Supplementary Online Content

Xing M, Alzahrani AS, Carson CA, et al. Association between *BRAF* V600E mutation and mortality in patients with papillary thyroid cancer. *JAMA*. doi:10.1001/jama.2013.3190

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Radioiodine-131 Treatment Doses (mCi; median, interquartile range) by *BRAF* V600E Mutation Status and by Center and Country

Medical Center or Country		Number of Patients	BRAF+	BRAF-	*P* value
Medical Center	Johns Hopkins Hospital	387	76 (0-100)	30 (0-100)	0.03
	University of Pittsburgh	162	135 (106-161)	105 (0-134)	<0.001
	Memorial Sloan-Kettering Cancer Center	90	104 (30-197)	75 (0-150)	0.05
	University of Pisa	189	30 (30-30)	30 (30-30)	0.60
	University of Perugia	117	100 (50-100)	100 (50-100)	0.37
	University of Milan	110	80 (50-80)	50 (0-80)	0.07
	University of Padua	135	100 (100-150)	100 (100-150)	0.57
	Kanagawa Cancer Center	49	0 (0-0)	0 (0-0)	1.0
	MSC Memorial Cancer Centre and Institute of Oncology	98	100 (100-100)	100 (100-100)	0.84
	Griffith Medical School	(76)	-	-	-
	University of Sydney	84	143 (108-162)	162 (135-270)	0.26
	Hospital La Paz, Health Research Institute (IdiPAZ)	66	120 (100-150)	100 (100-150)	0.13
	Institute of Endocrinology, Prague	221	100 (0-102)	100 (0-119)	0.93
Country	USA	639	100 (0-137)	52 (0-103)	<0.001
	Italy	551	100 (30-100)	50 (30-100)	<0.001
	Japan	49	0 (0-0)	0 (0-0)	1.0
	Poland	98	100 (100-100)	100 (100-100)	0.84
	Australia	84	143 (108-162)	162 (135-270)	0.26
	Spain	66	120 (100-150)	100 (100-150)	0.13
	Czech Republic	221	100 (0-102)	100 (0-119)	0.93
Overall		1,708	100 (30-110)	80 (0-100)	<0.001

Notes: Some of the total case numbers are smaller than those for the corresponding centers in Table 1 due to some cases missing the information on radioiodine treatment. None of the 76 patients from the Medical Center of Griffith Medical School in Australia had available information on radioiodine treatment. Overall, 92.4% (1,708/1,849) patients had information available on radioiodine treatment.

eTable 2. Interactions of *BRAF* V600E With Conventional Risk Factors of Papillary Thyroid Cancer—Synergy Test

Risk factor tested for interaction with $BRAF^{V600E}$	Synergy Index	95% Confidence Interval
Lymph node metastasis	4.46	1.76-11.32
Extrathyroidal invasion	1.59	0.84-3.02
Distant metastasis	4.60	1.90-11.14
Stage IV disease	2.93	1.39-6.19
Patient age $\geq$ 45 years	3.15	1.37-7.27
Patient age $\geq$ 60 years	3.40	1.52-7.62

Notes: 1) A Synergy Index (SI) different than 1 is evidence of significant interaction. An SI > 1 is evidence of synergism and an SI < 1 is evidence of antagonism. All measures except for extrathyroidal extension show a statistically significant synergistic effect in an additive model. 2) Reference for the test method: Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology* 1992;3:452-6 (Ref #30 in the text).

eTable 3. Papillary Thyroid Cancer (PTC)-Related Mortality and Relative Risks (RR) in *BRAF* V600E Mutation-Positive vs -Negative Patients in Various Clinicopathological Categories of Conventional PTC

Category		Mortality-Percent Rate			Person Years	Deaths per 1000 Person Years		
		BRAF+, n/N (%)	BRAF –, n/N (%)	P value		BRAF+	BRAF-	RR (95% CI)
All Conventional PTC patients		33/659 (5.0)	6/574 (1.0)	<0.001	5466.75	11.80 (8.39-16.60)	2.25 (1.01-5.00)	5.25 (2.20-12.54)
Age < 45 yrs		5/280 (1.8)	0/308 (0)	0.02	2795.67	3.77 (1.57-9.06)	0	-
Age ≥ 45 yrs		28/379 (7.4)	6/266 (2.3)	0.004	2671.08	19.04 (13.15-27.58)	5.00 (2.25-11.12)	3.81 (1.58-9.20)
Age< 60 yrs		12/483 (2.5)	1/469 (0.2)	0.003	4439.25	5.54 (3.15-9.76)	0.44 (0.06-3.12)	12.61 (1.64-97.01)
Age ≥ 60 yrs		21/176 (11.9)	5/105 (4.8)	0.06	1027.50	33.22 (21.66-50.96)	12.64 (5.26-30.38)	2.63 (0.99-6.97)
Lymph node metastasis	No	2/326 (0.6)	2/337 (0.6)	1.0	2862.33	1.56 (0.39-6.25)	1.26 (0.32-5.05)	1.24 (0.17-8.78)
	Yes	29/277 (10.5)	4/204 (2.0)	<0.001	2181.42	22.96 (15.96-33.04)	4.35 (1.63-11.60)	5.27 (1.85-15.00)
Extrathyroidal invasion	No	8/402 (2.0)	1/424 (0.2)	0.02	3983.33	4.25 (2.13-8.51)	0.48 (0.07-3.38)	8.94 (1.12-71.50)
	Yes	24/250 (9.6)	5/144 (3.5)	0.03	1449.33	26.59 (17.82-39.67)	9.15 (3.81-21.97)	2.91 (1.11-7.62)
Distant metastasis	No	9/607 (1.5)	2/548 (0.4)	0.07	5041.92	3.61 (1.88-6.94)	0.78 (0.20-3.14)	4.60 (0.99-21.29)
	Yes	24/49 (49.0)	4/21 (19.0)	0.03	415.08	79.27 (53.13-118.27)	35.61 (13.36-94.88)	2.23 (0.77-6.42)
Multifocality	No	21/383 (5.5)	5/358 (1.4)	0.002	3423.00	12.42 (8.10-19.05)	2.89 (1.20-6.93)	4.31 (1.62-11.42)
	Yes	11/272 (4.0)	1/208 (0.5)	0.02	1971.92	10.05 (5.56-18.14)	1.14 (0.16-8.10)	8.81 (1.14-68.24)
Stage IV disease	No	4/550 (0.7)	0/508 (0)	0.13	4695.92	1.72 (0.65-4.58)	0	-
	Yes	28/92 (30.4)	6/48 (12.5)	0.02	611.92	68.33 (47.18-98.97)	29.68 (13.33-66.06)	2.30 (0.95-5.56)
Stage I		1/361 (0.3)	0/400 (0)	0.47	3476.92	0.62 (0.09-4.42)	0	-
Stage II		0/55 (0)	0/49 (0)	-	462.25	0	0	-
Stage III		3/134 (2.2)	0/59 (0)	0.55	756.75	5.77 (1.86-18.88)	0	-
Tumor ≤1.0 cm		2/136 (1.5)	0/201 (0)	0.16	1397.50	3.94 (0.99-15.75)	0	-
Tumor 1.0- 2.0 cm		4/319 (1.2)	2/251 (0.8)	0.70	2619.25	2.95 (1.11-7.86)	1.58 (0.40-6.33)	1.86 (0.34-10.18)
Tumor 2.0-3.0 cm		12/183 (6.6)	1/116 (0.9)	0.02	1416.17	15.48 (8.79-27.25)	1.56 (0.22-11.08)	9.92 (1.29-76.26)
Tumor 3.0-4.0 cm		8/89 (9.0)	1/57 (1.8)	0.09	682.92	21.41 (10.71-42.82)	3.23 (0.46-22.95)	6.62 (0.83-52.96)
Tumor ≥ 4.0 cm		6/66 (9.1)	2/60 (3.3)	0.28	642.17	18.62 (8.37-41.46)	6.25 (1.56-24.99)	2.98 (0.60-14.76)