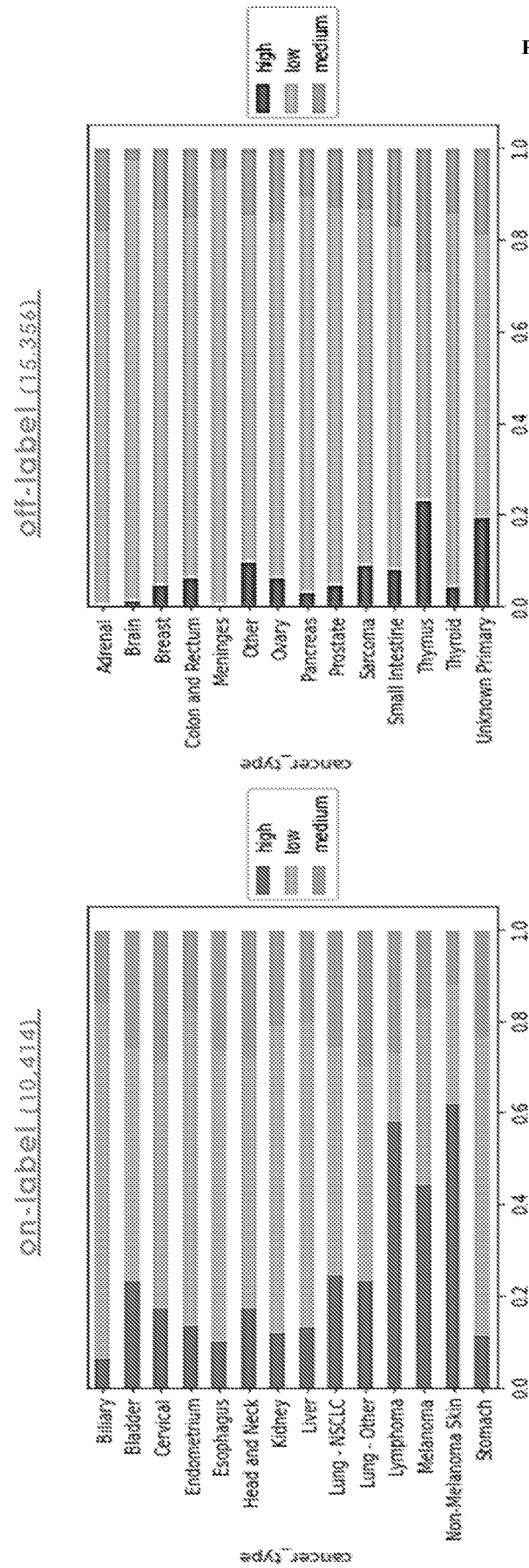


Fig. 12

Pembro mono vs. combo for IRS Groups

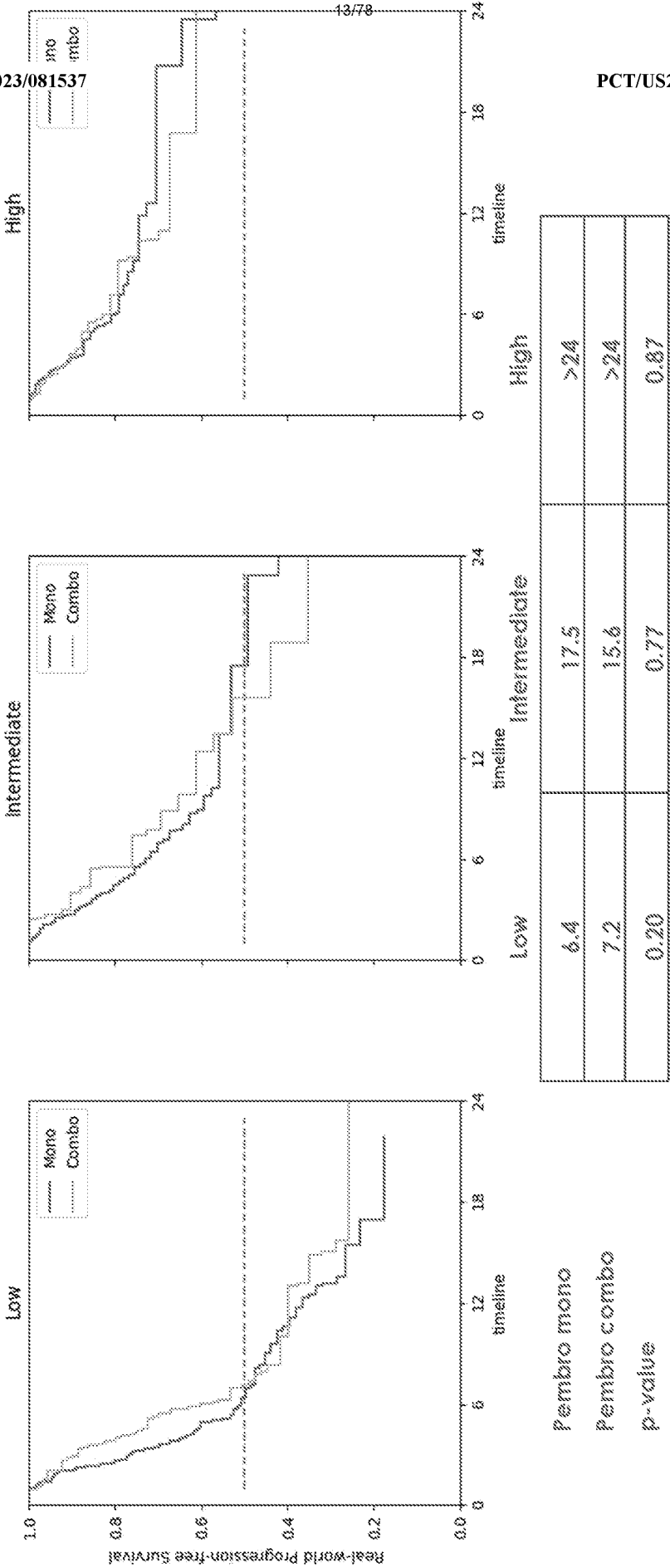


Fig. 13

TMB-H / TMB-L

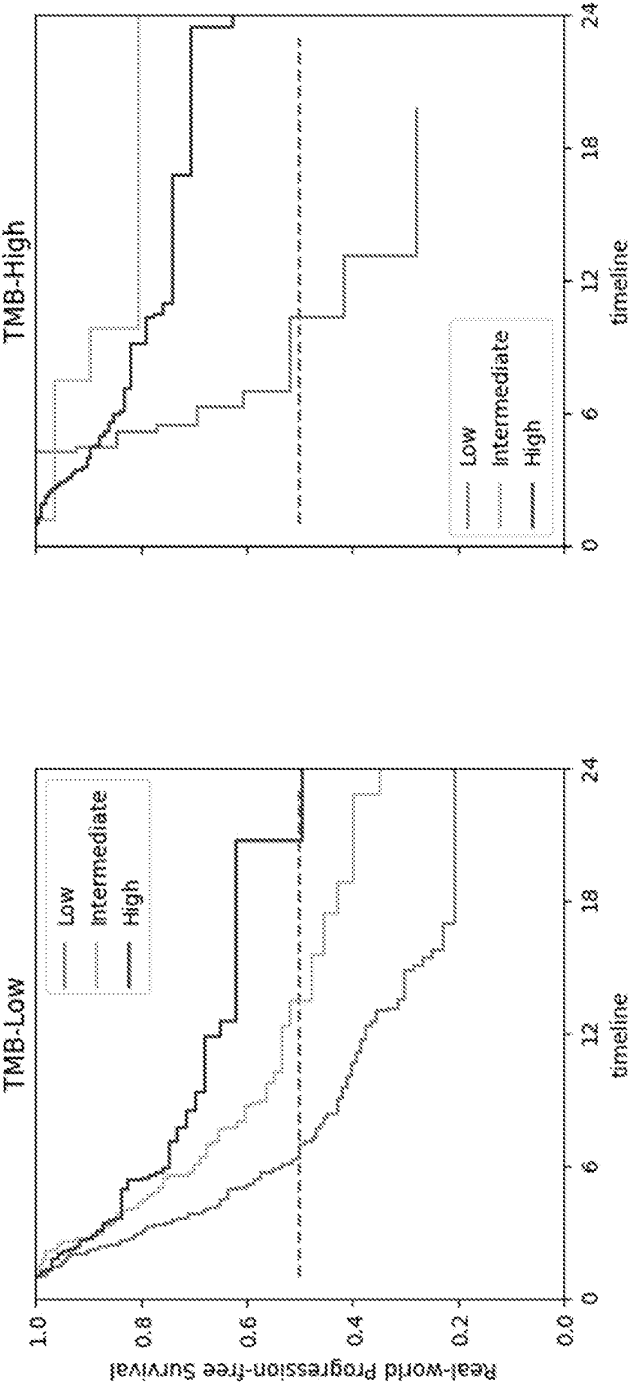


Fig. 14

Immunotherapy Response Groups vs. TMB-H/L

strata_lo_high_med_low	TMB-H	TMB-L
high	1736	1629
intermediate	478	4041
low	217	17828

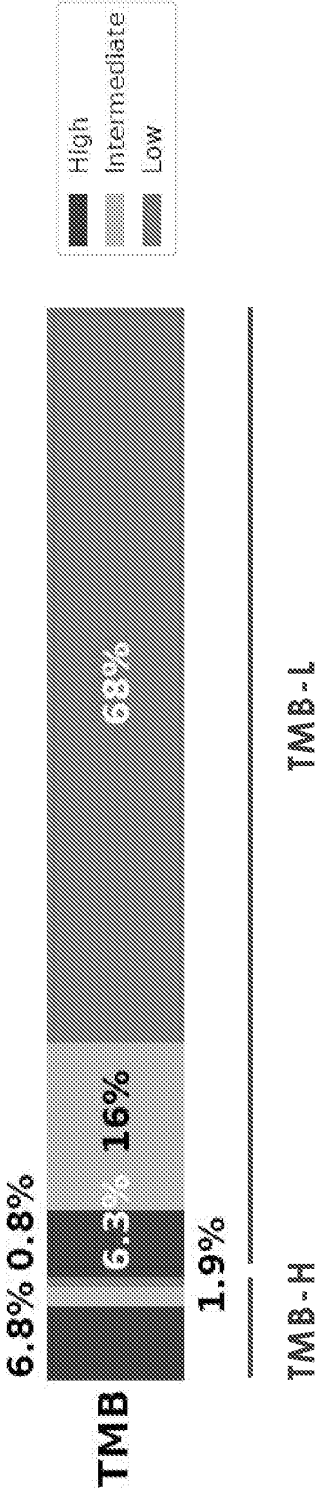


Fig. 15

WO 2023/081537

PCT/US2022/049332

Pembro by Tumor Content

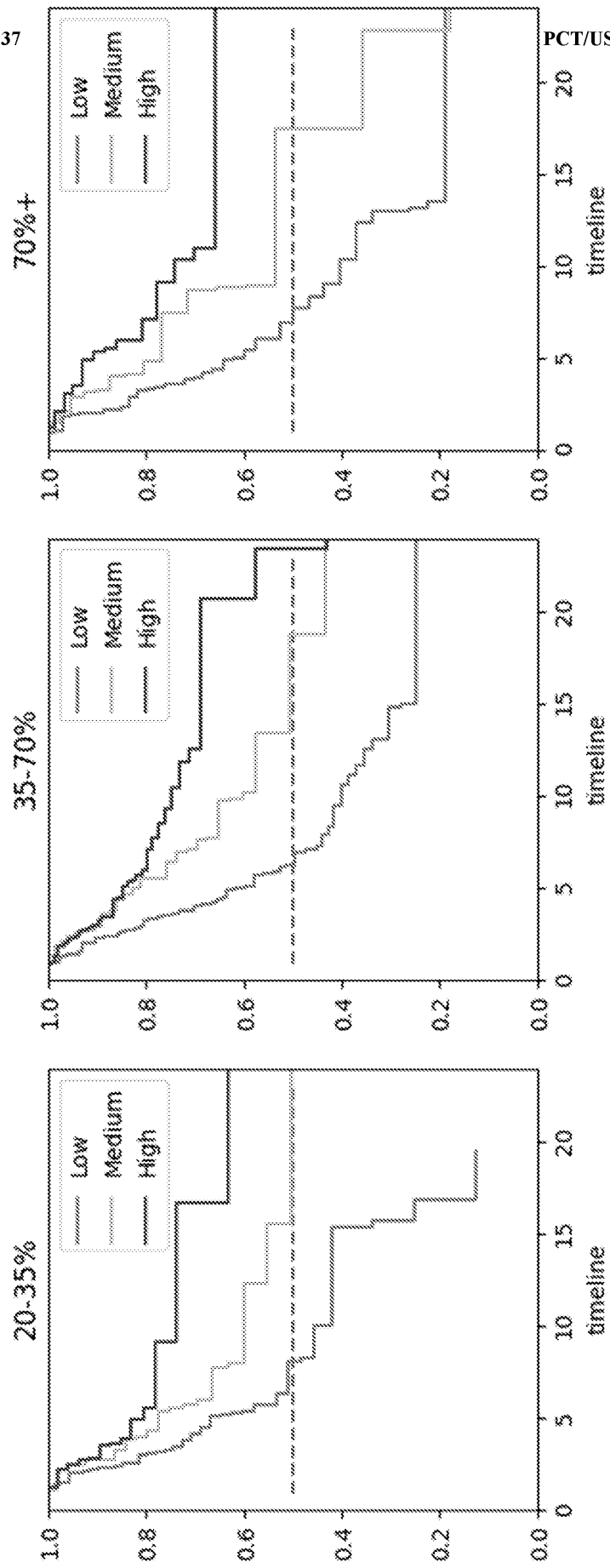


Fig. 16

WO 2023/081537

PCT/US2022/049332

Chemo by Tumor Content

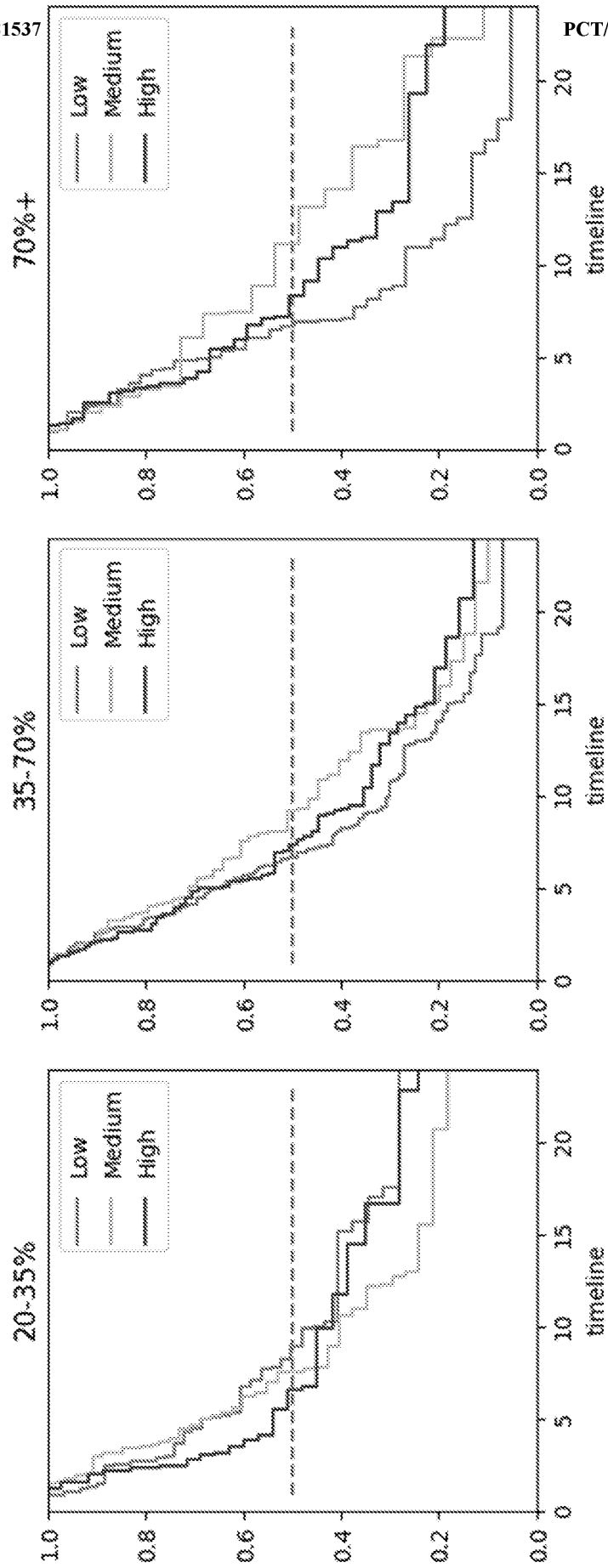


Fig. 17

2/3-Dataset Brute-Force Search

For each cut of the dataset a brute-force search was performed for 2 best covariates to add to the bare-bone model (PD-1, PD-L2, and TMB). The model with the lowest AIC was selected to derive train/test statistics for that cut.

covariates		(Row Count)	Median (AIC_partial)	Median (train_score)	Median (test_score)
[ADAM12.E10E11.NM_003474.4; NM_000619:IFNG; PD1C1; log2TMB; NM_025239:PD1C1LG2]		16	1862.41	-926.2	-1.71
[ADAM12.E10E11.NM_003474.4; NM_006144:GZMA; PD1C1; log2TMB; NM_025239:PD1C1LG2]		11	1856.17	-923.08	-1.72
[ADAM12.E10E11.NM_003474.4; NM_000616:CD4; PD1C1; log2TMB; NM_025239:PD1C1LG2]		10	1876.88	-933.44	-1.68
[ADAM12.E10E11.NM_003474.4; HAVCR2.E2E3.NM_032782.3; PD1C1; log2TMB; NM_025239:PD1C1LG2]		8	1845.61	-917.81	-1.74
[ADAM12.E10E11.NM_003474.4; VTCN1.E5E6.NM_024626.2; PD1C1; log2TMB; NM_025239:PD1C1LG2]		5	1853.75	-921.87	-1.73
Other		50			
Covariate		Count			
ADAM12.E10E11.NM_003474.4		60			
NM_000619:IFNG		27			
NM_000616:CD4		22			
VTCN1.E5E6.NM_024626.2		15			
NM_006144:GZMA		14			
HAVCR2.E2E3.NM_032782.3		12			
CD274		11			
NM_014143:CD274		10			
TCF7.E3E4.NM_001134851.2		7			
LAG3.E7E8.NM_002286.5		6			
NM_001067:TOP2A		5			
CTLA4.E1E2.NM_001037631.2		3			
TNFRSF4.E2E3.NM_003327.3		2			
TNFRSF9.E2E3.NM_001561.5		2			
AXLE13E14.NM_001699.4		1			
NM_171827:CD6A		1			
TIGIT.E2E3.NM_173799.3		1			
FOXP3.E6E7.NM_001114377.1		1			

- The overall "Brute-force" model shows up in 10% of the cuts
- ADAM12 shows up in 60% of the cuts
- IFNG and CD4 show up in ~25% of the cuts, but only once together
- Brute force search results from full dataset:
 - 5-factor: CD4 + IFNG + ADAM12 + + PD-1 + PD-L2 + TMB AIC = 2991.9
 - 4-factor: CD4 + ADAM12 + PD-1 + PD-L2 + TMB AIC = 2993.43
 - 3-factor: ADAM12 + PD-1 + PD-L2 + TMB AIC = 2995.80

Fig. 18

Start with 21 IO markers + TMB Exhaustive Search for Small Model Results
Test all combinations of 4 factors + TMB and report AICs

21 choose 4 "winner" (5985 combos)

ADAM12 + CD4 + PD-1 + PD-L2 + TMB

Partial AIC = 2993.43

model	lifelines.CoxPHFitter
duration col	'months_on_treatment'
event col	'likely_progressed'
baseline estimation	breslow
number of observations	708
number of events observed	260
partial log-likelihood	-1491.71
time fit was run	2021-08-11 03:31:13 UTC

19/78

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	z	p	-log2(p)
log2TMB	-0.29	0.75	0.05	-0.38	-0.20	0.69	0.82	-6.20	<0.005	30.68
ADAM12.E10E11.NM_003474.4	0.07	1.08	0.03	0.01	0.14	1.01	1.15	2.17	0.03	5.06
NM_000616.CD4	0.14	1.15	0.07	0.01	0.27	1.01	1.31	2.08	0.04	4.74
PDCD1	-0.15	0.86	0.04	-0.23	-0.06	0.79	0.94	-3.48	<0.005	10.96
NM_025239.PDCD1LG2	-0.14	0.87	0.04	-0.23	-0.06	0.79	0.95	-3.22	<0.005	9.58

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Concordance	0.64
Partial AIC	2993.43
log-likelihood ratio test	66.07 on 5 df
-log2(p) of ll-ratio test	40.44

Fig. 19

Brute-force "Best" model (no PD-L1)

Trained on the full dataset

model Lifelines CoxPHFilter
duration col 'months_on_treatment'
event col 'weekly_progressed'
baseline estimation breslow
number of observations 708
number of events observed 280
partial log-likelihood -1491.71
time fit was run 2021-06-18 13:20:01 UTC

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	z	p	-log2(p)
log2TMB	-0.29	0.75	0.05	-0.36	-0.20	0.69	0.82	-6.20	<0.005	30.68
NM_025239:PDCD1LG2	-0.14	0.87	0.04	-0.23	-0.05	0.79	0.95	-3.22	<0.005	9.59
PDCD1	-0.15	0.86	0.04	-0.23	-0.05	0.79	0.94	-3.49	<0.005	10.96
ADAM12:NM_083474.4	0.07	1.08	0.03	0.01	0.14	1.01	1.15	2.17	0.03	5.06
NM_000616:CD4	0.14	1.15	0.07	0.01	0.27	1.01	1.31	2.08	0.04	4.74

Concordance 0.64
Partial AIC 2993.43
log-likelihood ratio test 56.07 on 5 df
-log2(p) of ll-ratio test 40.44

lifelines_cross_validate(df_fit, bms, cph)
running k-fold cross-validation: [|||||] 99 / 99 (100%) loops completed in 21 seconds
Mean concordance index = 0.6313814725797583
Std concordance index = 0.034592754879585323

Fig. 21

Bare-bones model with just PD-1, PD-L2 and TMB

Trained on the full dataset

model lifelines.CoxPHFitter
duration col 'months_on_treatment'
event col 'likely_progressed'
baseline estimation breslow
number of observations 708
number of events observed 260
partial log-likelihood -1496.12
time fit was run 2024-08-18 13:21:33 UTC

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	z	p	-log2(p)
PD1	-0.11	0.90	0.04	-0.19	-0.03	0.83	0.97	-2.77	0.01	7.49
MM_025239:PD1LG2	-0.06	0.92	0.04	-0.15	0.00	0.85	1.00	-1.92	0.05	4.20
log2TMB	-0.30	0.74	0.05	-0.39	-0.21	0.68	0.81	-6.67	<0.005	35.19

Concordance 0.63
Partial AIC 2598.23
log-likelihood ratio test 57.2% on 3 df
-log2(p) of lratio test 32.69

lifelines_cross_validate(df_fit, bms, cph)

running k-fold cross-validation: [|||||] 99 / 99 (100%) loops completed in 21 seconds
Mean concordance index = 0.6277421178514535
Std concordance index = 0.02643619845360604

Fig. 23

Large-ish model from backward selection
Trained on the full dataset

model lifelines.CoxPHFitter
duration col 'months_on_treatment'
event col 'likely_progressed'
baseline estimation breslow
number of observations 708
number of events observed 289
partial log-likelihood -1486.87
time fit was run 2021-08-18 13:21:54 UTC

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	z	p	-log2(p)
NM_025239:PDCT11.G2	-0.14	0.87	0.05	-0.24	-0.05	0.79	0.95	-3.00	<0.005	8.55
PDCT1	-0.18	0.83	0.05	-0.28	-0.09	0.75	0.92	-3.99	<0.005	12.15
log2TMB	-0.20	0.74	0.05	-0.39	-0.21	0.68	0.81	-6.43	<0.005	32.85
CD274	-0.03	0.92	0.04	-0.17	0.00	0.85	1.00	-1.93	0.05	4.21
NM_000616:CD4	0.03	1.02	0.04	0.01	0.15	1.01	1.16	2.19	0.03	5.14
ADAM12:ETHE11.NM_003474.4	0.15	1.16	0.07	0.02	0.29	1.02	1.33	2.20	0.03	5.19
NM_000616:IFNG	0.06	1.06	0.03	0.01	0.11	1.01	1.11	2.34	0.02	5.70
VTCN1:ESR.NM_024626.2	-0.02	0.98	0.01	-0.05	0.00	0.95	1.00	-1.61	0.11	3.23

Concordance 0.65
Partial AIC 2989.74
log-likelihood ratio test 75.76 on 8 df
-log2(p) of likelihood ratio test 41.39

lifelines_cross_validate(df_fit, bms, cph)
running k-fold cross-validation:  99 / 99 (100%) loops completed in 24 seconds
Mean concordance index = 0.6345307180390252
Std concordance index = 0.025607437870135122

Fig. 24

Coefficients from iterations of 2/3 cross-validation
“Brute-force” model without and with PD-L1, Yellow lines are final model coefficients from the model w/o PD-L1

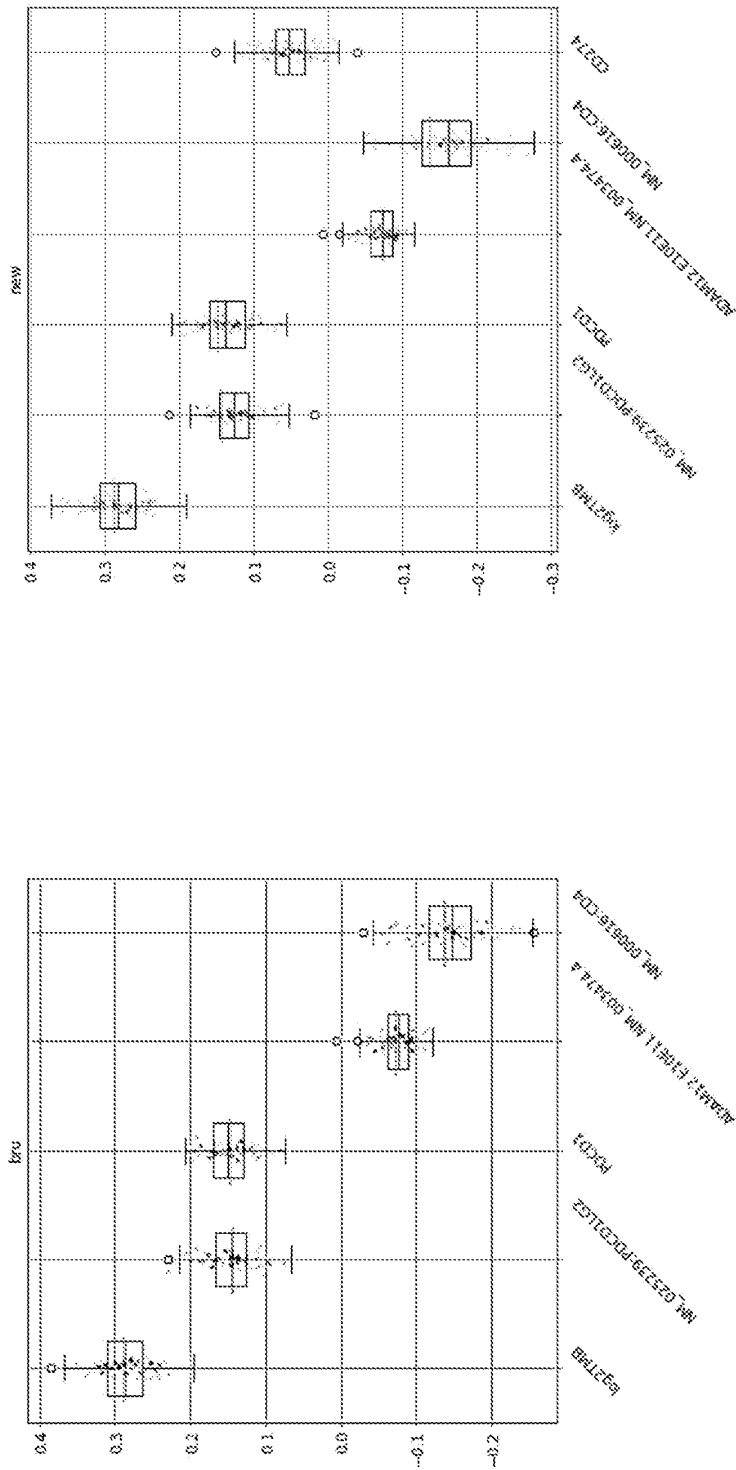


Fig. 25

Coefficients from iterations of 2/3 cross-validation
Small ("Bare-bones") and Large ("Backward Selection") models
Yellow lines are brute-force ("bru") model coefficients from the model w/o PD-L1

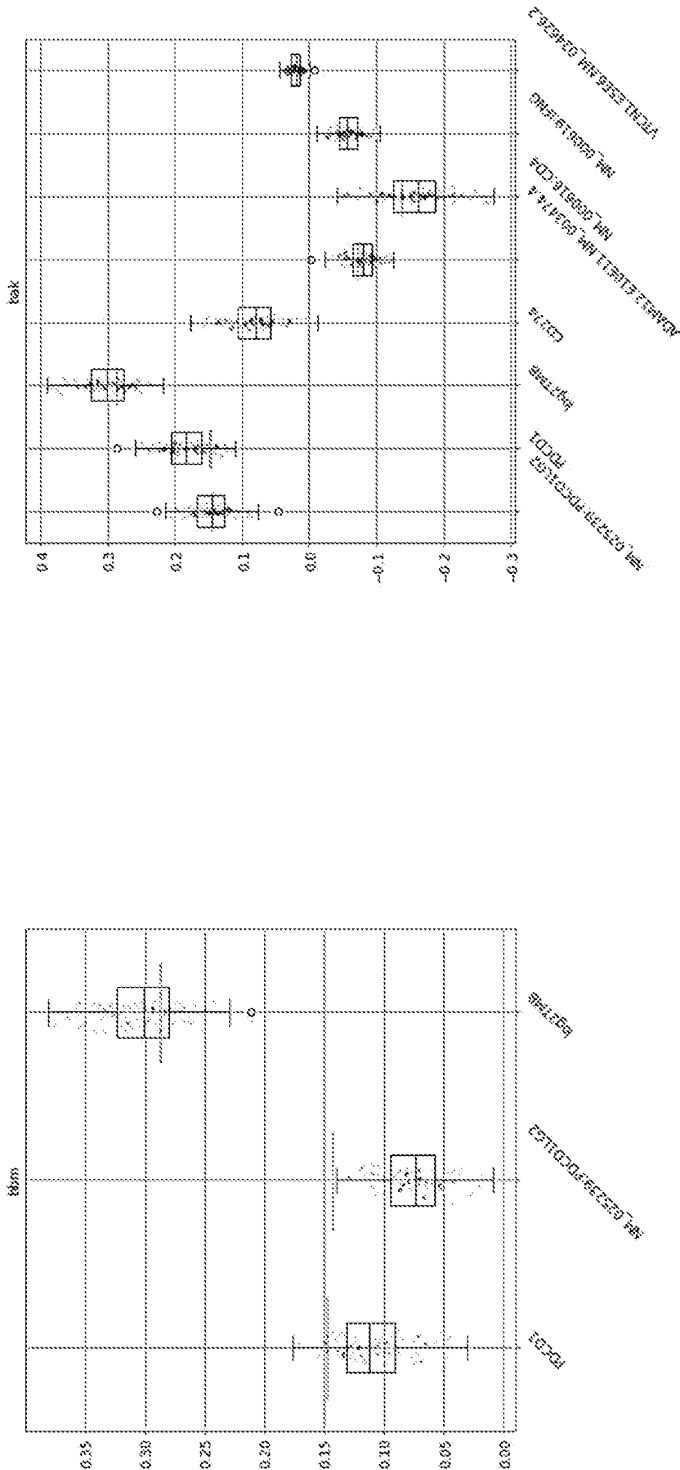


Fig. 26

Model Cross-Validation – Apply to Specimen Collection Date >= Pembro Start Date

Purpose: to test the robustness of median survival within groups and pembro vs chemo comparison

- 1. Obtain set of 84 samples taken out of previous fit set whose specimen was collected after start of pembro
 - 2. Calculate IRS scores
 - 3. Plot and summarize survival
1. Results: Group 1 and Group 4 have similarly high survival times – still an overall effect for StrataIO high vs low

covariate	coef	hr	hrci_lower	hrci_upper	\	
0 Group 1 pembro-v-chemo	-0.645963	0.524158	0.282013	0.974215		
0 Group 2 pembro-v-chemo	-0.226177	0.797577	0.476855	1.334008		
0 Group 3 pembro-v-chemo	-0.832437	0.434988	0.187024	1.011711		
0 Group 4 pembro-v-chemo	0.153778	1.166233	0.470825	2.888755		
p pembro_n pembro_median_tint chemo_n chemo_median_tnt						
0 0.041095	23	15.6	16	6.9		
0 0.388777	28	7.9	21	7.9		
0 0.053245	20	21.9	12	11.6		
0 0.739672	13	15.9	7	12.8		

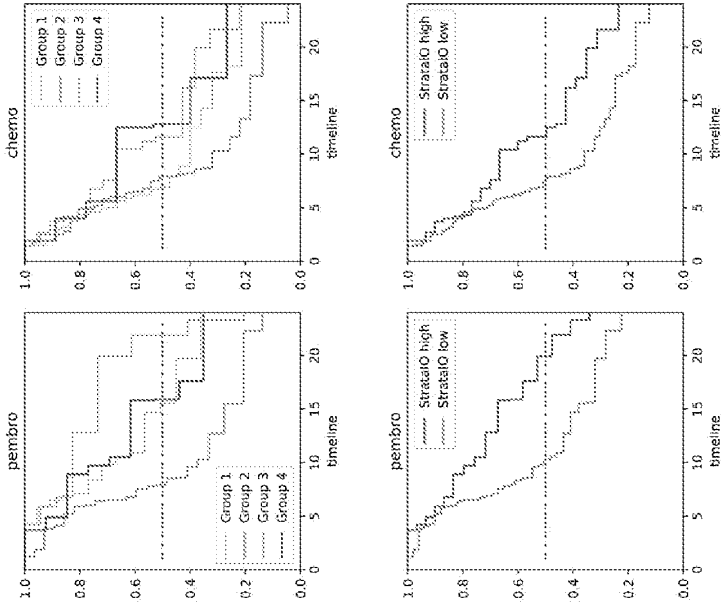


Fig. 27

TMB + PD-L2 + PD-1 + ADAM12 + CD4 + PD-L1
Trained on the full dataset

Formula:
$$3.95 * \exp($$
$$'log2TMB' * 0.280 +$$
$$'PDCD1LG2' * 0.122 +$$
$$'PDCD1' * 0.134 +$$
$$'ADAM12' * -0.070 +$$
$$'CD4' * -0.154 +$$
$$'CD274' * 0.052$$
$$)$$

model: Rlmres.CoxPH.fitter
duration col: 'months_on_treatment'
event col: 'likely_progressed'
baseline estimation: Breslow
number of observations: 788
number of events observed: 268
partial log-likelihood: -1490.90
time fit was run: 2021-08-18 13:20:22 UTC

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	z	p	-log2(p)
NM_025239:PDCD1LG2	log2TMB	-0.28	0.76	0.05	-0.37	-0.19	0.69	0.33	-6.95	<0.005
		-0.12	0.88	0.05	-0.22	-0.03	0.81	0.97	-2.54	0.01
	PDCD1	-0.13	0.87	0.04	-0.22	-0.05	0.80	0.95	-3.05	<0.005
ADAM12:EBIE11.NM_003474.4		0.07	1.07	0.03	0.00	0.14	1.00	1.15	2.85	0.04
		0.15	1.17	0.07	0.02	0.29	1.32	1.23	2.25	0.02
	NM_008616:CD4		0.95	0.04	-0.13	0.03	0.88	1.03	-1.30	0.19
CD274	-0.05								0.19	2.38

Concordance: 0.64
Partial AIC: 2993.88
log-likelihood ratio test: 67.70 on 6 df
-log2(p) of ll-ratio test: 39.59

lifelines_cross_validate(df_fit, bms, cph)
running k-fold cross-validation: [|||||] 99 / 99 (100%) loops completed in 22 seconds
Mean concordance index = 0.6328746556256706
Std concordance index = 0.02721801482092686

Fig. 28

TMB + PD-L2 + PD-1

Trained on the full dataset

model lifelines.CoxPHFitter
duration col 'months_on_treatment'
event col 'likely_progressed'
baseline estimation breslow
number of observations 708
number of events observed 250
partial log likelihood -1486.12
time fit was run 2021-08-18 13:21:33 UTC

Formula:

$$3.97 * \exp('log2TMB' * 0.301 + 'PDCD1LG2' * 0.078 + 'PDCD1' * 0.110)$$

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	z	p	-log2(p)
PDCD1	-0.11	0.90	0.04	-0.19	-0.03	0.83	0.97	-2.77	0.01	7.49
NM_025238:PDCD1LG2	-0.06	0.92	0.04	-0.16	0.00	0.85	1.00	-1.92	0.05	4.20
log2TMB	-0.30	0.74	0.05	-0.39	-0.21	0.68	0.91	-6.67	<0.005	35.19

Concordance 0.63
Partial AIC 2998.23
log-likelihood ratio test 57.28 on 3 df
-log2(p) of ll-ratio test 38.69

lifelines_cross_validate(df_fit, bms, cph)
running k-fold cross-validation:  99 / 99 (100%) loops completed in 21 seconds
Mean concordance index = 0.6277421178614535
Std concordance index = 0.026436198453606004

Fig. 29

Trained on the full dataset

TMB + PD-L2 + PD-L1 + ADAM12

Formula:

$$3.90 * \exp(\text{'log2TMB' * 0.307 + 'PDCD1LG2' * 0.106 + 'PDCD1' * 0.115 + 'ADAM12' * -0.070 + })$$

model

lifelines.CoxPHFilter

duration col 'months_on_treatment'

event col 'likely_progressed'

baseline estimation breslow

number of observations 708

number of events observed 260

partial log-likelihood -1493.90

time fit was run 2021-10-12 15:21:42 UTC

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	z	p	-log2(p)
NM_025239:PDCD1LG2	-0.11	0.90	0.04	-0.19	-0.03	0.83	0.98	-2.56	0.01	6.60
PDCD1	-0.11	0.89	0.04	-0.19	-0.04	0.82	0.96	-2.90	<0.005	8.07
log2TMB	-0.31	0.74	0.05	-0.40	-0.22	0.67	0.80	-6.78	<0.005	36.30
ADAM12.E10E11.NM_003474.4	0.07	1.07	0.03	0.00	0.14	1.00	1.15	2.06	0.04	4.66

Concordance 0.63

Partial AIC 2995.80

log-likelihood ratio test 61.70 on 4 df

-log2(p) of ll-ratio test 39.51

Fig. 30

Trained on the full dataset

TMB + PD-L2 + PD-L1 + PD-L1

Formula:
$$3.91 * \exp(\log2TMB' * 0.296 + \text{'PDCD1LG2'} * 0.056 + \text{'PDCD1'} * 0.097 + \text{'PD-L1'} * 0.043)$$

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	z	p	-log2(p)
NM_025239:PDCD1LG2	-0.06	0.95	0.06	-0.15	0.03	0.86	1.03	-1.24	0.21	2.22
PDCD1	-0.10	0.91	0.04	-0.18	-0.02	0.84	0.98	-2.33	0.02	5.66
log2TMB	-0.30	0.74	0.05	-0.38	-0.21	0.68	0.81	-6.58	<0.005	34.27
CD274	-0.04	0.96	0.04	-0.12	0.03	0.89	1.03	-1.11	0.27	1.90

Concordance 0.63
Partial AIC 2999.05
log-likelihood ratio test 58.45 on 4 df
-log2(p) of fit-ratio test 37.24

Fig. 31

Trained on the full dataset

TMB + PD-L2 + PD-1 + CD4

Formula:
$$4.10 * \exp(\log2TMB' * 0.281 + PDCD1LG2' * 0.112 + PDCD1' * 0.139 + CD4' * -0.128)$$

model	lifelines.CoxPHFitter
duration col	'months_on_treatment'
event col	'likely_progressed'
baseline estimation	breslow
number of observations	708
number of events observed	280
partial log-likelihood	-1494.19
time fit was run	2021-10-12 16:04:10 UTC

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	z	p	-log2(p)
NM_025239:PDCD1LG2	-0.11	0.89	0.04	-0.20	-0.03	0.82	0.97	-2.55	0.01	6.55
PDCD1	-0.14	0.87	0.04	-0.22	-0.06	0.80	0.95	-3.30	<0.005	10.01
log2TMB	-0.28	0.76	0.05	-0.37	-0.19	0.69	0.83	-6.08	<0.005	29.63
NM_008616:CD4	0.13	1.14	0.07	-0.00	0.26	1.00	1.29	1.96	0.05	4.31

Concordance	0.64
Partial AIC	2996.37
log-likelihood ratio test	61.12 on 4 df
-log2(p) of ll-ratio test	39.11

Fig. 32

Formula:

3.90 * exp(
'log2TMB' * 0.309
'PDCD1LG2' * 0.005 +
'PDCD1' * 0.104 +
'VTCN1' * 0.021
)

TMB + PD-L2 + PD-1 + VTCN1

Trained on the full dataset

model	lifelines.CoxPHFitter
duration col	'months_on_treatment'
event col	'likely_progressed'
baseline estimation	breslow
number of observations	708
number of events observed	260
partial log-likelihood	-1494.84
time fit was run	2021-10-12 16:04:11 UTC

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	z	p	-log2(p)
NM_025239:PDCD1LG2	-0.09	0.92	0.04	-0.17	-0.01	0.85	0.99	-2.13	0.03	4.93
PDCD1	-0.10	0.90	0.04	-0.18	-0.03	0.83	0.97	-2.62	0.01	8.84
log2TMB	-0.31	0.73	0.05	-0.40	-0.22	0.67	0.80	-6.82	<0.005	36.63
VTCN1.E5E6.NM_024626.2	-0.02	0.98	0.01	-0.05	0.00	0.95	1.00	-1.61	0.11	3.22

Concordance	0.53
Partial AIC	2997.69
log-likelihood ratio test	59.81 on 4 df
-log2(p) of ll-ratio test	38.20

Fig. 33

WO 2023/081537

PCT/US2022/049332

Formula:

$$3.95 * \exp($$

$$'log2TMB' * 0.295$$

$$'PDCD1LG2' * 0.15) +$$

$$'PDCD1' * 0.142 +$$

$$'VTCN1' * 0.020 +$$

$$'ADAM12' * -.0070 +$$

$$'CD4' * -.0139$$

$$)$$

TMB + PD-L2 + PD-1+ CD4 + ADAM12 + VTCN1

Trained on the full dataset

model	Meines.CoxPHFilter
duration col	'months_on_treatment'
event col	'likely_progressed'
baseline estimation	breslow
number of observations	708
number of events observed	260
partial log-likelihood	-1490.57
time fit was run	2021-10-12 16:04:11 UTC

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	z	p	-log2(p)
log2TMB	-0.30	0.74	0.05	-0.39	-0.20	0.68	0.82	-6.33	<0.005	31.93
NM_025239.PDCD1LG2	-0.15	0.86	0.04	-0.24	-0.06	0.79	0.94	-3.37	<0.005	16.37
PDCD1	-0.14	0.87	0.04	-0.23	-0.06	0.80	0.94	-3.35	<0.005	16.29
ADAM12.E10E11.NM_003474.4	0.07	1.07	0.03	0.00	0.14	1.00	1.15	2.09	0.04	4.76
NM_000616.CD4	0.14	1.15	0.07	0.01	0.27	1.01	1.31	2.09	0.04	4.77
VTCN1.E3E6.NM_024626.2	-0.02	0.98	0.01	-0.05	0.01	0.96	1.01	-1.53	0.13	2.98

Concordance	0.64
Partial AIC	2933.14
log-likelihood ratio test	69.35 on 6 df
-log2(p) of ll-ratio test	40.03

Fig. 34

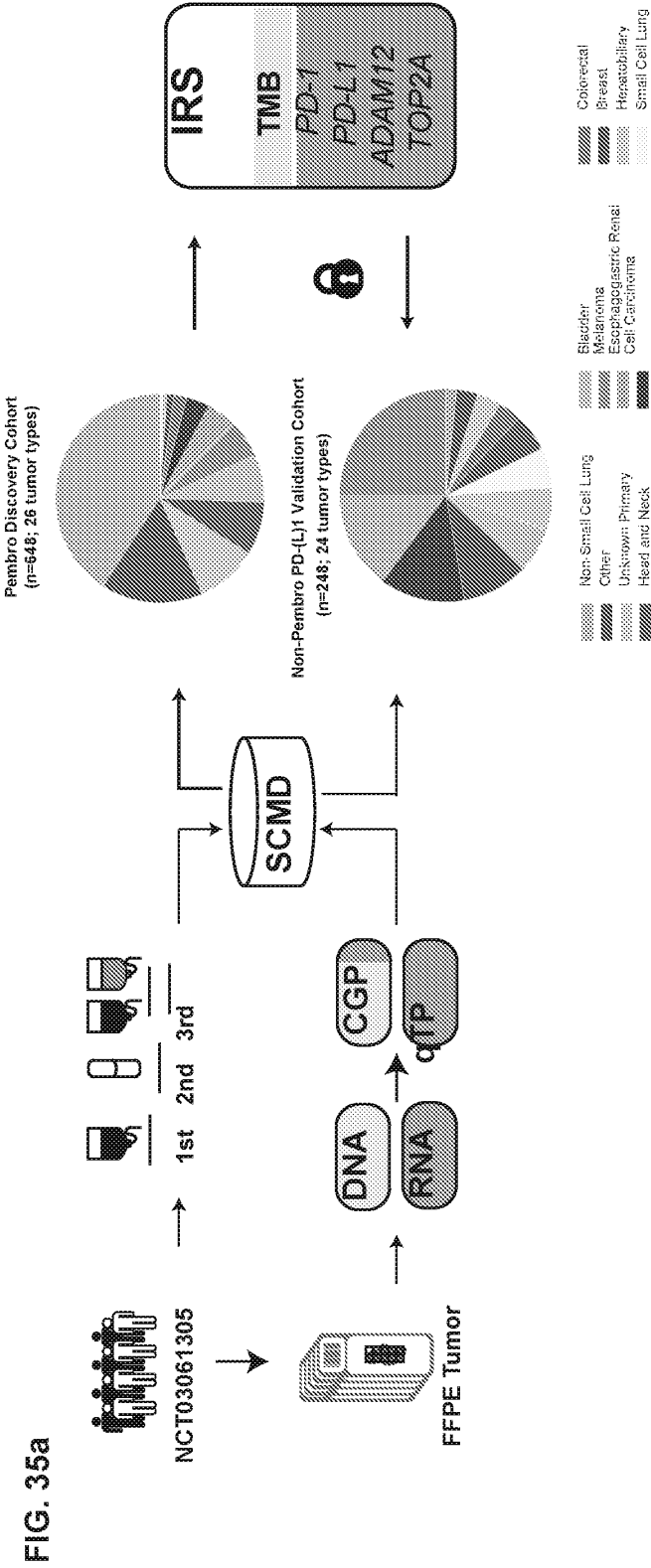


FIG. 35a

FIG. 35b

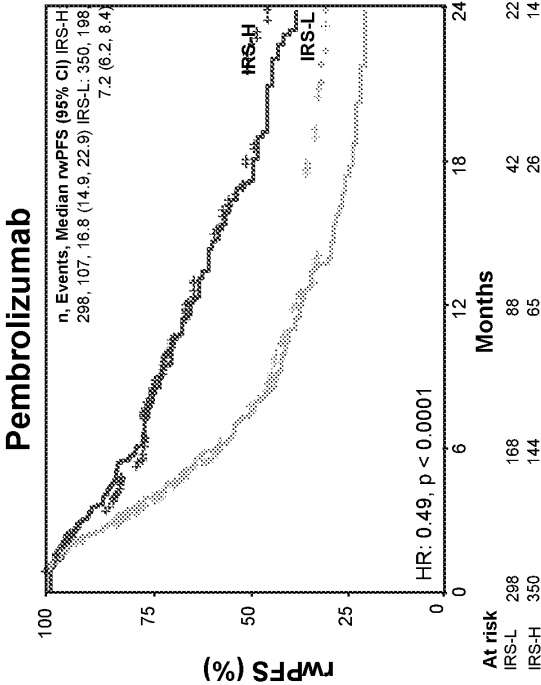
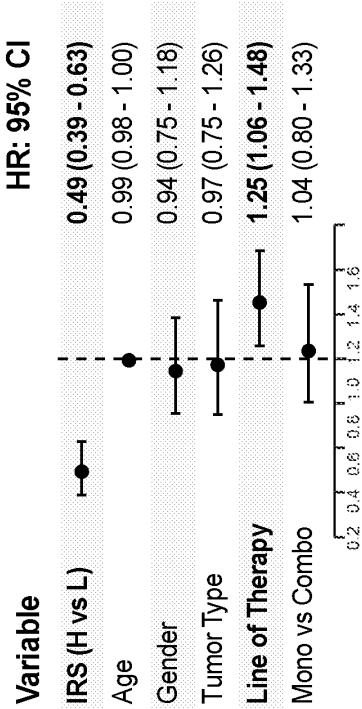
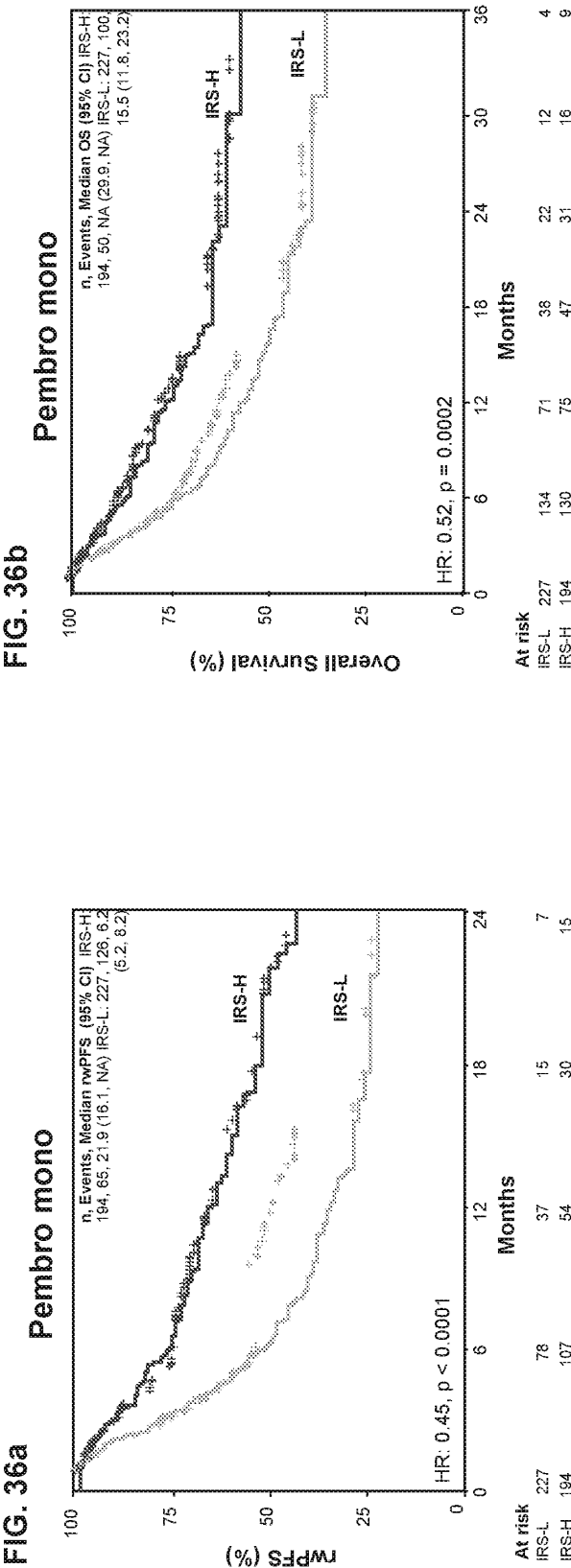


FIG. 35c



FIGS. 35b-c



FIGS. 36a-b

FIG. 36c

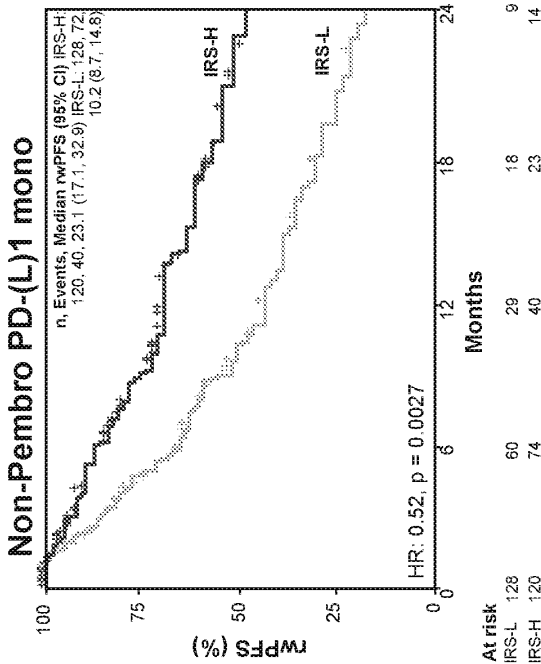
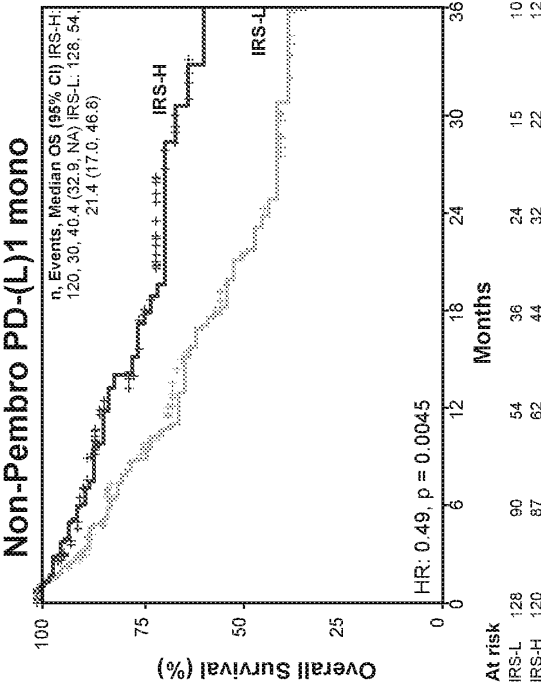


FIG. 36d



FIGS. 36c-d

FIG. 37a

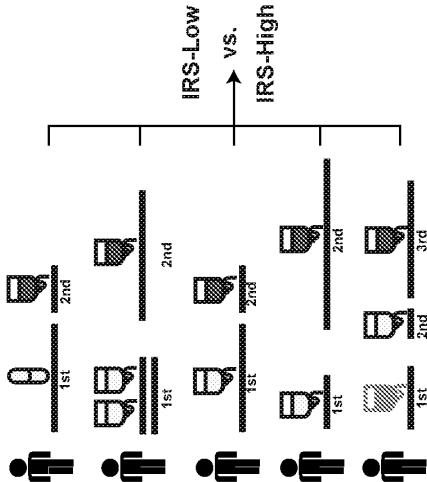


FIG. 37b

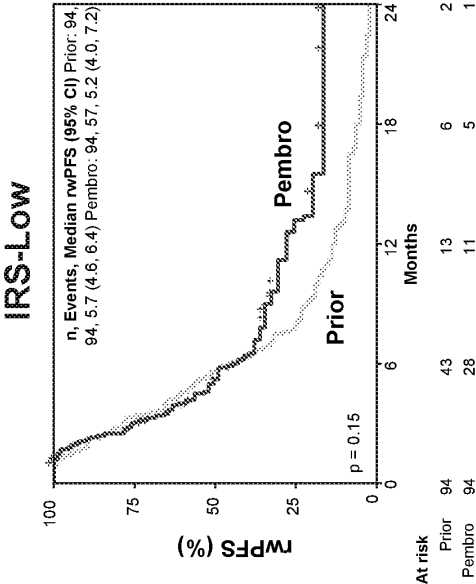
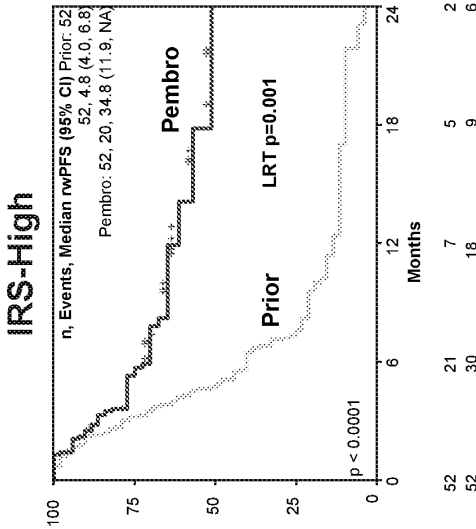


FIG. 37c



FIGS. 37a-c

FIG. 38a

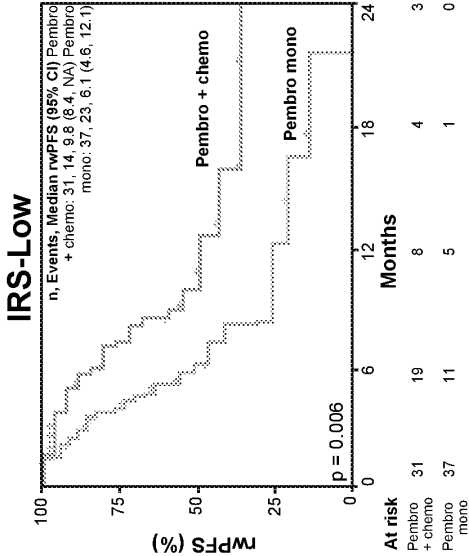


FIG. 38b

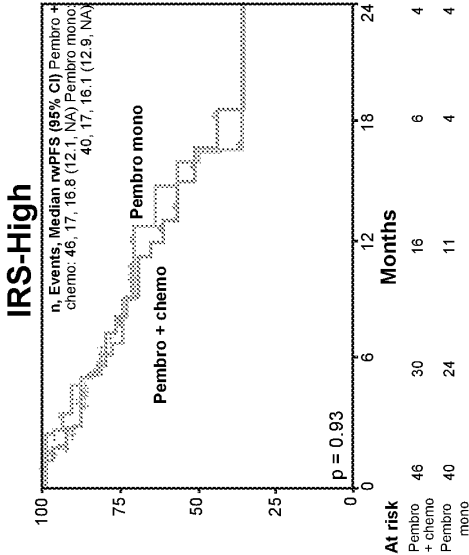
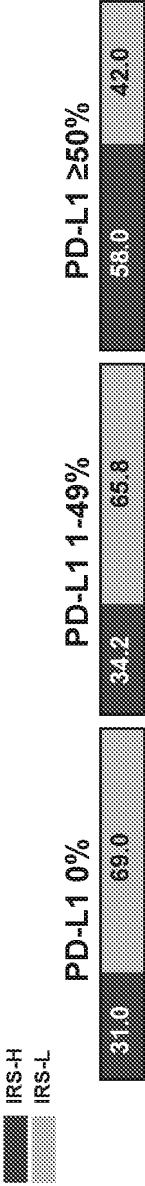
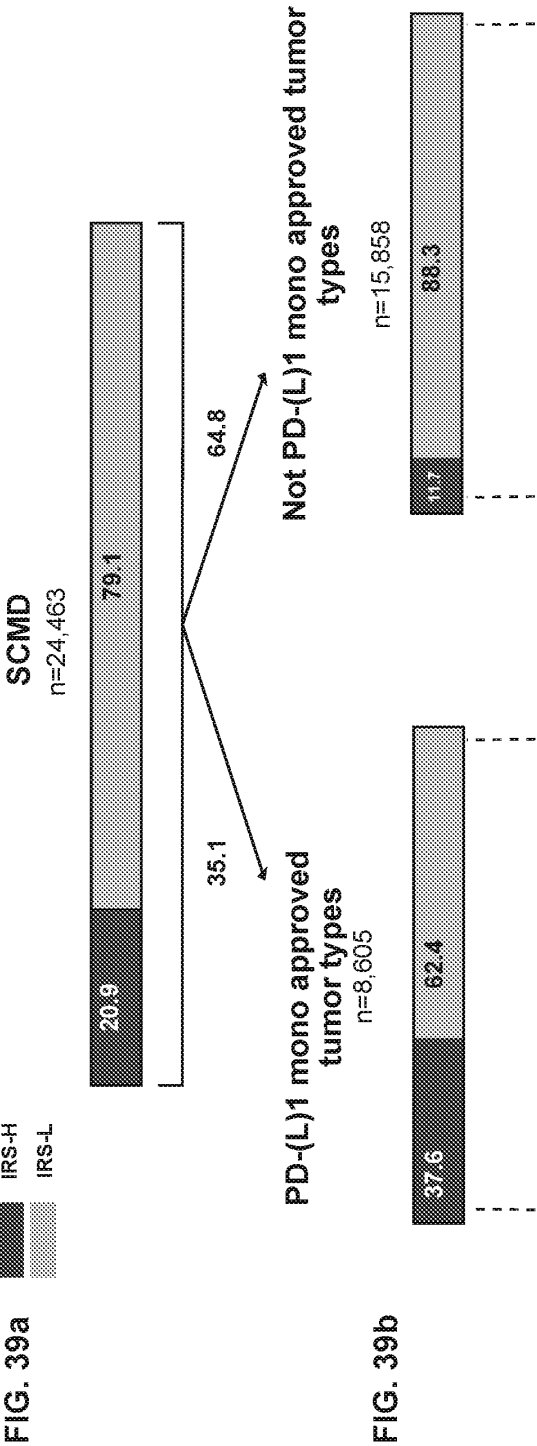
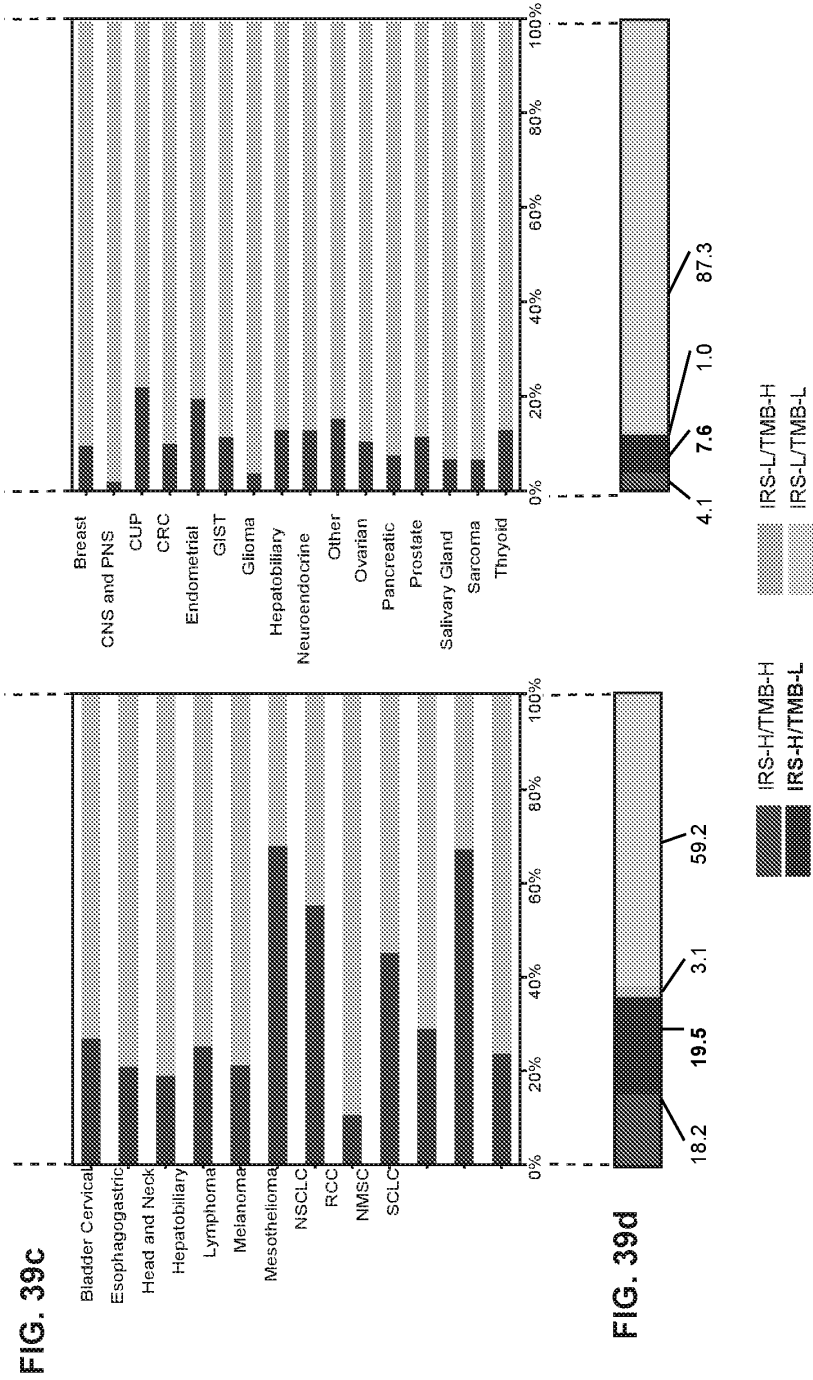


FIG. 38c



FIGS. 38a-c





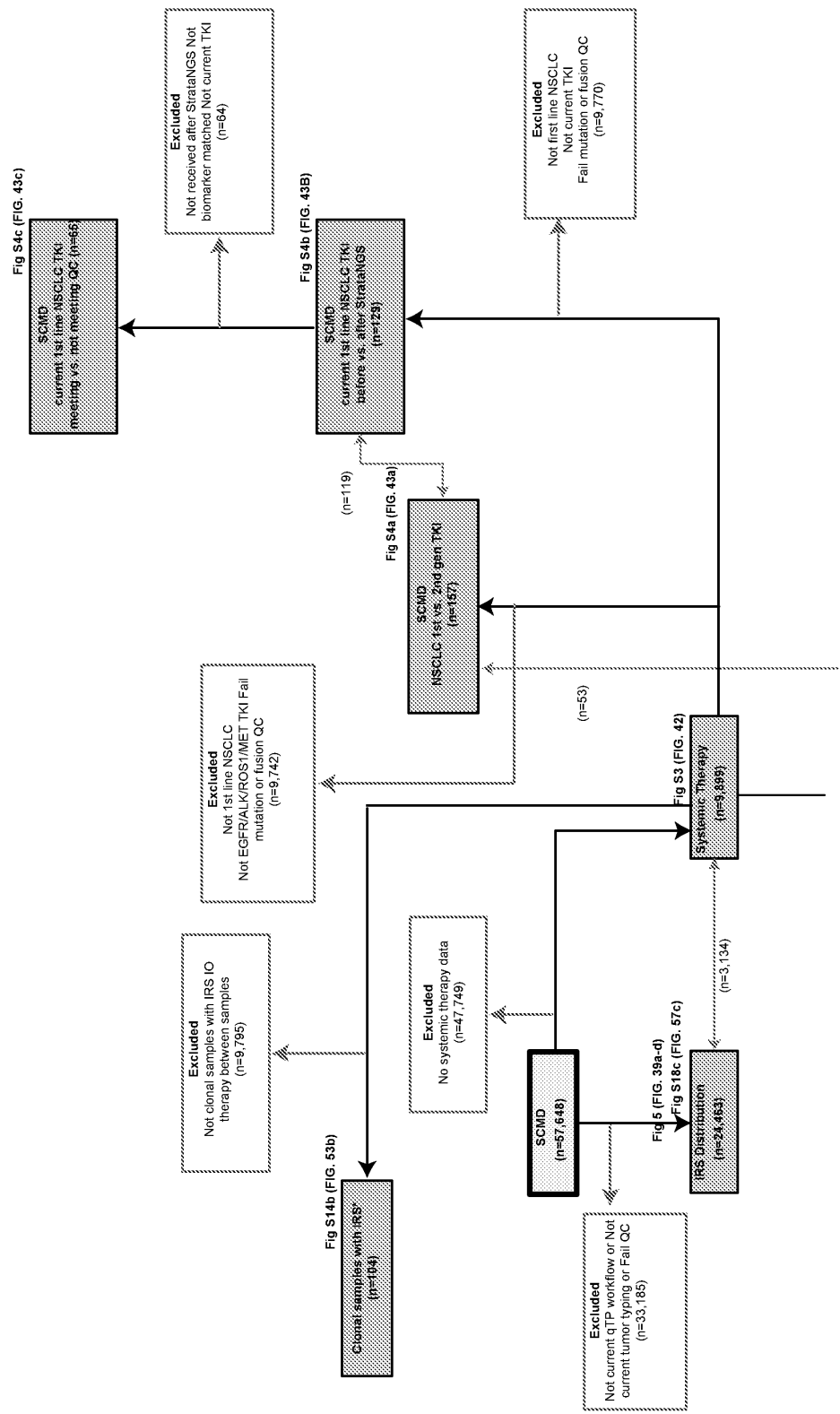
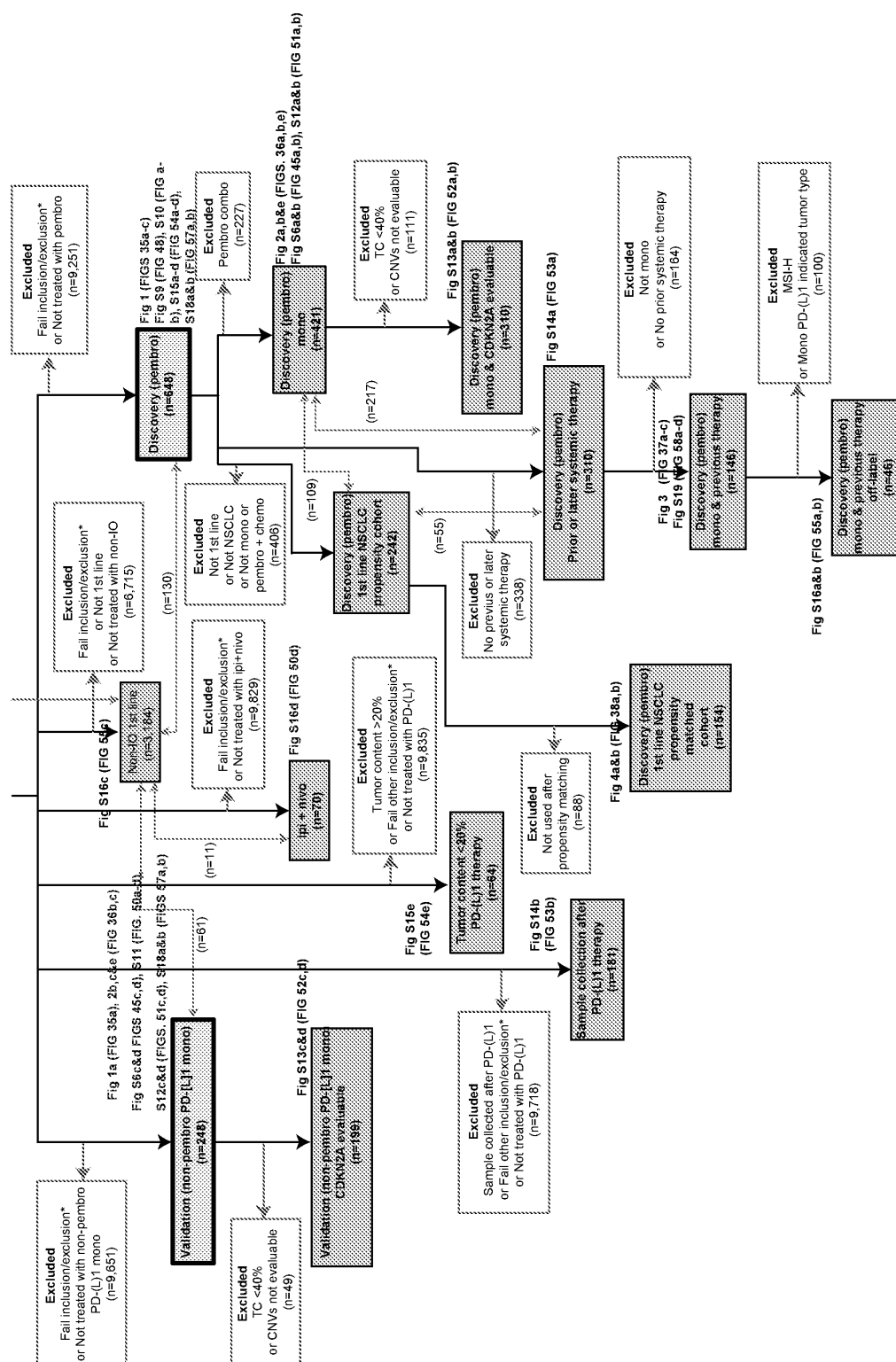


FIG. 40



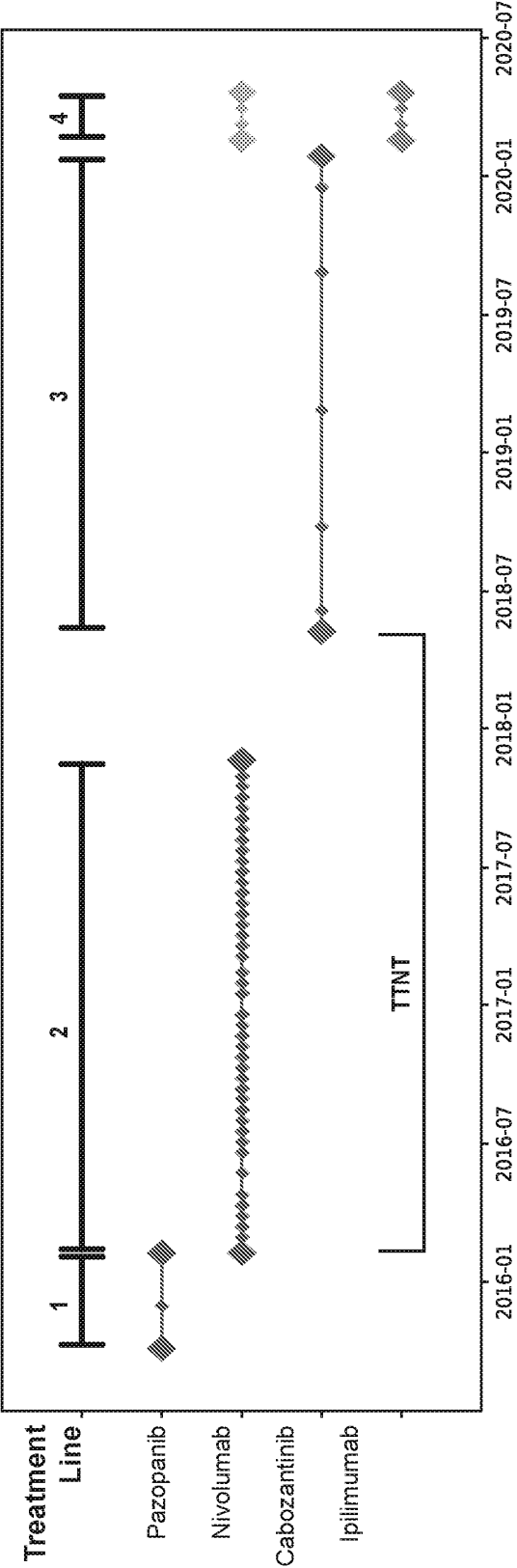


FIG. 41

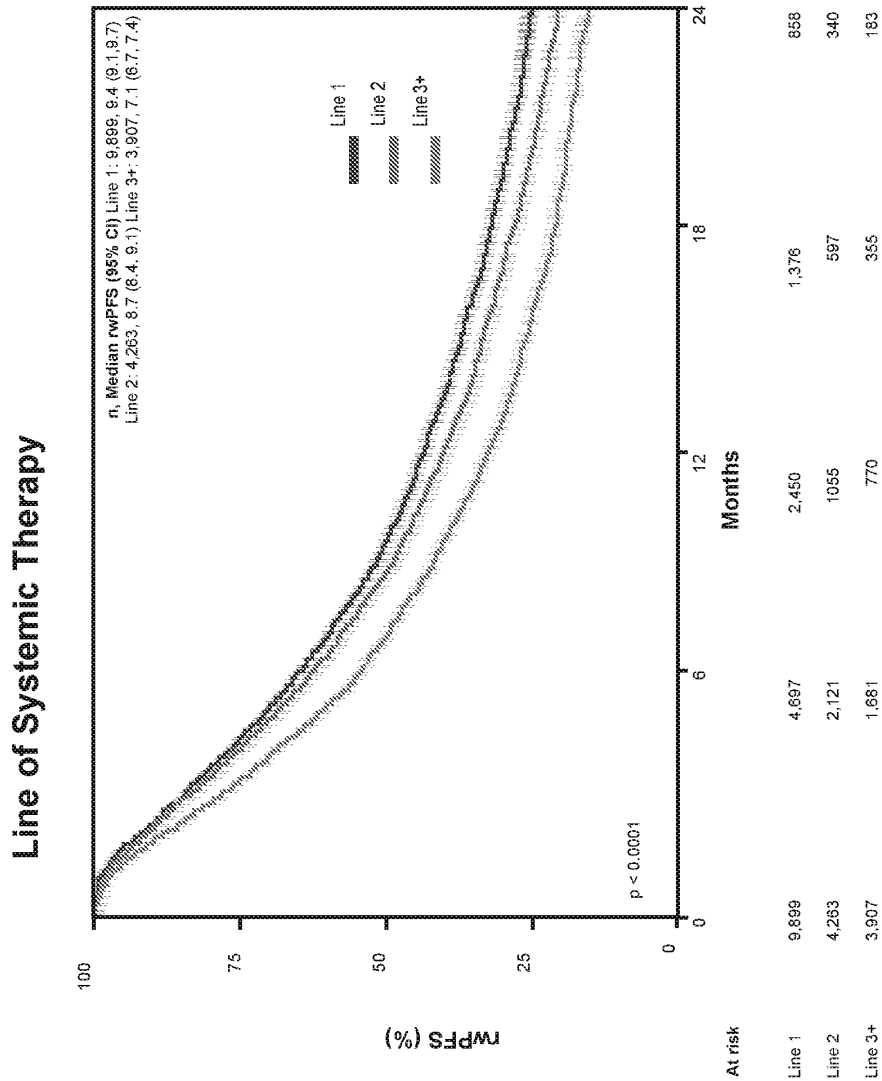


FIG. 42

FIG. 43a

TKI rwpFS in 1st line NSCLC by later vs.
first generation TKI

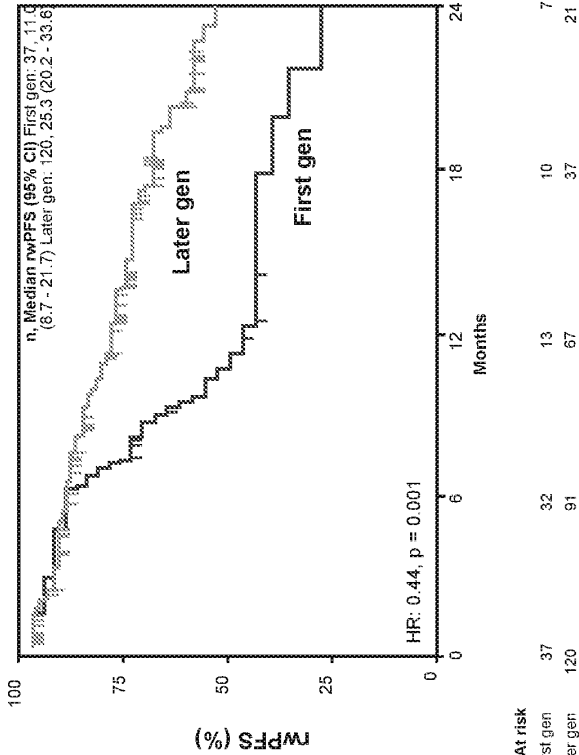
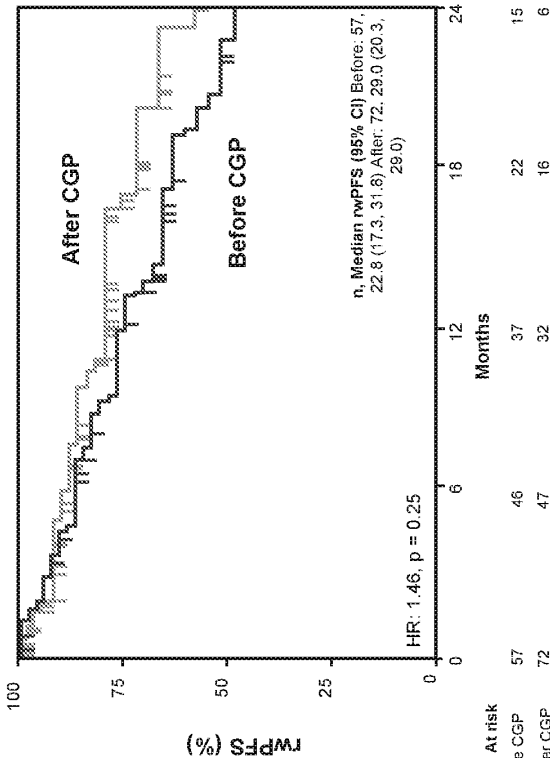


FIG. 43b

TKI rwpFS in 1st line NSCLC by CGP
results timing



FIGS. 43a-b

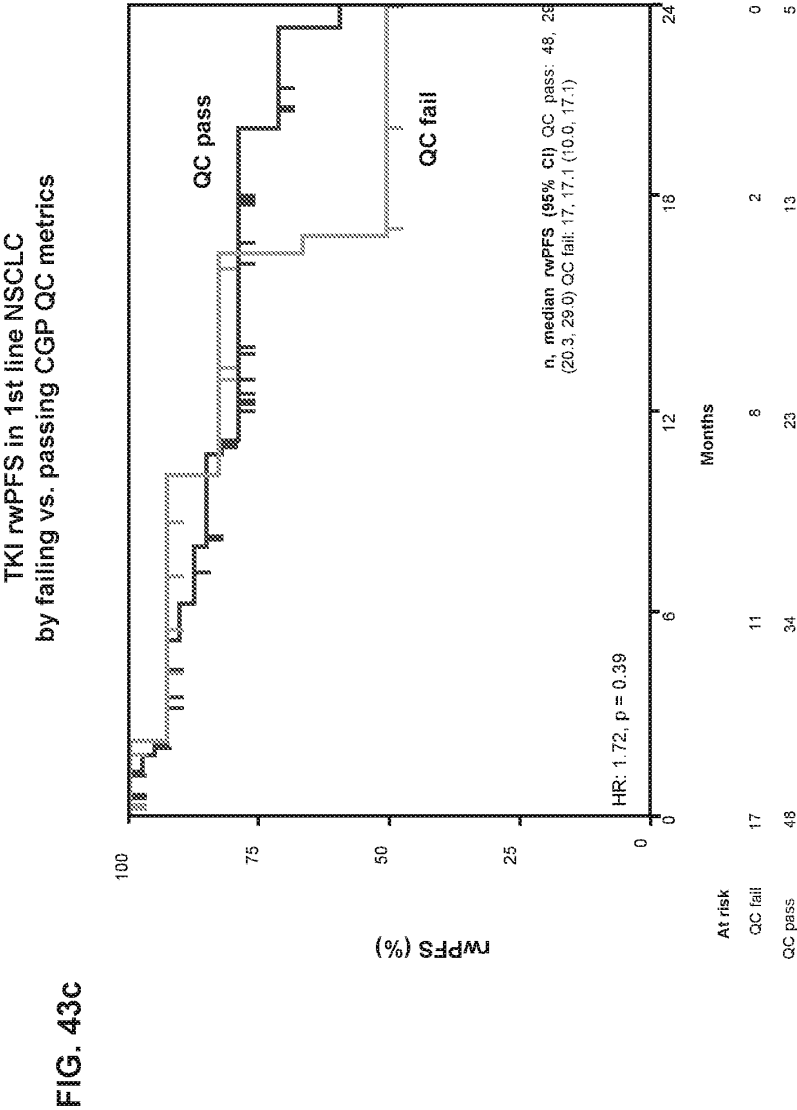


FIG. 43c

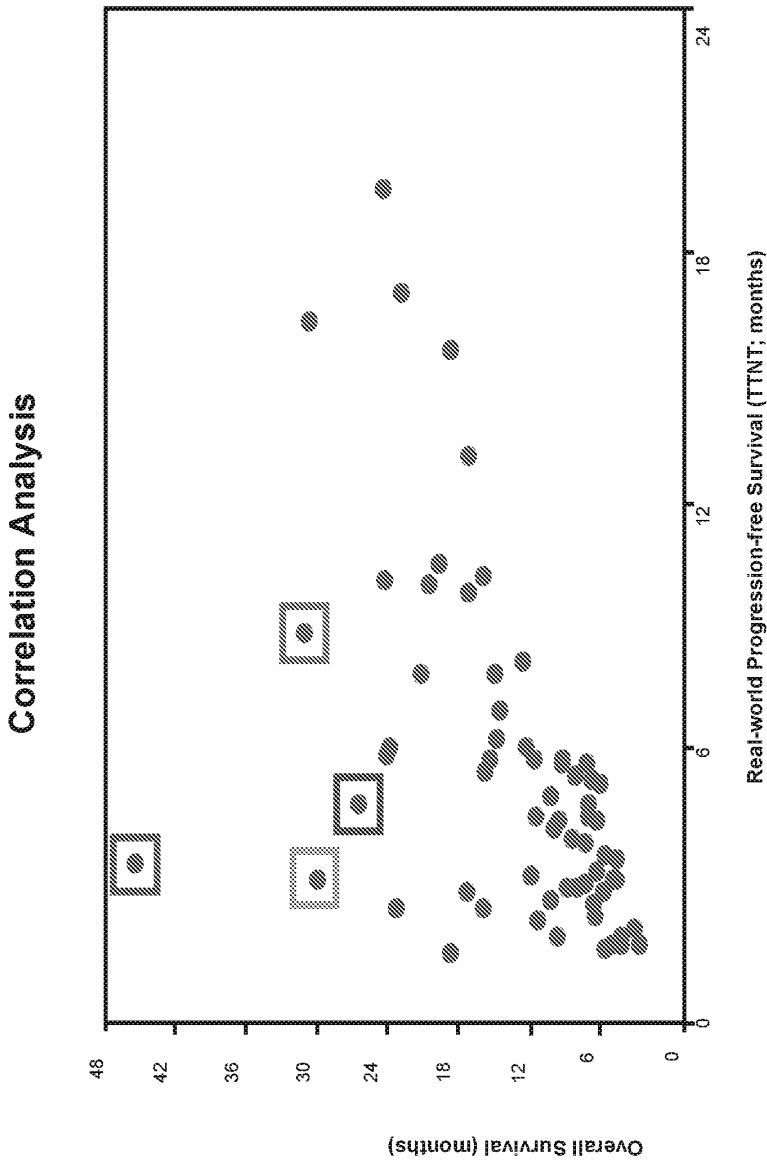


FIG. 44

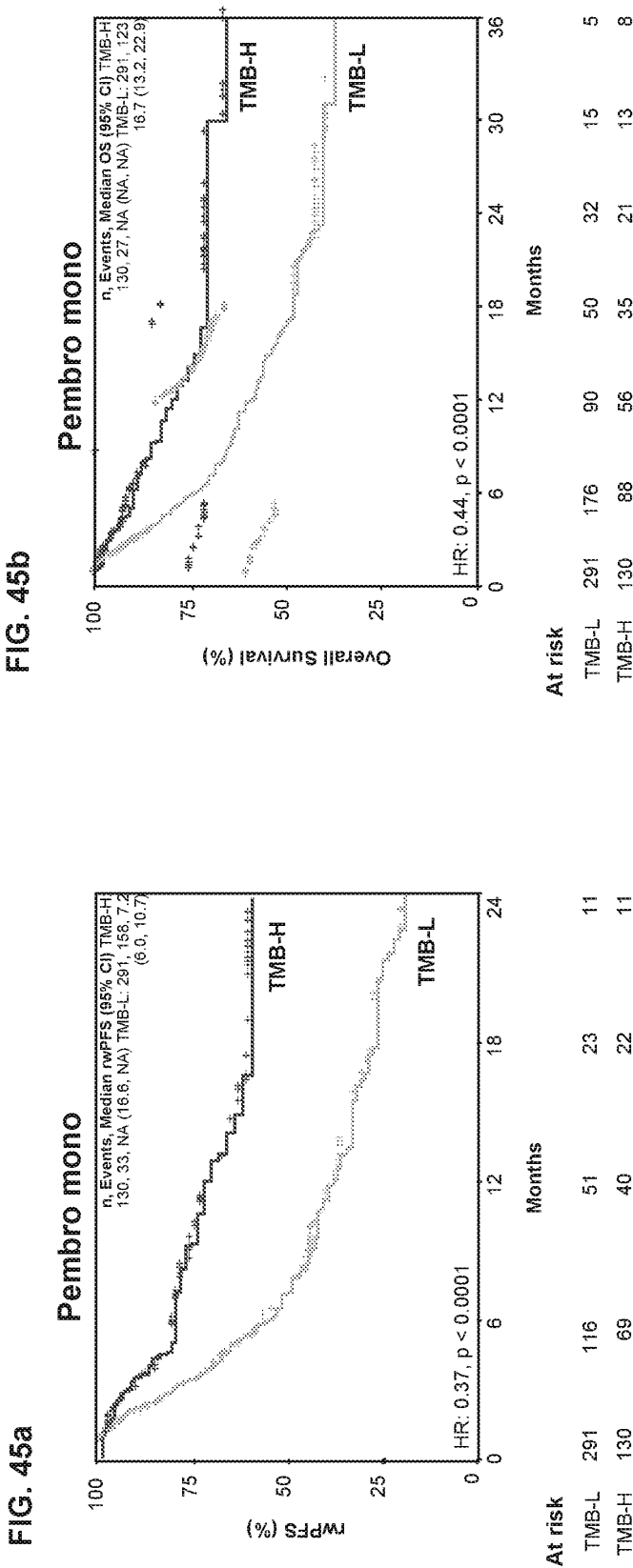


FIG. 45c

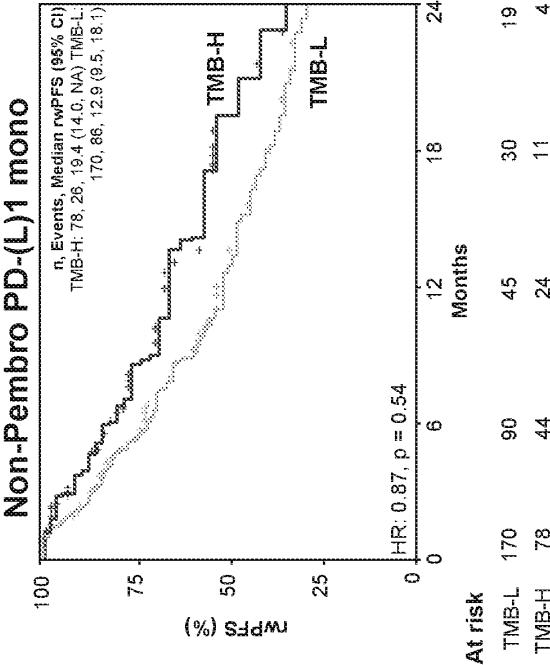
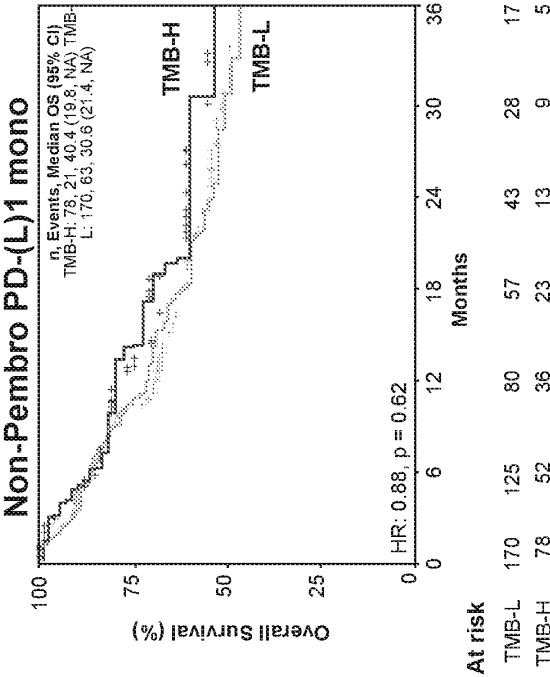


FIG. 45d

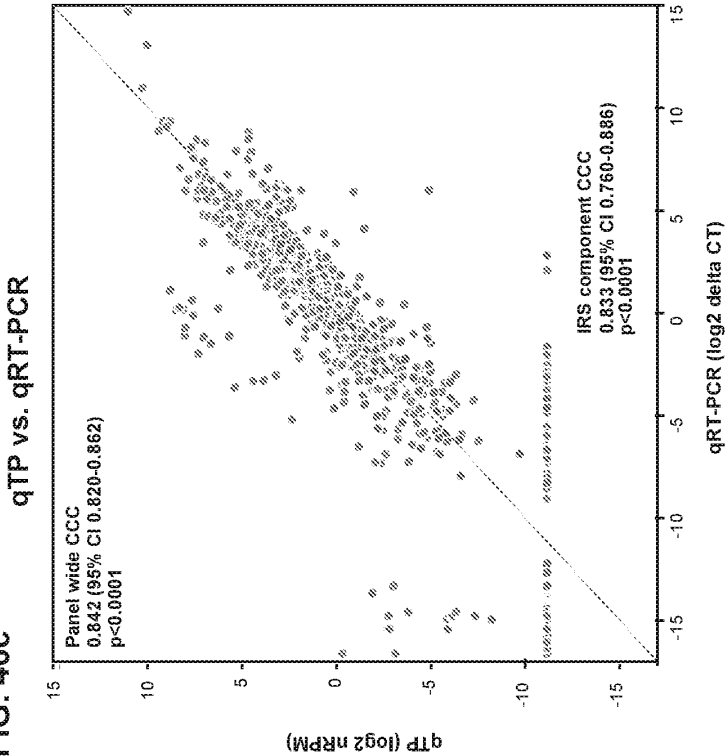


FIGS. 45c-d

FIG. 46a

Type	Gene	Average (TPM)	Coefficient of Variation		
			All (n=20,841)	Cell line (n=935)	Normal (n=9,968)
TCGA stable	SLC4A1AP	16.3	46.2%	50.0%	47.6%
TCGA stable	CTCF	13.1	45.5%	44.5%	42.1%
TCGA stable	EIF2B1	27.5	42.5%	37.5%	42.4%
TCGA stable	ELAVL1	3.4	53.5%	34.9%	47.8%
TCGA stable	CIAO1	36.5	44.3%	36.6%	35.5%
TCGA stable	GGNBP2	41.3	44.7%	33.4%	45.0%
TCGA stable	FAM32A	58.8	43.7%	34.5%	41.3%
TCGA stable	KHDRBS1	61.1	50.5%	37.3%	48.7%
TCGA stable	DHX9	70.4	47.2%	39.1%	43.9%
TCGA stable	ZNF207	78.0	50.2%	38.4%	51.0%
TCGA stable	TARDBP	112.5	44.0%	36.5%	42.4%
TCGA stable	PTBP1	120.1	63.0%	35.7%	55.8%
TCGA stable	SF3B2	126.7	43.4%	34.7%	45.8%
TCGA stable	EWSR1	138.2	47.5%	31.8%	40.1%
TCGA stable	EIF4H	169.3	41.2%	31.2%	38.5%
TCGA stable	HNRNPL	187.4	43.8%	33.2%	40.4%
TCGA stable	PCBP1	213.2	47.5%	36.6%	47.4%
TCGA stable	HNRNPK	281.2	46.4%	23.5%	40.1%
OPA positive	ITGB7	5.4	845.4%	845.6%	191.0%
OPA positive	TBP	11.1	53.2%	40.4%	57.0%
OPA positive	HMBIS	18.1	63.7%	96.1%	67.9%
OPA positive	MRPL13	34.5	79.2%	61.6%	46.8%
OPA positive	MYC	59.3	128.4%	126.3%	145.8%
OPA positive	LRP1	93.7	108.0%	208.5%	88.5%
HK gene	GAPDH	2543.4	82.8%	49.6%	50.7%

FIG. 46c



FIGS. 46a, 46c

FIG. 46b

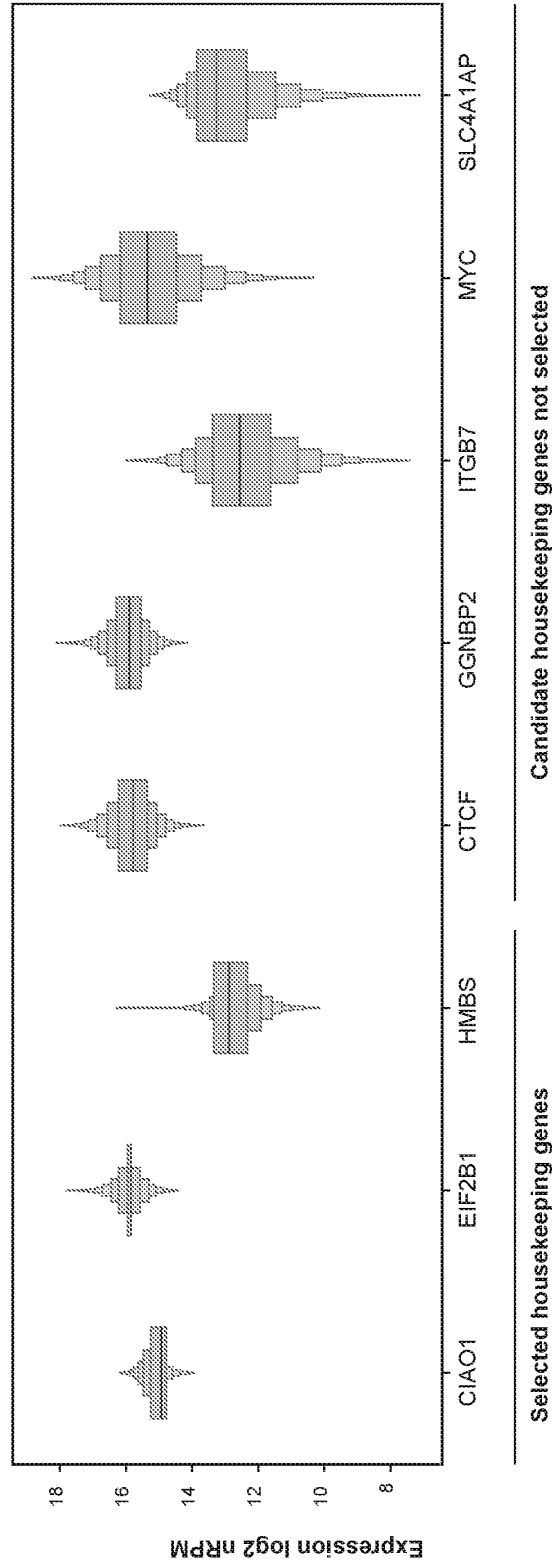
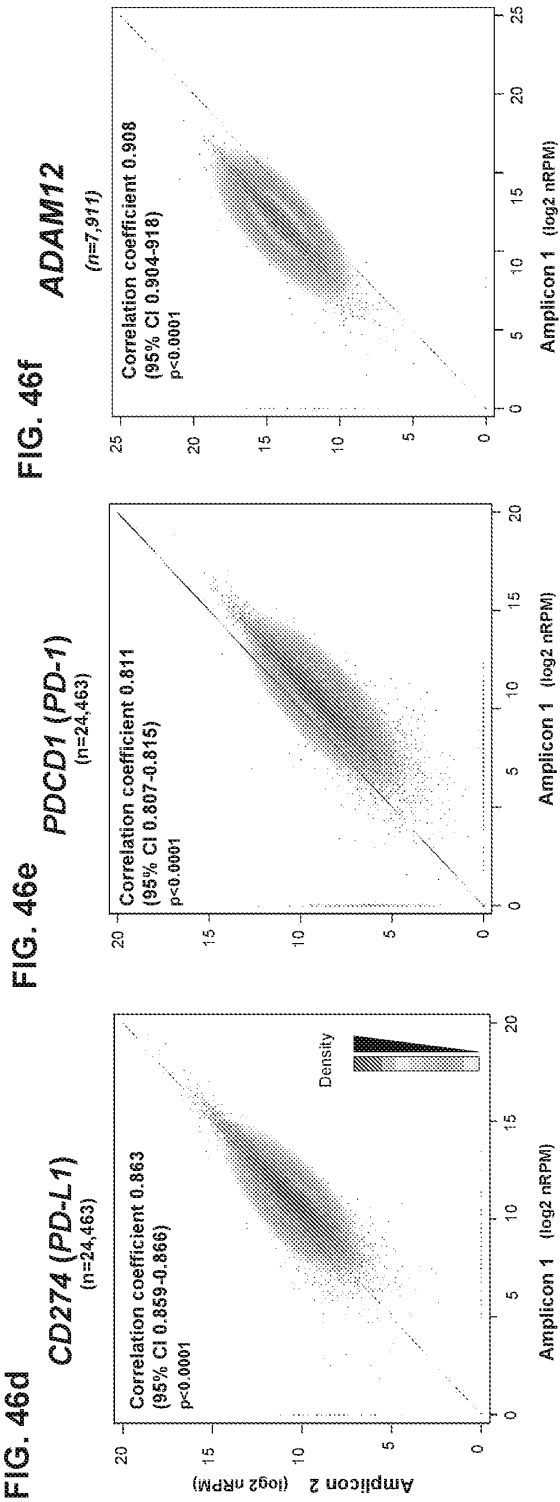


FIG. 46b



FIGS. 46d-f

FIG.47a

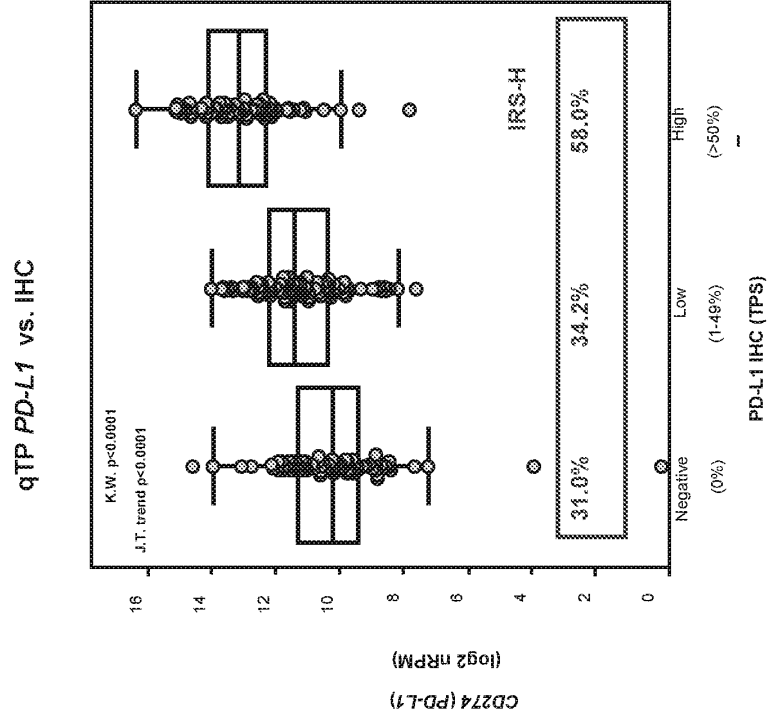
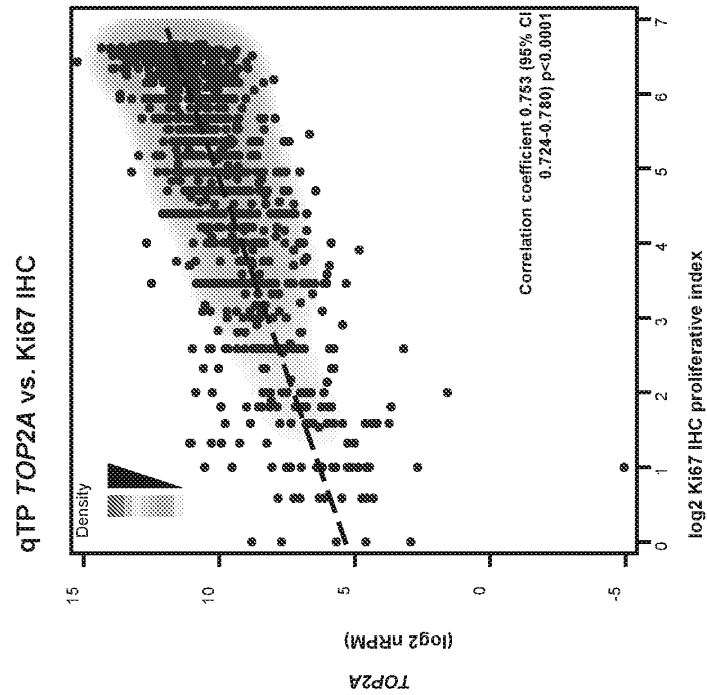


FIG. 47b



FIGS. 47a-b

FIG. 47c

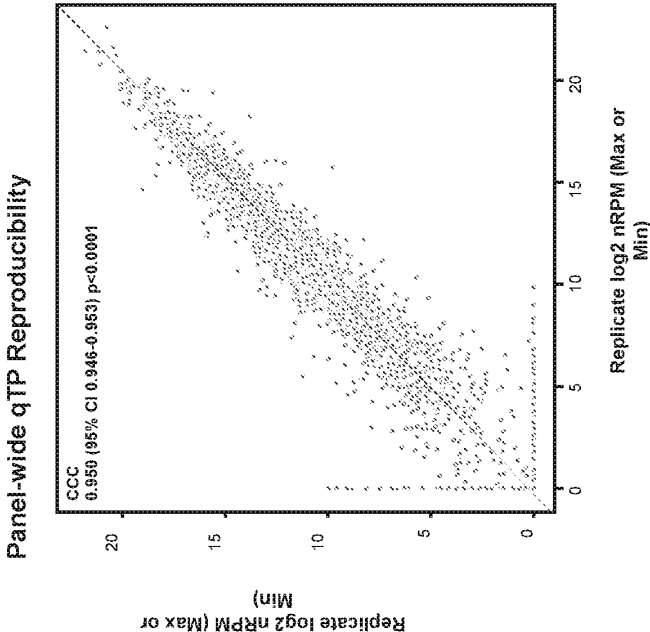
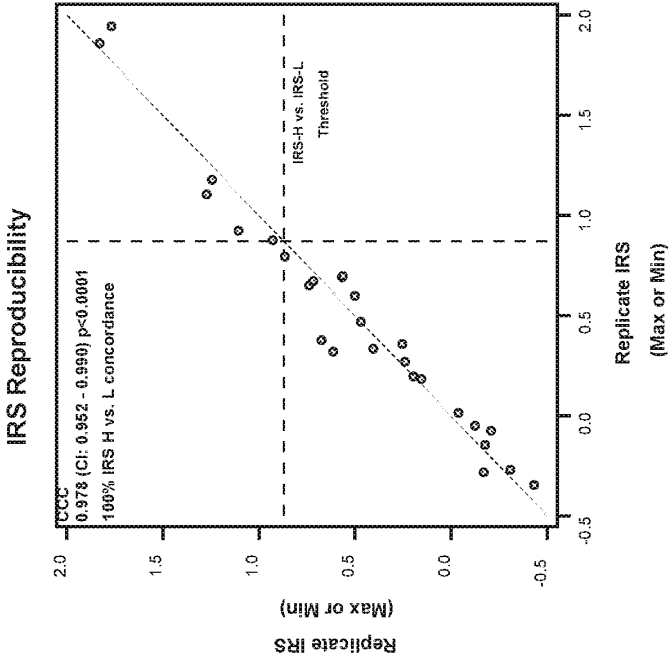


FIG. 47d



FIGS. 47c-d

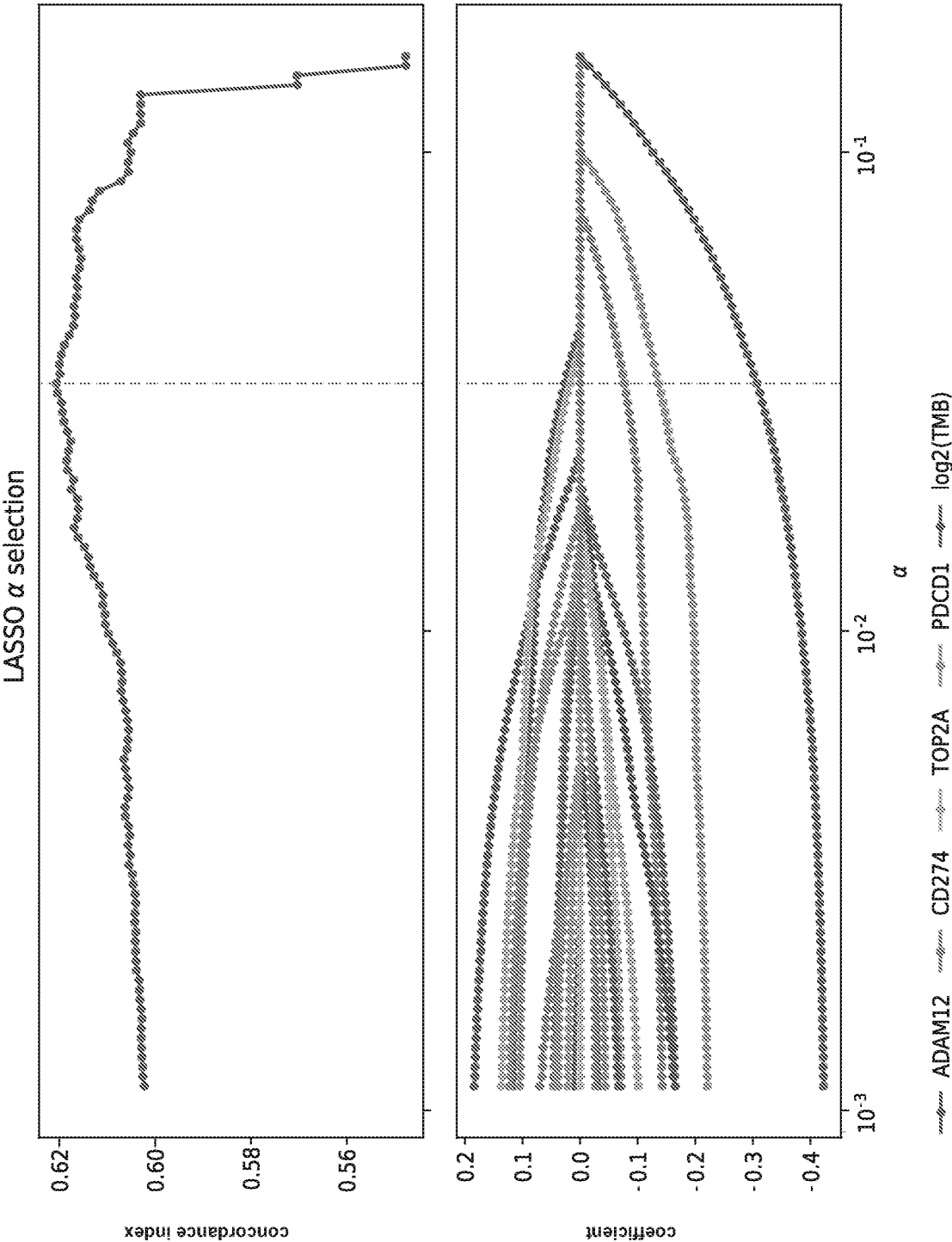


FIG. 48

FIG. 49a

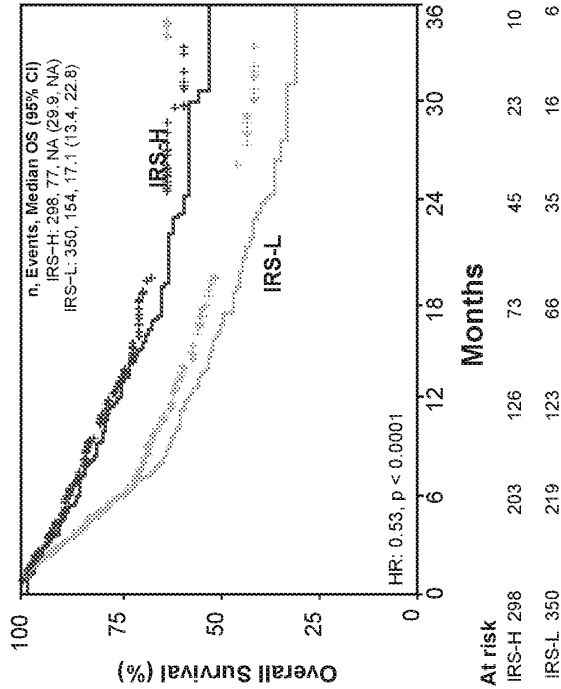
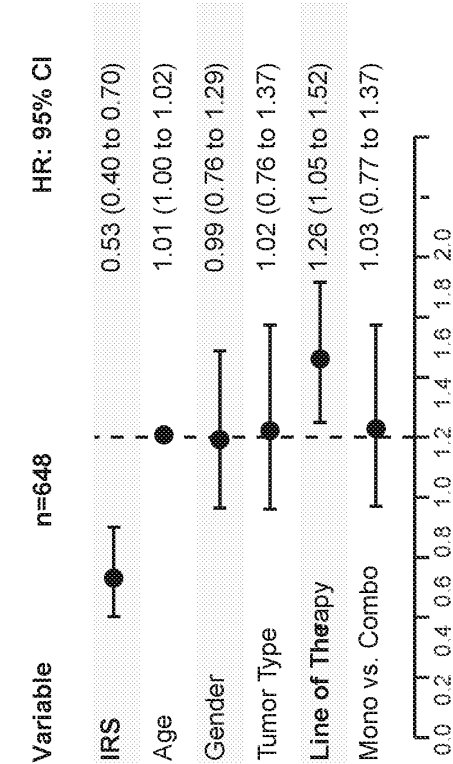
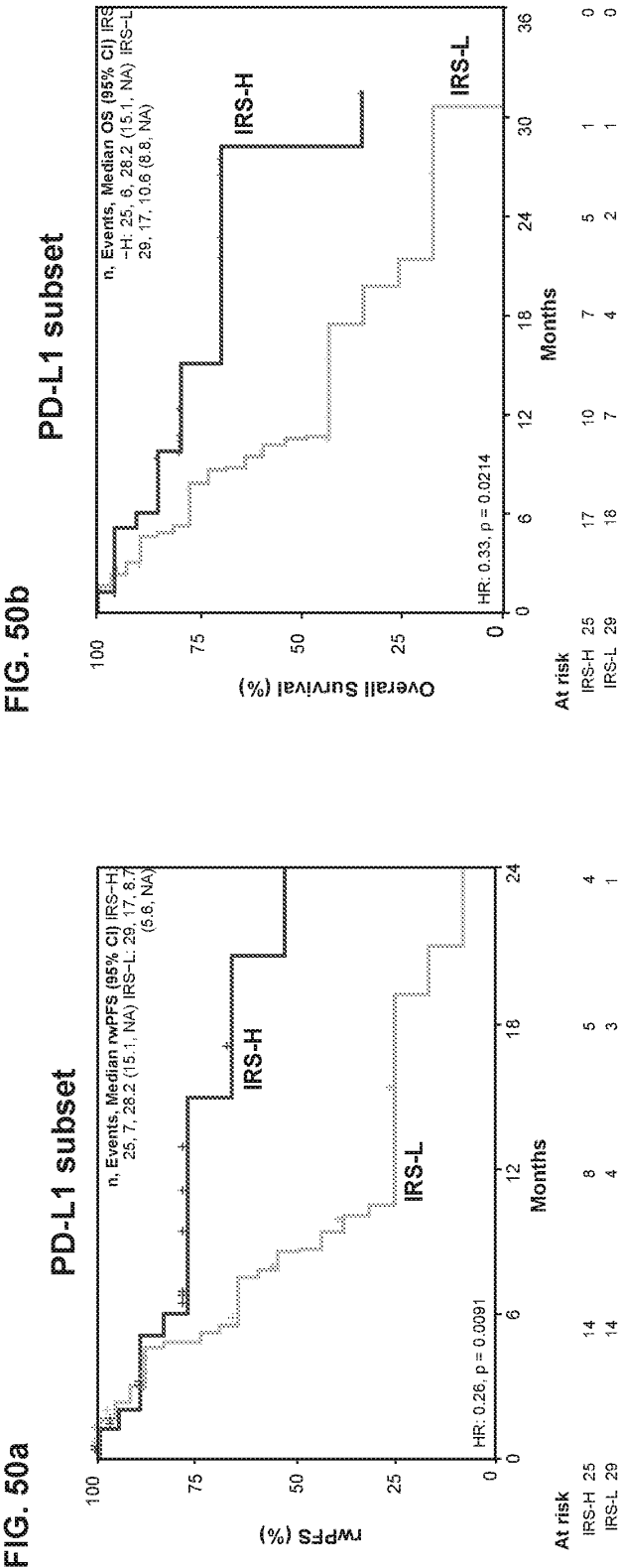


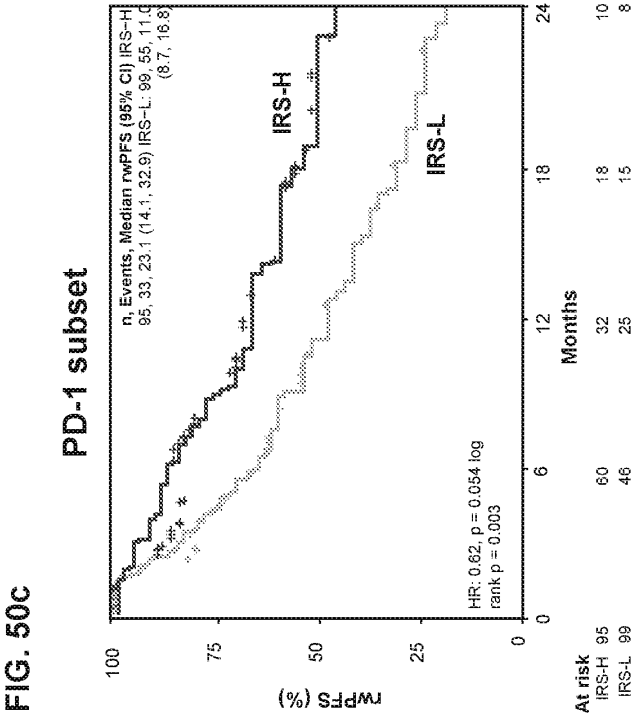
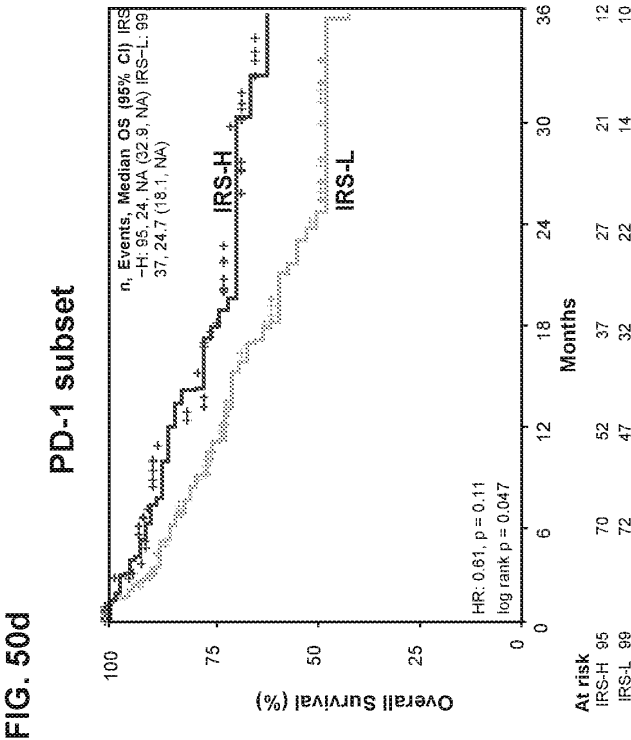
FIG. 49b



FIGS. 49a-b



FIGS. 50a-b



FIGS. 50c-d

FIG. 51a

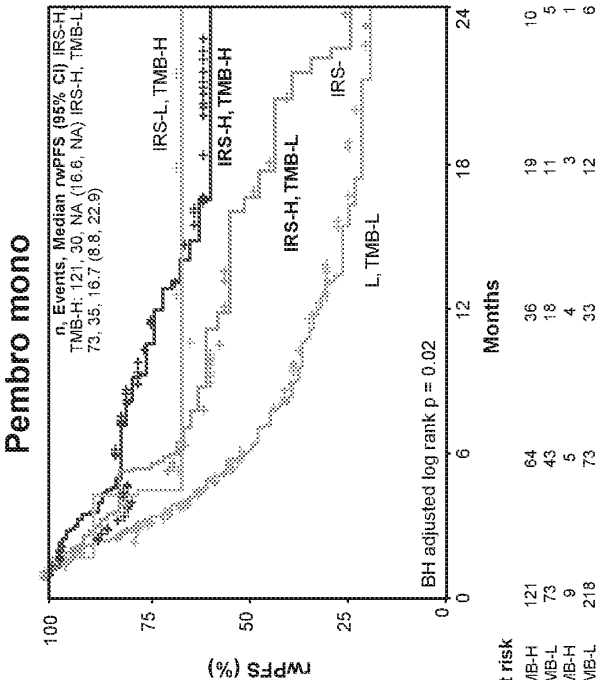
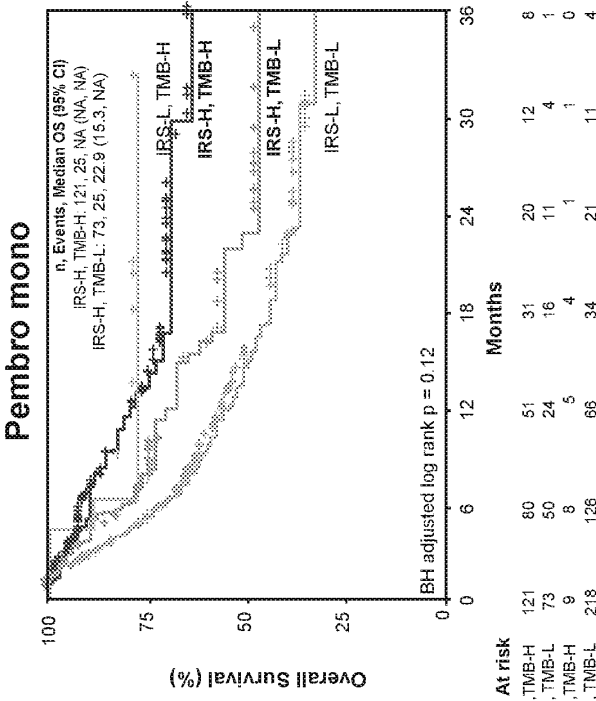


FIG. 51b



FIGS. 51a-b

FIG. 51c

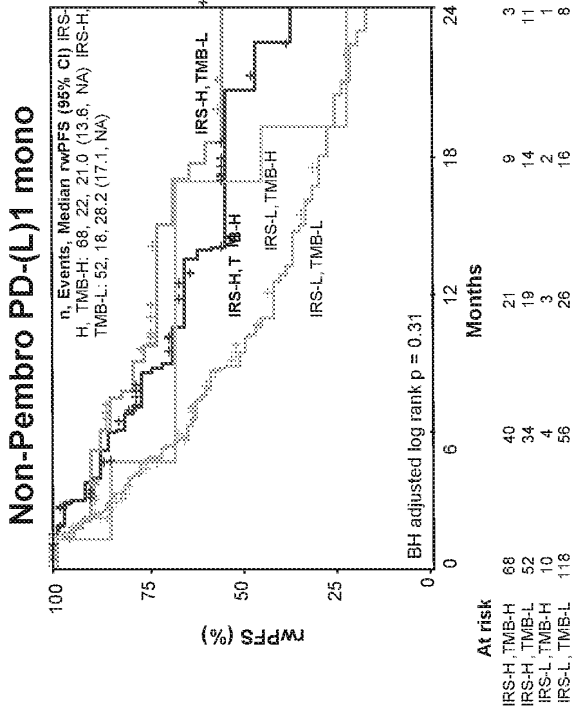
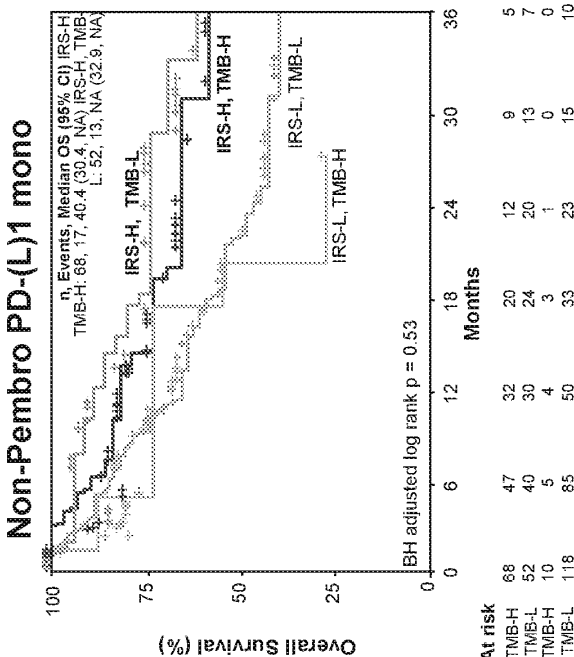


FIG. 51d



FIGS. 51c-d

FIG. 52a

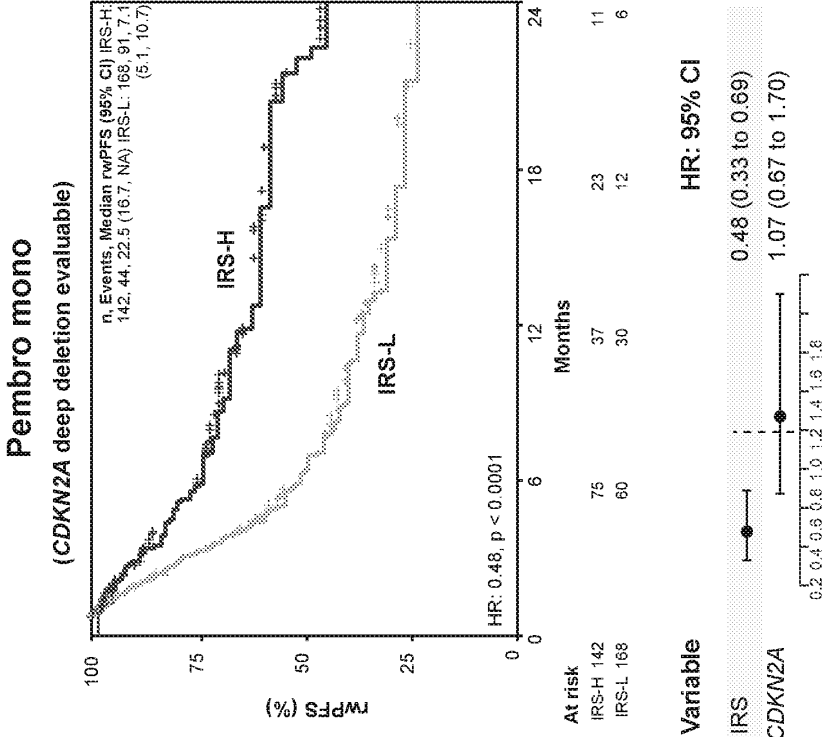
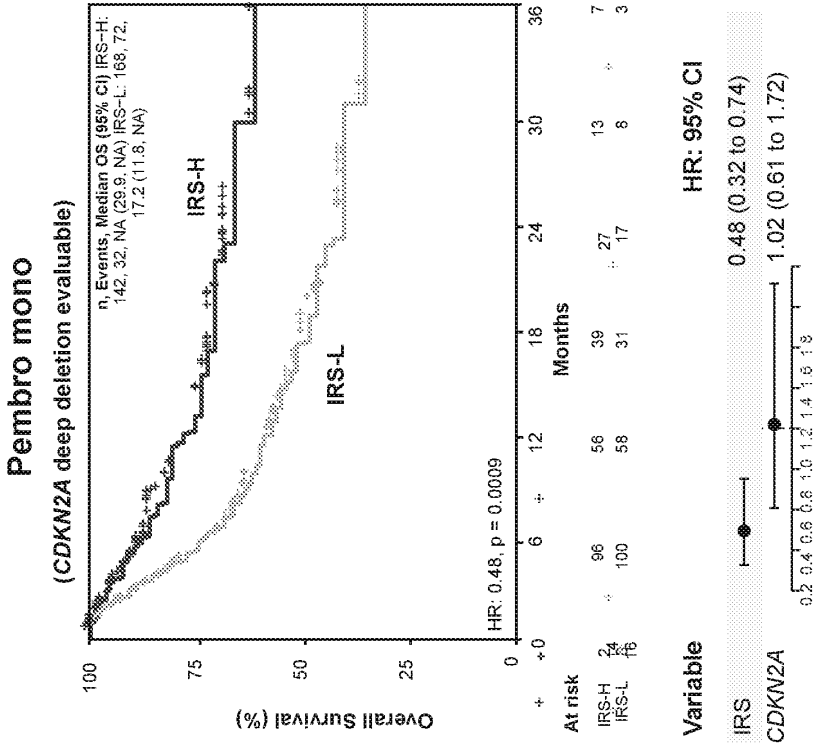


FIG. 52b



FIGS. 52a-b

FIG. 52c

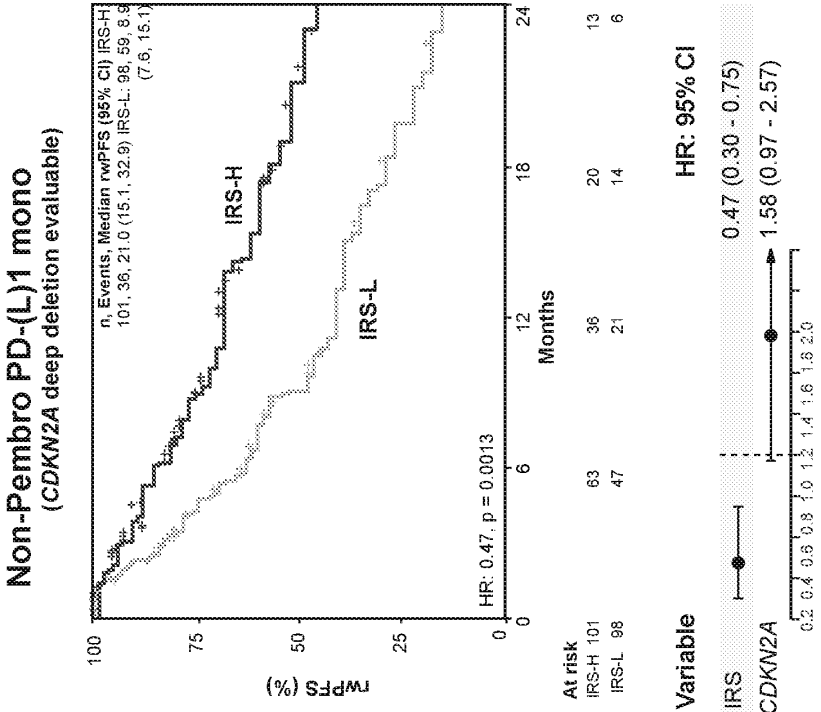
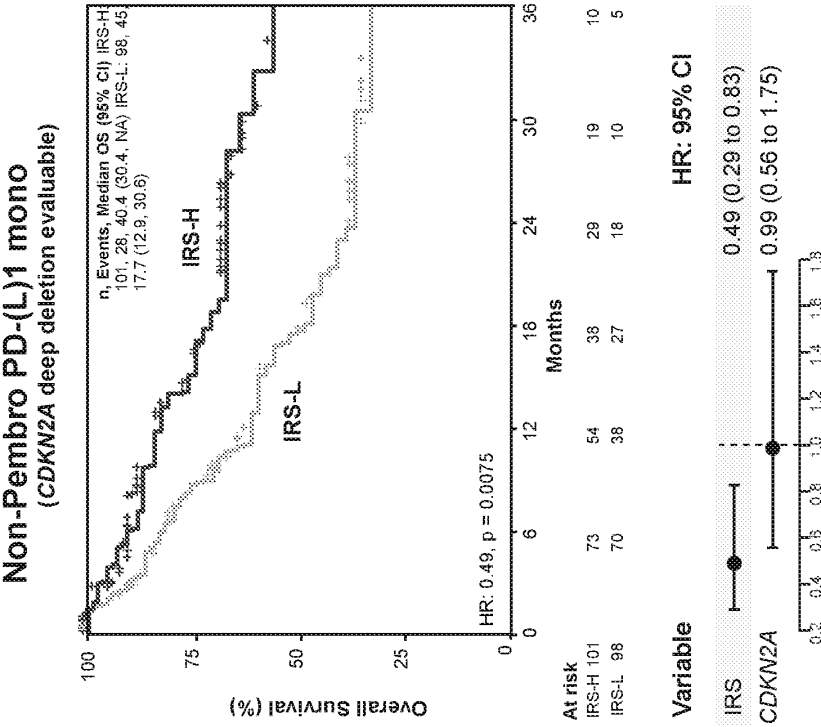


FIG. 52d



FIGS. 52c-d

FIG. 53a

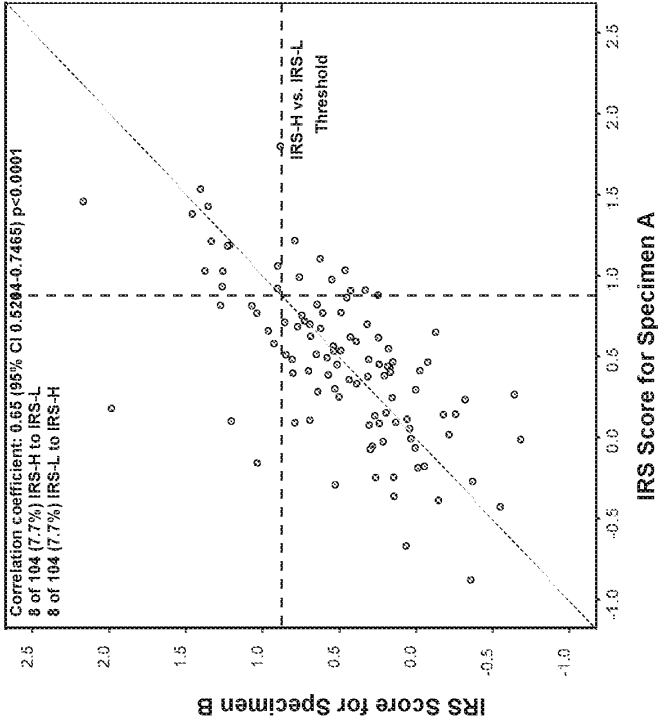
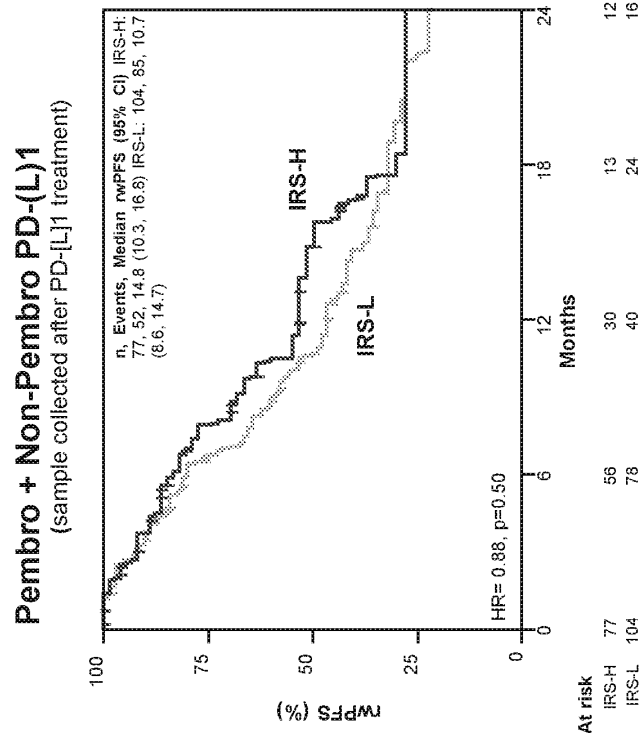
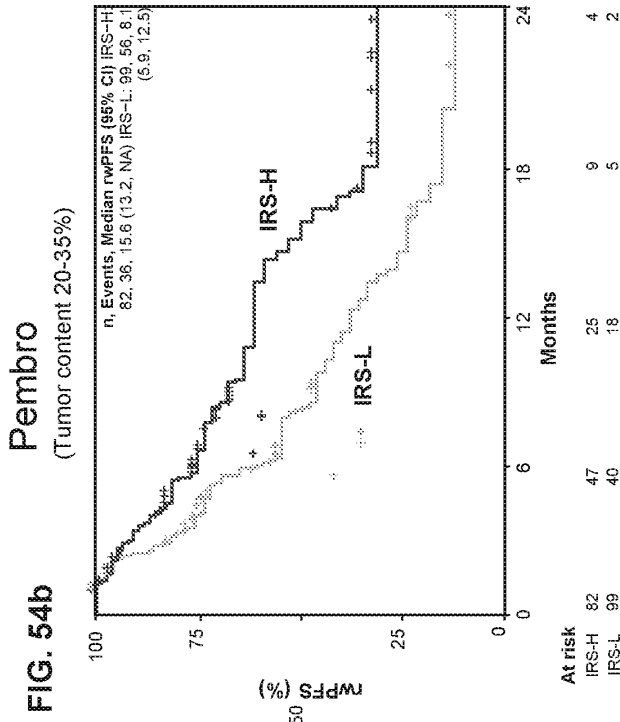
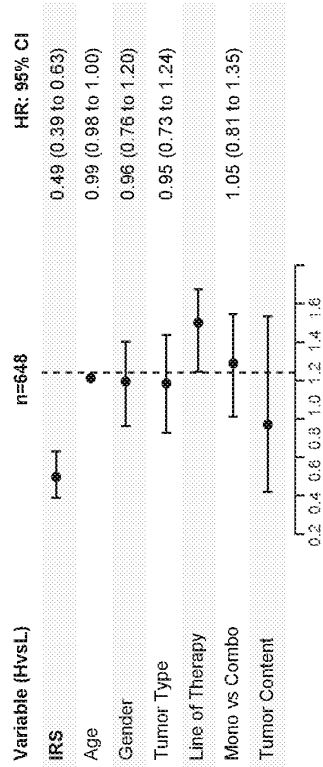


FIG. 53b



FIGS. 53a-b

FIG. 54a



FIGS. 54a-b

FIG. 54c

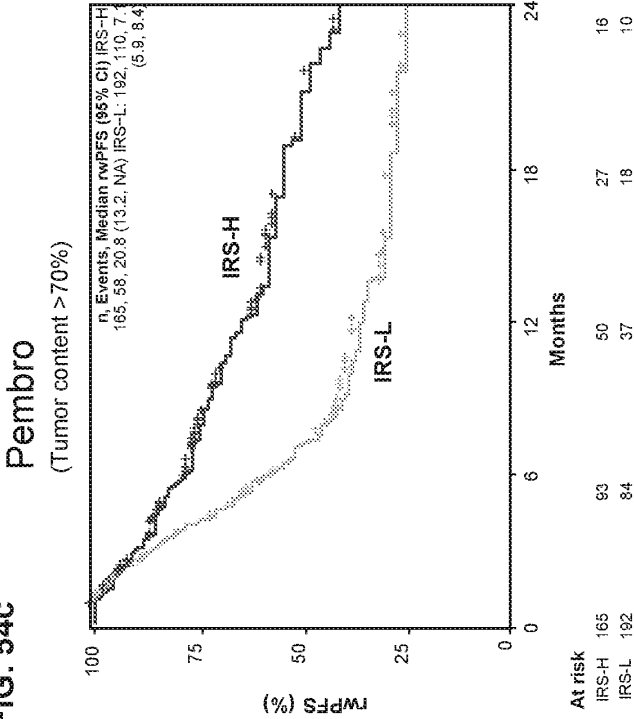
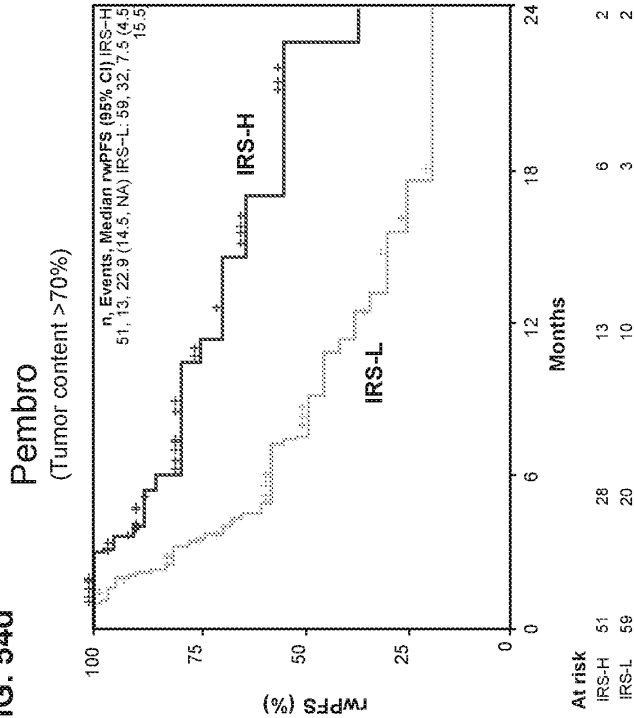


FIG. 54d



FIGS. 54c-d

FIG. 54e

Pembro + Non-Pembro PD-(L)1
(Tumor content <20%)

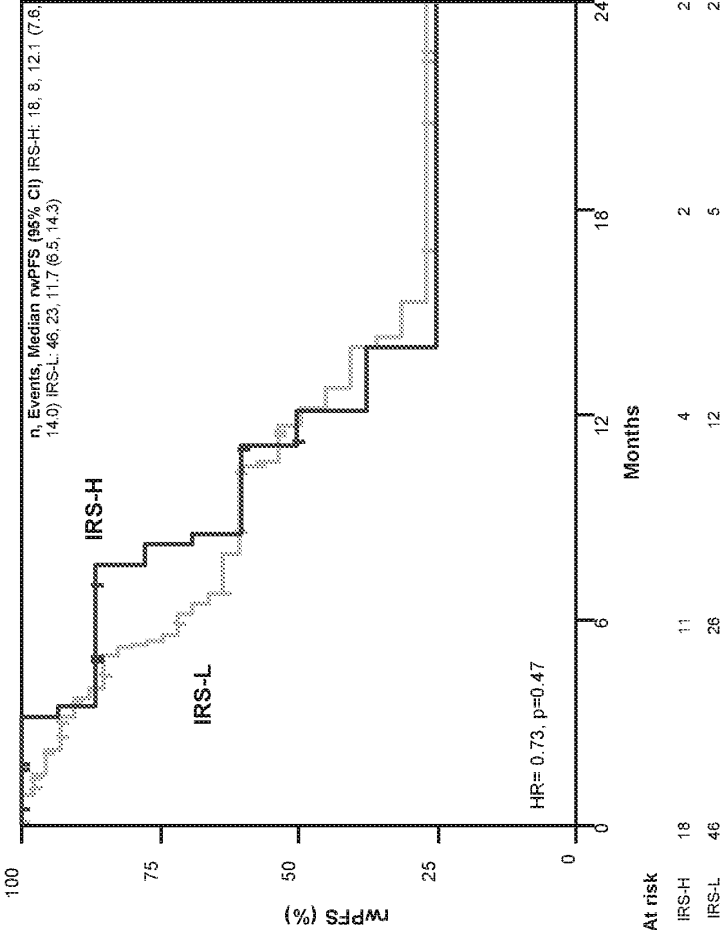


FIG. 54e

FIG. 55a

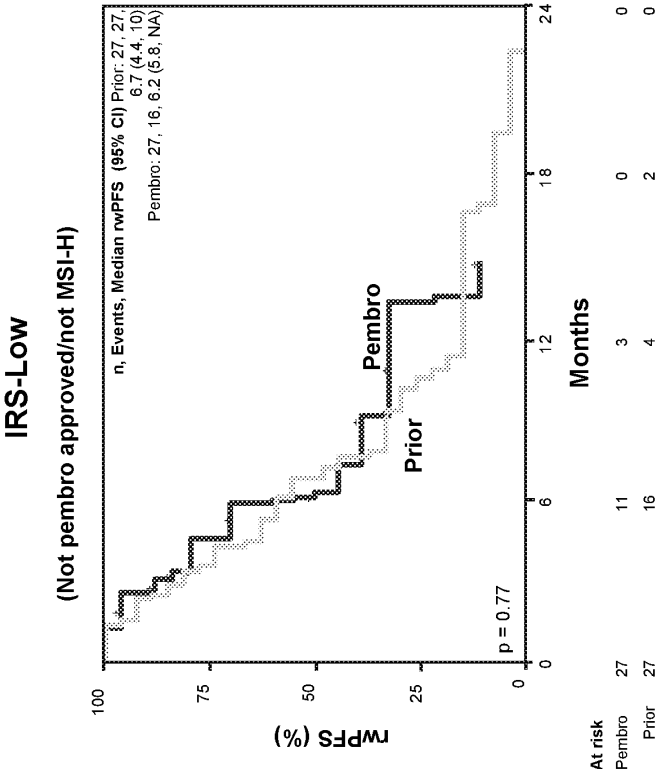
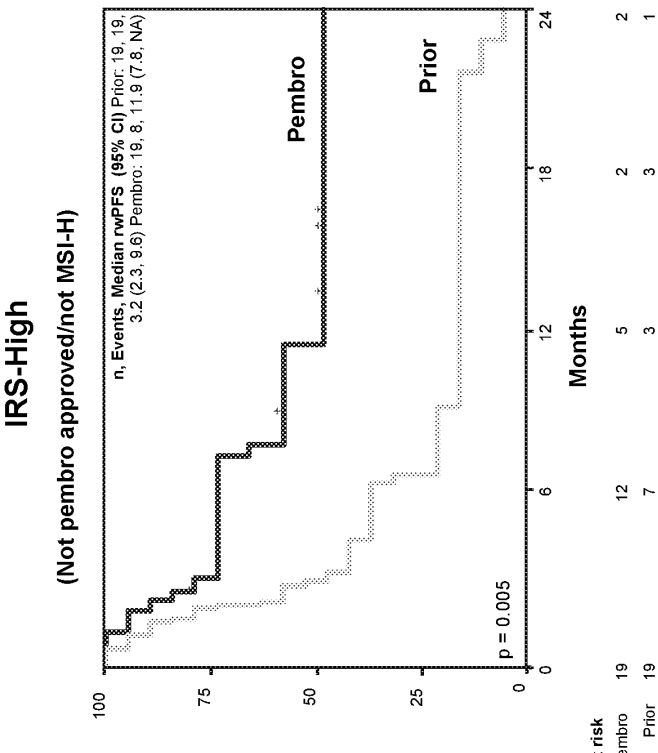


FIG. 55b



FIGS. 55a-b

FIG. 55c

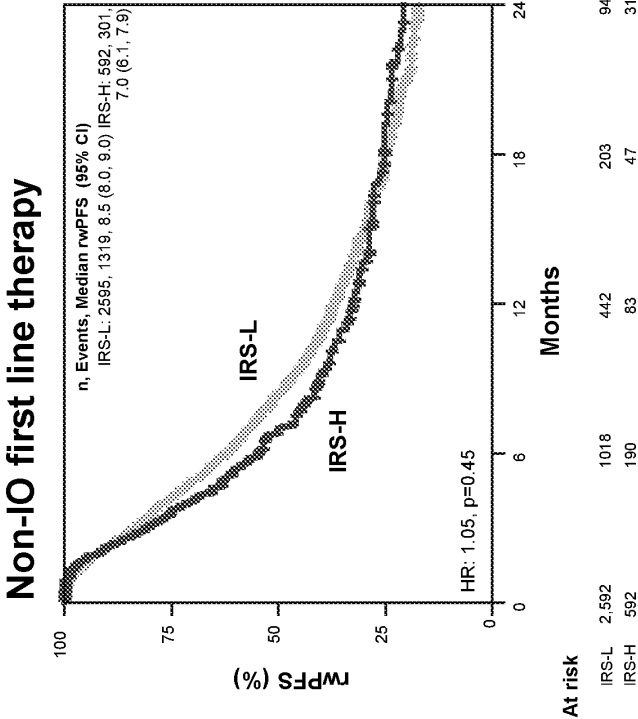
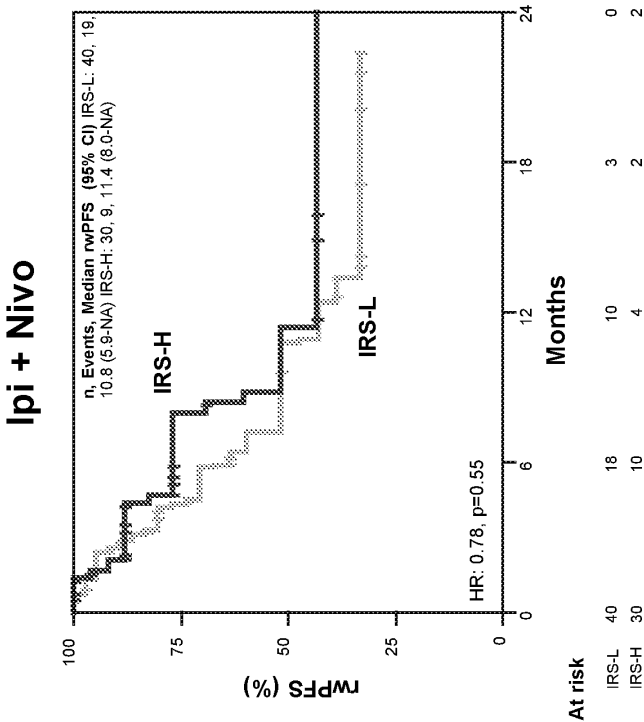


FIG. 55d



FIGS. 55c-d

FIG. 56a

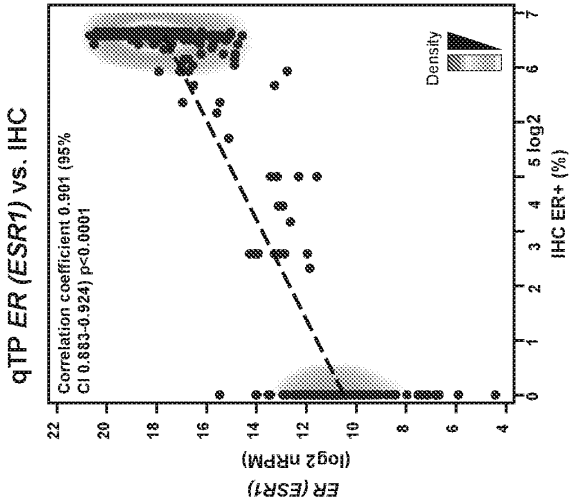


FIG. 56b

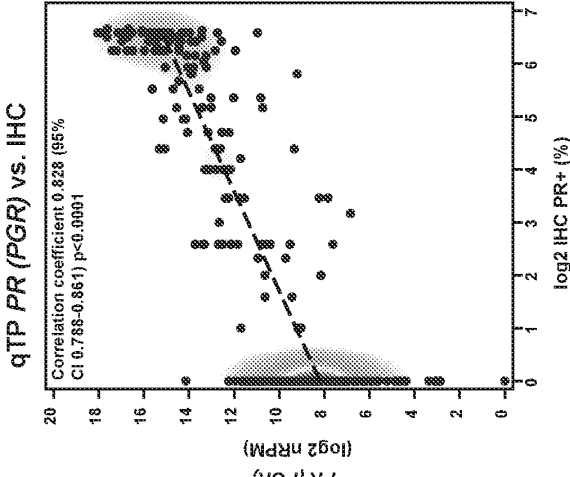
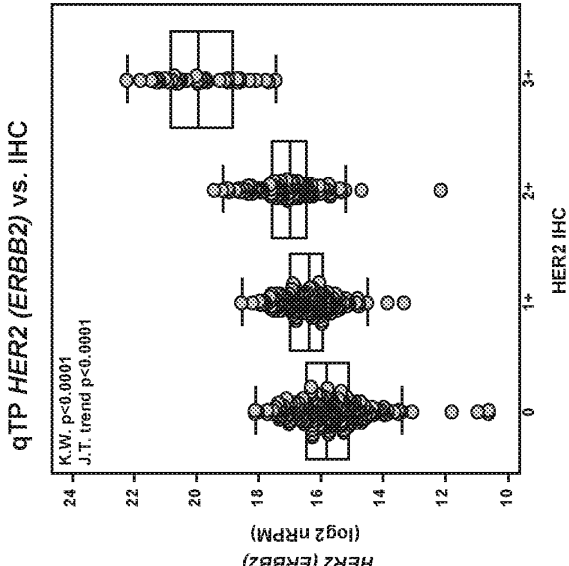


FIG. 56c



FIGS. 56a-c

FIG. 56d
qTP ER vs. IHC
(validation cohort)

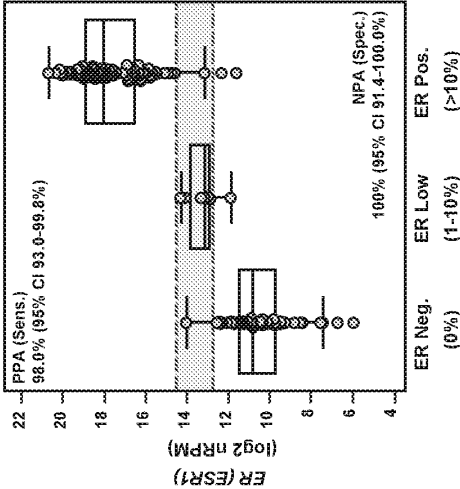


FIG. 56e
qTP PR vs. IHC
(validation cohort)

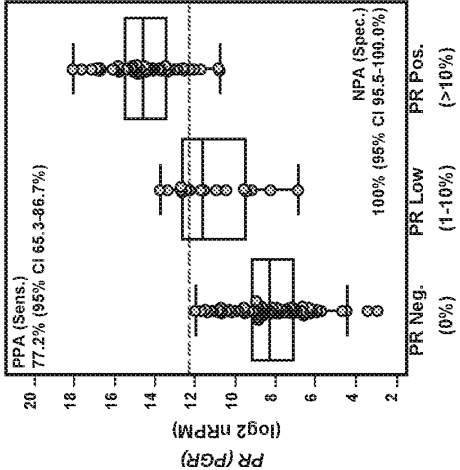
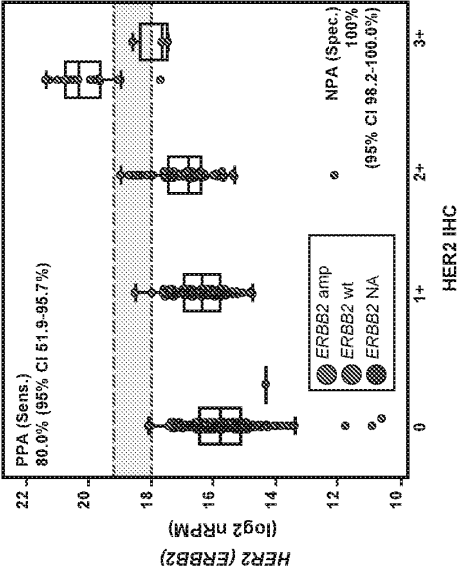


FIG. 56f
qTP HER2 (ERBB2) vs. IHC
(validation cohort)



FIGS. 56d-f

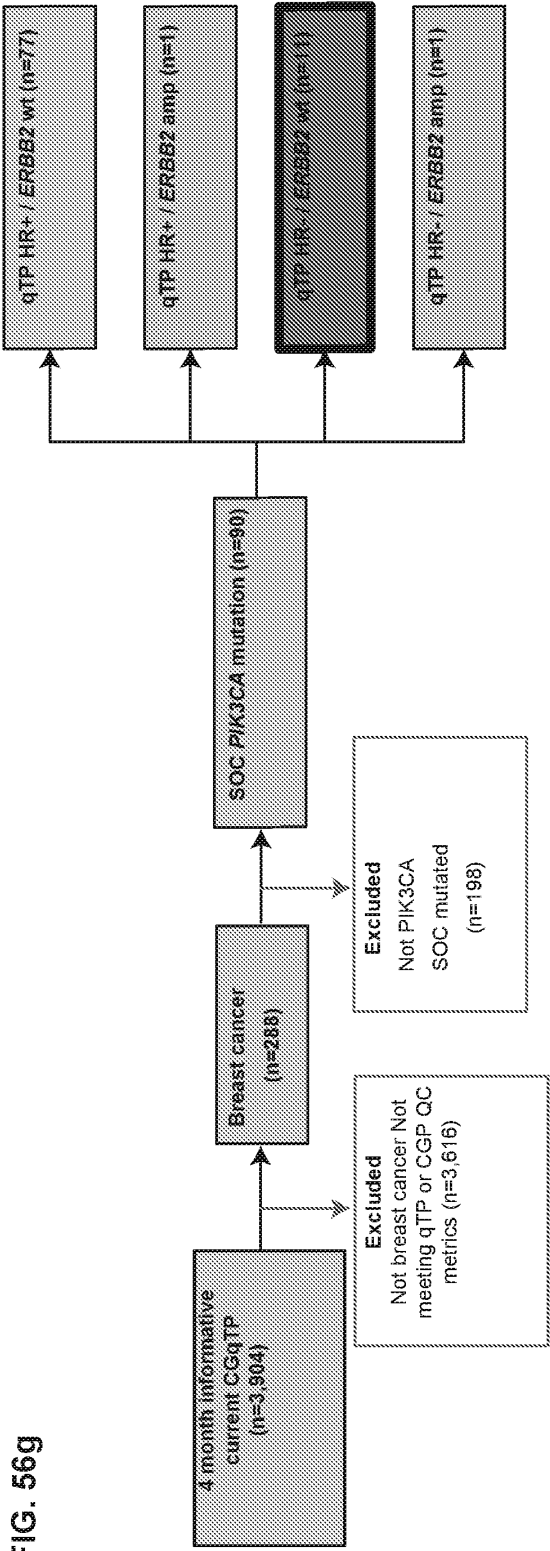


FIG. 56g

FIG. 56g

FIG. 57a

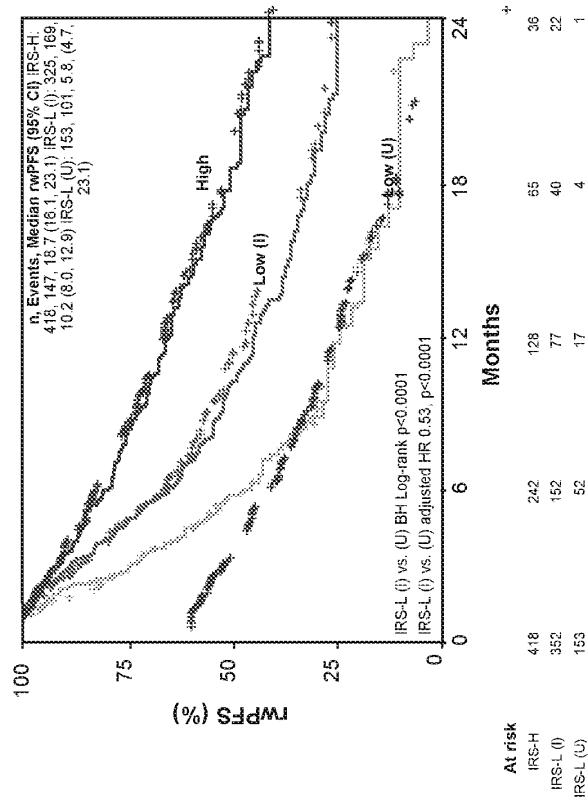
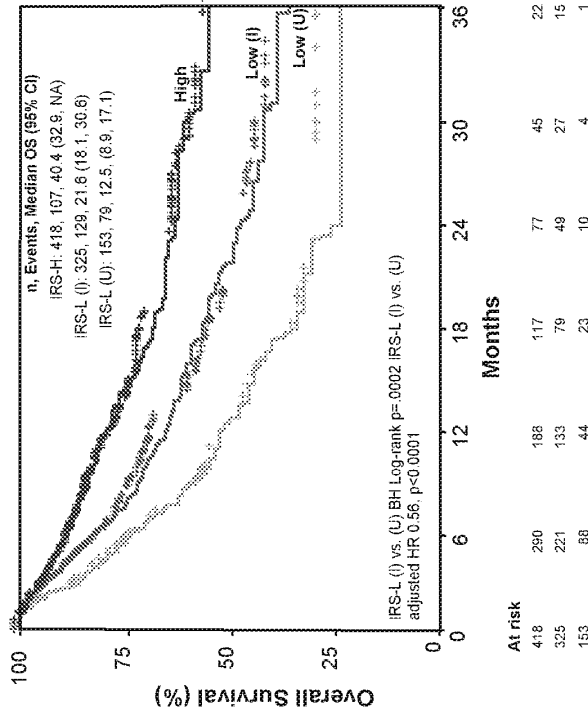


FIG. 57b



FIGS. 57a-b

FIG. 57c

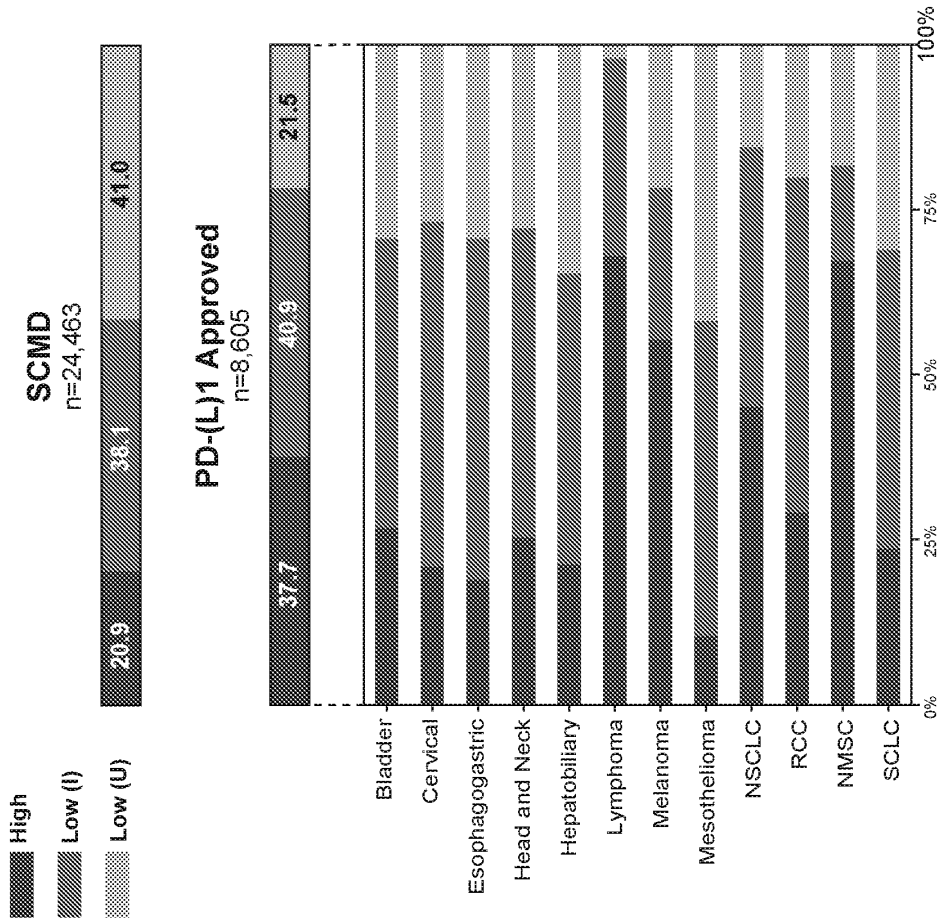


FIG. 57c

FIG. 58a

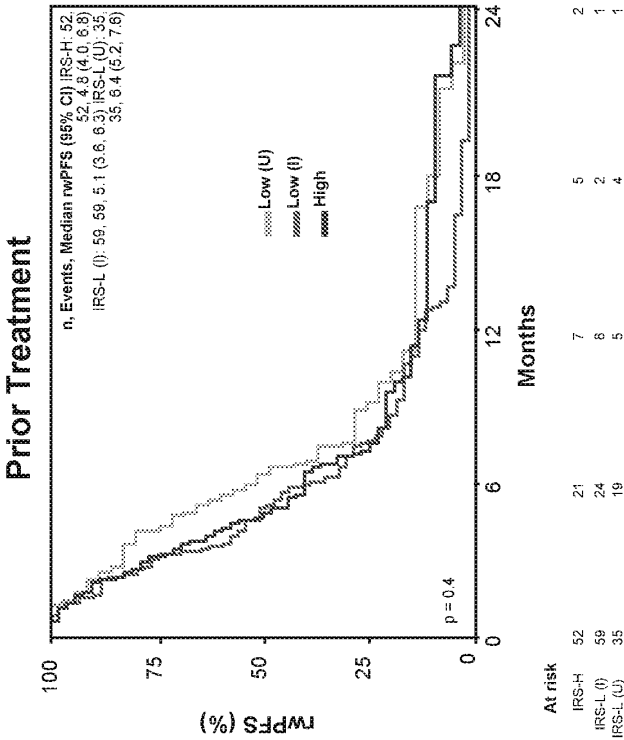
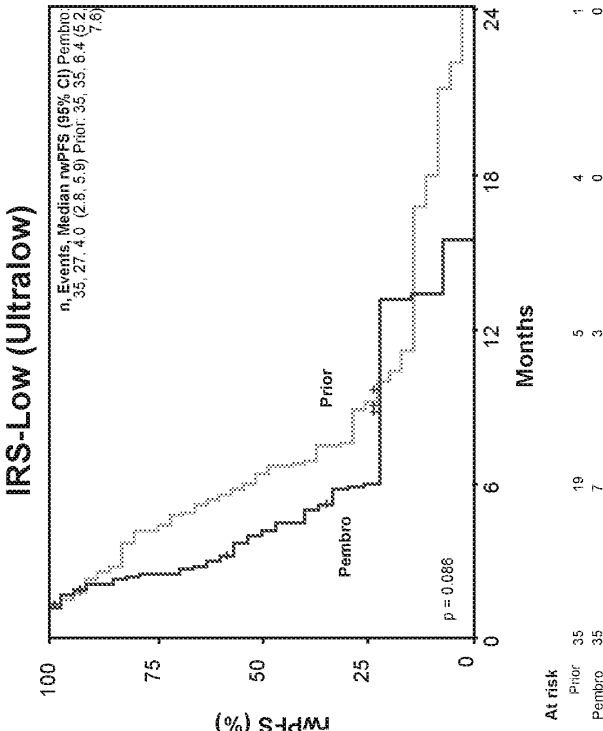


FIG. 58b



FIGS. 58a-b

FIG. 58c

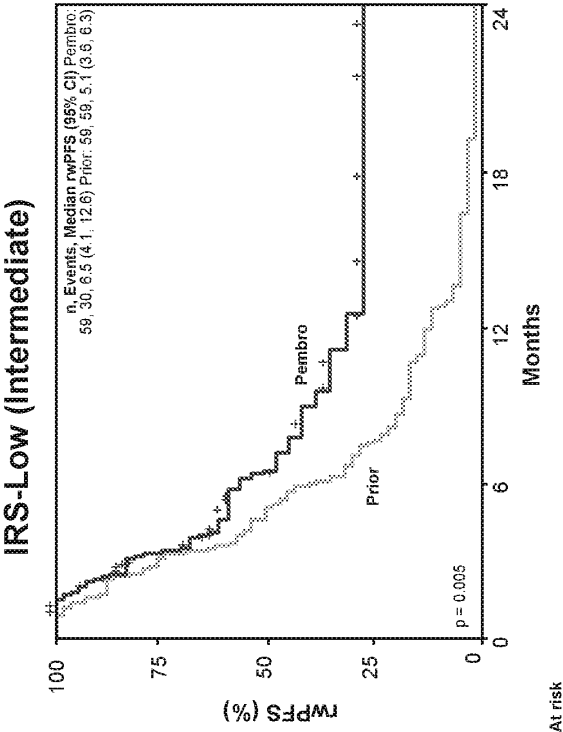
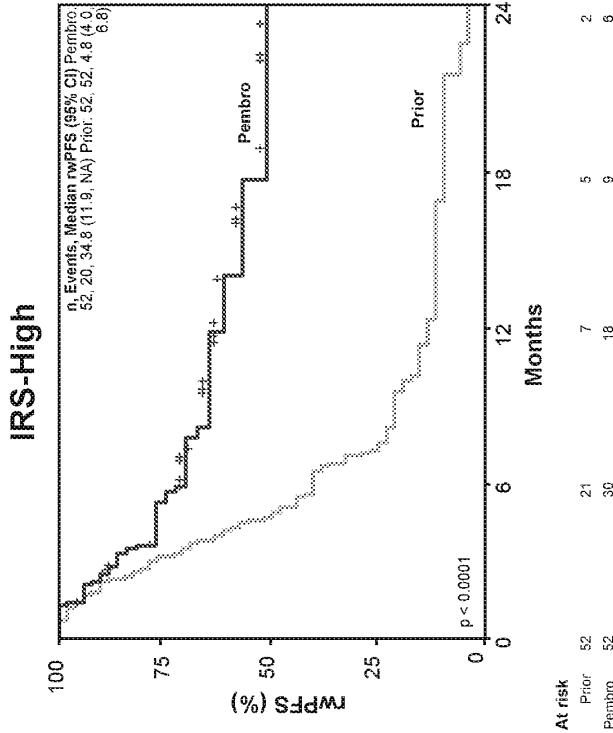


FIG. 58d



FIGS. 58c-d