The Oncologist
The official journal of the Society for Translational Oncology

Supplemental Appendix for:
Immune-Related Adverse Events and Immune Checkpoint Inhibitor Efficacy in Gastrointestinal Cancer Patients with FDA Approved Indications for Immunotherapy

Supplemental Appendices

Appendix S1. Data collection instrument used to gather patient information for study (raw data of each patient is also included)

Appendix S2. Sample size calculation

Appendix S3. Cox proportional-hazards model for analysis, detailing rationale for variable selection

Appendix S4. Time-dependent covariate analysis for IRAE

Appendix S1. Data Collection Instrument Used to Collect Data from Study Patients Along with Raw Data

Record ID	Gender	AGE_IOS	IO	FDA_Ind	Date_IOS	BR	DOBR	IRAE	Num_IRAE	Grade_IRA	Site_IRAE1	Grade_IRA	Site_IRAE2	Grade_IRA	Site_IRAE3	DOS_IRAE1	DOS_IRAE2	DOS_IRAE3	Mgmt_IRA	Mgmt_IRA	Mgmt_IRA	Time_IO	DOP	DO_LV	DOD	DOA	Primary	Side (if CR	COD	COD_notti	MSI-H	Trial	TimetoAE1	Site	LOT_pICI
1	1	63	Nivolumat	1	7/28/2017	SD	12.97	1	2	1	Dermatolc	0	Dermatologic			4/4/2018	4/4/2018		1	0		18.53		2/13/2019		0	HCC					0	250	1	1
2	1	59	Nivolumat	1	6/14/2016	PR	16.9	1	1	1	Muscle					6/28/2017			0			16.8		2/15/2019		0	colon	R			1	1	379	1	2
3	1	59	Nivolumat	1	7/26/2016	SD	16.1	1	1	1	Gastrointestinal					1/24/2017			2			7.3		11/29/2018		0	colon	R			1	0	182	1	5
4	1	63	Nivolumat	1	5/24/2017	SD	7.2	0														20.43	2/14/2018	2/12/2019		0	HCC					0		1	1
5	1	57	Nivolumat	1	10/27/2017	PR	8	1	1	0	Other					8/17/2018			0			14.73		1/18/2019		0	HCC					0	294	1	1
6	1	71	Pembroliz	1	9/1/2017	SD	3.9	0														10.1	5/8/2018	11/14/2018	12/29/2018	1	colon	R			1	0		1	2
7	1	67	Nivolumat	1	11/16/2017	PD		0														5.7	2/6/2018	5/19/2018	6/2/2018	1	HCC		1			0		1	1
8	1	82	Nivolumat	1	4/26/2018	PD		1	1	0	Dermatologic					6/10/2018			0			3.4	6/27/2018	10/11/2018	11/5/2018	1	HCC		1			0	45	1	0
9	1	76	Pembroliz	1	1/2/2018	PD		1	1	0	Dermatologic					2/16/2018			0			3.6	4/20/2018	5/2/2018	6/27/2018	1	gastric/GEJ		1			0	45	1	5
10	1	44	Pembroliz	1	3/19/2018	PD		0														3.4	8/15/2018	10/20/2018	10/31/2018	1	gastric/GEJ		1			0		1	3
11	0	70	Pembroliz	1	3/19/2018	SD	5.03	0														5.03	8/20/2018	8/18/2018	8/20/2018	1	gastric/GEJ		1			1		1	2
12	1	67	Nivolumat	1	1/22/2018	SD	5.2	0														12.66		2/11/2019		0	HCC					0		1	2
13	1	58	Pembroliz	1	1/24/2018	SD	1.2	1	1	0	Endocrine					4/30/2018			1			5.1	6/9/2018	7/13/2018	7/27/2018	1	gastric/GEJ		1			0	96	1	4
14	1	60	Nivolumat	1	1/29/2018	PD		0														4.3	7/30/2018	7/5/2018	7/30/2018	1	HCC		1			0		1	1
15	1	65	Nivolumat	1	2/15/2018	SD		0														9.96	9/12/2018	12/14/2018		0	HCC					0		1	0
16	0	38	Pembroliz	1	2/21/2018	SD	7.5	1	2	0	Dematolo	0	Muscle			4/25/2018	6/6/2018		0	1		9	11/18/2018	1/24/2019		0	colon	R			1	0	63	1	2
17	1	58	Nivolumat	1	5/31/2018			0														0.5	6/7/2018	6/6/2018	6/7/2018	1	gastric/GEJ		1			0		1	2
18	1	66	Nivolumat	1	6/22/2018	SD	5.46	0														6.9		1/18/2019		0	HCC					0		1	0
19	1	69	Nivolumat	1	3/7/2018	SD	5.8	1	1	0	Muscle					3/20/2018			1			10.53	8/30/2018	2/6/2019		0	HCC					0	13	1	1
20	0	75	Nivolumat	1	8/27/2018			0														0.5	9/9/2018	9/5/2018	9/9/2018	1	HCC		1			0		1	0
21	0	71	Nivolumat	1	5/31/2018	PR	4.23	1	1	0	Muscle					8/6/2018			0			7.8		1/24/2019		0	colon	T			1	0	67	1	0
22	1	45	Pembroliz	1	8/13/2017	PD		0														5.03	11/9/2017	2/1/2018	2/21/2018	1	colon	T	1		1	0		1	2
23	1	74	Pembroliz	1	5/8/2018	SD	4.9	1	1	0	Dermatologic					5/29/2018			0			8.7		1/29/2019		0	gastric/GEJ					0	21	1	2
24	1	59	Nivolumat	1	6/27/2018	PD		0														0.43	7/21/2018	9/4/2018	9/10/2018	1	HCC		1			0		1	1
31	0	26	Nivolumat	1	1/23/2017	SD	4.3	0														7.93	10/7/2017	1/28/2019		0	HCC					0		1	1
32	0	55	Nivolumat	1	8/29/2018			0														1.03	9/30/2018	9/26/2018	9/30/2018	1	HCC		0	cardiac arrest		0		1	0
35	1	66	Nivolumat	1	6/22/2018	SD	3.66	1	1	0	Endocrine					7/20/2018			0			6.9		1/18/2019		0	HCC					0	28	1	0
36	1	67	Nivolumat	1	8/23/2018			0														1	12/31/2018	10/30/2018	12/31/2018	0	HCC					0		1	1
37	0	88	Nivolumat	1	3/29/2018	PD		0														0.93	5/15/2018	5/19/2018		0	colon	R			1	0		2	0
38	1	83	Nivolumat	1	1/11/2017	PD		0														1.4	3/1/2017	3/4/2017		0	colon	R			1	0		2	0
39	1	57	Pembroliz	1	5/22/2018	PD		0														2.9	7/10/2018	9/4/2018	9/11/2018	1	colon	R	1		1	0		2	5
40	0	82	Pembroliz	1	5/23/2018	PR	3.1	1	2	1	Endocrine	0	Endocrine			7/27/2018			0	0		3.1		10/17/2018		0	colon	R			1	0	65	2	1
41	0	75	Pembroliz	1	11/2/2017	PR	9	0														9		10/5/2018		0	colon	R			1	0		2	0
42	1	53	Nivolumat	1	2/5/2018	PR	5.3	0														8.1		10/8/2018		0	colon	R			1	0		2	1
43	1	30	Pembroliz	1	6/9/2017	PR	12.8	0														16.1		10/12/2018		0	colon	R			1	0		2	3
44	0	81	Nivolumat	1	5/3/2018	SD	3.3	0														2.5	9/27/2018	10/18/2018		0	colon	R			1	0		2	1
45	1	61	Nivolumat	1	3/12/2018	PR	1.7	0														7		10/12/2018		0	colon	L			1	0		2	1
46	0	46	Nivolumat	1	10/11/2014	SD	47.1	1	1	1	Endocrine					7/7/2015			1			43.5		10/17/2018		0	colon	R			1	1	269	2	4
47	1	60	Nivolumat	1	8/8/2016	PR	24.4	1	1	0	Endocrine					5/23/2018			0			26.1		10/10/2018		0	colon	R			1	1	653	2	1
48	0	79	Pembroliz	1	4/18/2018	PR	4.57	1	1	0	Dermatologic		Muscle	0		7/11/2018	1/16/2019		1	2		8.26		1/16/2019		0	colon	R			1	0	65	1	0
49	1	34	Pembroliz	1	8/28/2017	CR	11.03	1	2	1	Muscle	0	Endocrine			10/23/2017	10/23/2017		2	0		1.33		12/10/2018		0	colon	R			1	0	56	1	2
50	1	62	Pembroliz	1	12/5/2016	SD	23.37	1	1	0	Muscle					6/21/2018			0			23.37		11/15/2018		0	colon	L			1	0	563	3	3
51	0	76	Pembroliz	1	9/1/2016	PR	25.89	1	1	0	Dermatologic					1/9/2017			0			23.98		10/29/2018		0	colon	T			1	1	130	3	2
52	0	53	Pembroliz	1	10/17/2016	SD	25.07	1	2	0	Other	0	Muscle			1/30/2017	9/7/2017		0	2		19.48		11/19/2018		0	colon	T			1	0	105	3	1
53	0	47	Pembroliz	1	4/14/2015	CR	32.39	1	3	0	Endocrine	0	Muscle	1	Cardiac	9/8/2015	8/30/2016	12/18/2017	0	0	1	23.46	12/25/2017	12/23/2017	12/25/2017	1	colon	R	0	myocarditi	1	1	147	3	4
54	1	51	Pembroliz	1	2/2/2017	CR	21.68	1	2	0	Other	0	Dermatolc	0		5/17/2017	6/8/2017		0	0		22.31		11/24/2018		0	colon	T			1	0	104	3	1
55	1	63	Pembroliz	1	7/12/2017			0											0			0	8/4/2017	8/4/2017	8/4/2017	1	colon	R	1		1	0		3	1
56	1	49	Nivolumat	1	9/7/2017	PR	13.8	1	1	0	Renal					9/29/2017			2			13.87		11/1/2018		0	HCC					0	22	3	2
57	0	65	Nivolumat	1	4/18/2017	SD	3.25	0														3	7/26/2017	12/24/2018	1/3/2018	1	HCC		1			0		3	2
58	1	67	Nivolumat	1	12/15/2017	SD	6.44	0														6.63	6/29/2018	11/5/2018		0	HCC					0		3	1
59	1	60	Nivolumat	1	9/12/2016	SD	5.16	1	1	0	Gastrointestinal					2/9/2017			2			4.4	2/16/2017	5/11/2017		0	HCC					0	150	3	1
60	1	69	Nivolumat	1	12/20/2016			0														0		1/26/2017		0	HCC					0		3	1
61	1	49	Pembroliz	1	9/29/2015	CR	25.53	1	2	0	Muscle	0	Other			10/11/2016	10/25/2016		0	0		21.13		11/14/2017		0	colon	T			1	1	378	3	3
62	1	64	Nivolumat	1	10/30/2017	SD	10.25	0														12.98	9/7/2018	11/25/2018		0	HCC					0		3	2
63	1	62	Nivolumat	1	7/12/2017	PR	16.53	0														16.53		11/27/2018		0	HCC					0		3	1
64	1	83	Nivolumat	1	10/24/2017			0														0	10/27/2017	10/25/2017	10/27/2017	1	HCC		1			0		3	1
65	1	71	Nivolumat	1	7/14/2017	SD	2	0														2.3	9/13/2017	10/20/2017		0	HCC					0		3	1
66	1	66	Nivolumat	1	9/11/2017	SD	2.17	0														1.73	11/16/2017	5/30/2018		0	HCC					0		3	2
67	0	66	Nivolumat	1	5/1/2017	PR	3.94	0														3.71	8/29/2017	9/29/2017	10/4/2017	1	HCC		1			0		3	1
68	1	59	Nivolumat	1	4/5/2017	SD	3.52	0														1.84	7/21/2017	7/21/2017	8/4/2017	1	HCC		1			0		3	5
69	0	46	Pembroliz	1	1/31/2017	SD	2.3	0														0.69	4/11/2017	4/11/2017	5/6/2017	1	rectal	L	1		1	0		3	2
70	1	54	Pembroliz	1	7/11/2014	SD	35.03	1	1	0	Endocrine					11/24/2014			0			23.6		1/8/2019		0	duodenal				1	1	136	3	3
72	1	48	Pembroliz	1	7/28/2015	PR	35	1	1	0	Gastrointestinal					9/14/2015			0			39.57		1/2/2019		0	colon	R			1	1	48	3	3
73	1	49	Pembroliz	1	9/29/2015	PR	22.37	1	2	0	Dermatolc	0	Muscle			8/30/2016	7/5/2016		0	0		23.43		1/8/2019		0	colon	T			1	1	336	3	3
74	1	61	Pembroliz	1	1/28/2016	PR	32.43	1	3	1	Endocrine	1	Cardiac	0	Gastrointe	11/20/2016	11/21/2016	3/4/2017	1	1	1	9.04		1/3/2019		0	poorly differentiated NEC of the colon				1	1	297	3	1
75	0	68	Pembroliz	1	2/16/2016	SD	33.03	1	1	1	Dermatological					1/4/2019			1			35.2		1/25/2019		0	biliary				1	1	1053	3	1
76	1	48	Pembroliz	1	5/24/2016	PR	22.33	1	1	1	Endocrine					4/17/2017			1			10.6		1/2/2019		0	pancreas				1	1	328	3	4
77	0	75	Pembroliz	1	8/22/2016	PR	19.53	0														24		12/6/2018		0	colon	R			1	1		3	1
78	0	58	Pembroliz	1	1/27/2017	SD	20.07	1	1	0	Gastrointestinal					6/28/2018			0			17.03		1/3/2019		0	pancreas				1	0	517	3	3
79	1	69	Pembroliz	1	1/10/2018	SD	8.87	0														12.67		1/30/2019		0	pancreas				1	0		3	1
80	1	79	Nivolumat	1	12/14/2018	SD	1.03	0														1.03	2/6/2019	1/15/2019	2/6/2019	0	HCC					0		1	1
81	0	61	Nivolumat	1	11/21/2018			0														0.43	12/16/2018	12/4/2018	12/16/2018	1	HCC					0		1	1
82	1	74	Nivolumat	1	12/20/2018			0														0.47	1/15/2019	1/12/2019	1/15/2019	1	HCC					0		1	0
83	1	62	Nivolumat	1	1/7/2019			1	1	0	Muscle					1/22/2019			0			0.996		2/5/2019		0	HCC					0	15	1	0
84	0	41	Nivolumat	1	1/5/2016	CR	18.6	1	2	0	Dermatologic		Muscle	0		2/1/2016	3/14/2016		0	0		24.1		1/21/2019		0	CRC	R			1	1	27	1	0
85	1	69	Pembroliz	1	11/14/2018	PD		0														0.66	12/18/2018	1/24/2019		0	gastric/GEJ				0	0		1	1
86	0	47	Nivolumat	1	11/29/2018	SD	1.2	0														1.4		2/11/2019		0	gastric/GEJ				0	0		1	2
87	1	71	Pembroliz	1	7/6/2018	PD		0														0.6	8/17/2018	8/22/2018	8/23/2018	1	gastric/GEJ					0		1	2

*Please note patients 45 and 47 were excluded from the analysis given patients received nivolumab plus ipilimumab.

Abbreviations: FDA_Ind, FDA approved indication; Date_IOS, date of immunotherapy start; DOBR, duration of best response; Num_IRAE, number of IRAEs; DOS_IRAE1, date of IRAE1; Mgmt_IRAE1, management of IRAE1; DOP, date of progression; DO_LV, date of last visit; DOA, dead (1) or alive (0); COD, cause of death; MSI, microsatellite unstable (1); TimetoAE1, time to adverse event (days); Site, institution where patient was enrolled (1= VICC, 2 = WCE, 3 = SCI); LOT_pICI, lines of therapy prior to ICI.

Appendix S2. Sample size calculation

6.1 Primary endpoint: PFS

- PS (Power and Sample Size Calculation) software is used.
- type I error rate = 0.05, power = 0.8
- Medina survival of non-IRAE = 3.5 (months)
- Accrual time = 0
- Additional follow-up time = 24 (months)
- Allocation ratio = 1

Table 6: Required sample sizes (HR = 0.126 in this study)

	HR of IRAE to non-IRAE				
	0.1	0.2	0.3	0.4	0.5
IRAEyes	3	6	11	19	33
IRAEno	3	6	11	19	33
total	6	12	22	38	66

Appendix S3.

Cox Proportional-Hazards Model for Analysis, PFS

The elastic net method (function *glmnet* in R package *glmpath*) is used for variable selection in Cox regression model. The estimated hazard ratios and 95% confidence intervals of the selected model for PFS are shown in Table 4.

```
## Call:
## coxph(formula = Surv(TTP_Mon, status_P) ~ IRAE + Trial + bcolorectal +
##     bHCC + Site1 + AGE_IOS, data = data_all3)
##
##                 coef exp(coef) se(coef)      z       p
## IRAEyes     -1.73183   0.17696  0.46716 -3.707 0.00021
## Trial       -1.83888   0.15900  1.03983 -1.768 0.07699
## bcolorectal -0.43973   0.64421  0.50047 -0.879 0.37961
## bHCC        -0.22177   0.80110  0.45641 -0.486 0.62704
## Site1        0.56380   1.75734  0.34852  1.618 0.10572
## AGE_IOS      0.02696   1.02733  0.01484  1.817 0.06922
##
## Likelihood ratio test=44.24  on 6 df, p=0.00000006617
## n= 76, number of events= 40
```

Table 4: Estimated hazard ratios (HR) and confidence intervals in the selected model for PFS

	HR	HR_CI95_low	HR_CI95_up	p.value
IRAE (yes vs. no)	0.1770	0.0708	0.4421	0.0002
Trial (yes vs. no)	0.1590	0.0207	1.2204	0.0770
Colorectal (yes vs. no)	0.6442	0.2416	1.7181	0.3796
HCC (yes vs. no)	0.8011	0.3275	1.9597	0.6270
Site1 (yes vs. no)	1.7573	0.8875	3.4795	0.1057
AGE_IOS	1.0273	0.9979	1.0576	0.0692

Cox Proportional-Hazards Model for Analysis, OS

Similarly, the estimated hazard ratios and 95% confidence intervals of the selected model for OS are shown in Table 5.

```
## Call:
## coxph(formula = Surv(TTD_Mon, status_D) ~ IRAE + Site1 + Trial +
##     bcolorectal + AGE_IOS, data = data_all3)
##
##                 coef exp(coef) se(coef)      z       p
## IRAEyes     -2.01290   0.13360  0.63234 -3.183 0.00146
## Site1        0.98319   2.67296  0.45120  2.179 0.02933
## Trial       -0.87675   0.41613  1.04857 -0.836 0.40308
## bcolorectal -0.26379   0.76814  0.48878 -0.540 0.58942
## AGE_IOS      0.02776   1.02815  0.01861  1.491 0.13583
##
## Likelihood ratio test=30.43  on 5 df, p=0.00001216
## n= 76, number of events= 26
```

Table 5: Estimated hazard ratios (HR) and confidence intervals in the selected model for OS

	HR	HR_CI95_low	HR_CI95_up	p.value
IRAE (yes vs. no)	0.1336	0.0387	0.4614	0.0015
Site1 (yes vs. no)	2.6730	1.1039	6.4723	0.0293
Trial (yes vs. no)	0.4161	0.0533	3.2494	0.4031
Colorectal (yes vs. no)	0.7681	0.2947	2.0022	0.5894
AGE_IOS	1.0282	0.9913	1.0664	0.1358

Appendix S4. Time-dependent covariate analysis for IRAE (PFS)

IRAE as a step function with values 0 and 1.

```
## Call:
## coxph(formula = Surv(TTP_Mon0, TTP_Mon, status_P) ~ IRAE1.varyP +
##     Trial + bcolorectal + bHCC + Site1 + AGE_IOS, data = SURV2)
##
##                 coef exp(coef) se(coef)      z      p
## IRAE1.varyP -0.55356   0.57490  0.45580 -1.214 0.2246
## Trial       -2.29360   0.10090  1.04285 -2.199 0.0279
## bcolorectal -0.45350   0.63540  0.49899 -0.909 0.3634
## bHCC         0.12341   1.13135  0.45616  0.271 0.7867
## Site1        0.33833   1.40260  0.34778  0.973 0.3306
## AGE_IOS      0.02924   1.02968  0.01560  1.875 0.0608
##
## Likelihood ratio test=27.76  on 6 df, p=0.0001045
## n= 1763, number of events= 40
```

Table 7: Estimated hazard ratios (HR) and confidence intervals in the selected model for PFS

	HR	HR_CI95_low	HR_CI95_up	p.value
IRAE (yes vs. no)	0.5749	0.2353	1.4047	0.2246
Trial (yes vs. no)	0.1009	0.0131	0.7791	0.0279
Colorectal (yes vs. no)	0.6354	0.2389	1.6896	0.3634
HCC (yes vs. no)	1.1313	0.4627	2.7662	0.7867
Site1 (yes vs. no)	1.4026	0.7094	2.7731	0.3306

IRAE as a step function with values 0, 1, 2 and 3.

```
## Call:
## coxph(formula = Surv(TTP_Mon0, TTP_Mon, status_P) ~ IRAE.varyP +
##     Trial + bcolorectal + bHCC + Site1 + AGE_IOS, data = SURV2)
##
##                 coef exp(coef) se(coef)      z      p
## IRAE.varyP  -0.22089   0.80180  0.34510 -0.640 0.5221
## Trial       -2.27258   0.10305  1.04375 -2.177 0.0295
## bcolorectal -0.44795   0.63894  0.49972 -0.896 0.3700
## bHCC         0.17314   1.18903  0.45290  0.382 0.7022
## Site1        0.28503   1.32980  0.34693  0.822 0.4113
## AGE_IOS      0.02782   1.02821  0.01549  1.796 0.0725
##
## Likelihood ratio test=26.58  on 6 df, p=0.0001736
## n= 1763, number of events= 40
```

Table 8: Estimated hazard ratios (HR) and confidence intervals in the selected model for PFS

	HR	HR_CI95_low	HR_CI95_up	p.value
IRAE (yes vs. no)	0.8018	0.4077	1.5770	0.5221
Trial (yes vs. no)	0.1030	0.0133	0.7971	0.0295
Colorectal (yes vs. no)	0.6389	0.2399	1.7015	0.3700
HCC (yes vs. no)	1.1890	0.4894	2.8888	0.7022
Site1 (yes vs. no)	1.3298	0.6737	2.6248	0.4113
AGE_IOS	1.0282	0.9975	1.0599	0.0725

Time-dependent covariate analysis for IRAE (OS)

IRAE as a step function with values 0 and 1.

```
## Call:
## coxph(formula = Surv(TTD_Mon0, TTD_Mon, status_D) ~ IRAE1.varyD +
##     Site1 + Trial + bcolorectal + AGE_IOS, data = SURV3)
##
##                 coef exp(coef) se(coef)      z      p
## IRAE1.varyD -0.97879   0.37577  0.59147 -1.655 0.0980
## Site1        0.86489   2.37473  0.45854  1.886 0.0593
## Trial       -1.53919   0.21456  1.04803 -1.469 0.1419
## bcolorectal -0.44422   0.64132  0.48170 -0.922 0.3564
## AGE_IOS      0.02640   1.02675  0.01877  1.407 0.1595
##
## Likelihood ratio test=18.52  on 5 df, p=0.002356
## n= 1274, number of events= 26
```

Table 9: Estimated hazard ratios (HR) and confidence intervals in the selected model for OS

	HR	HR_CI95_low	HR_CI95_up	p.value
IRAE (yes vs. no)	0.3758	0.1179	1.1978	0.0980
Site1 (yes vs. no)	2.3747	0.9667	5.8335	0.0593
Trial (yes vs. no)	0.2146	0.0275	1.6736	0.1419
Colorectal (yes vs. no)	0.6413	0.2495	1.6486	0.3564
AGE_IOS	1.0268	0.9897	1.0652	0.1595

IRAE as a step function with values 0, 1, 2 and 3.

```
## Call:
## coxph(formula = Surv(TTD_Mon0, TTD_Mon, status_D) ~ IRAE.varyD +
##     Site1 + Trial + bcolorectal + AGE_IOS, data = SURV3)
##
##                 coef exp(coef) se(coef)      z      p
## IRAE.varyD  -0.50809   0.60165  0.44308 -1.147 0.2515
## Site1        0.80652   2.24010  0.46004  1.753 0.0796
## Trial       -1.54755   0.21277  1.05118 -1.472 0.1410
## bcolorectal -0.47435   0.62229  0.48414 -0.980 0.3272
## AGE_IOS      0.02282   1.02308  0.01830  1.247 0.2124
##
## Likelihood ratio test=16.81  on 5 df, p=0.004867
## n= 1274, number of events= 26
```

Table 10: Estimated hazard ratios (HR) and confidence intervals in the selected model for OS

	HR	HR_CI95_low	HR_CI95_up	p.value
IRAE (yes vs. no)	0.6016	0.2525	1.4338	0.2515
Site1 (yes vs. no)	2.2401	0.9092	5.5190	0.0796
Trial (yes vs. no)	0.2128	0.0271	1.6699	0.1410
Colorectal (yes vs. no)	0.6223	0.2409	1.6073	0.3272
AGE_IOS	1.0231	0.9870	1.0604	0.2124