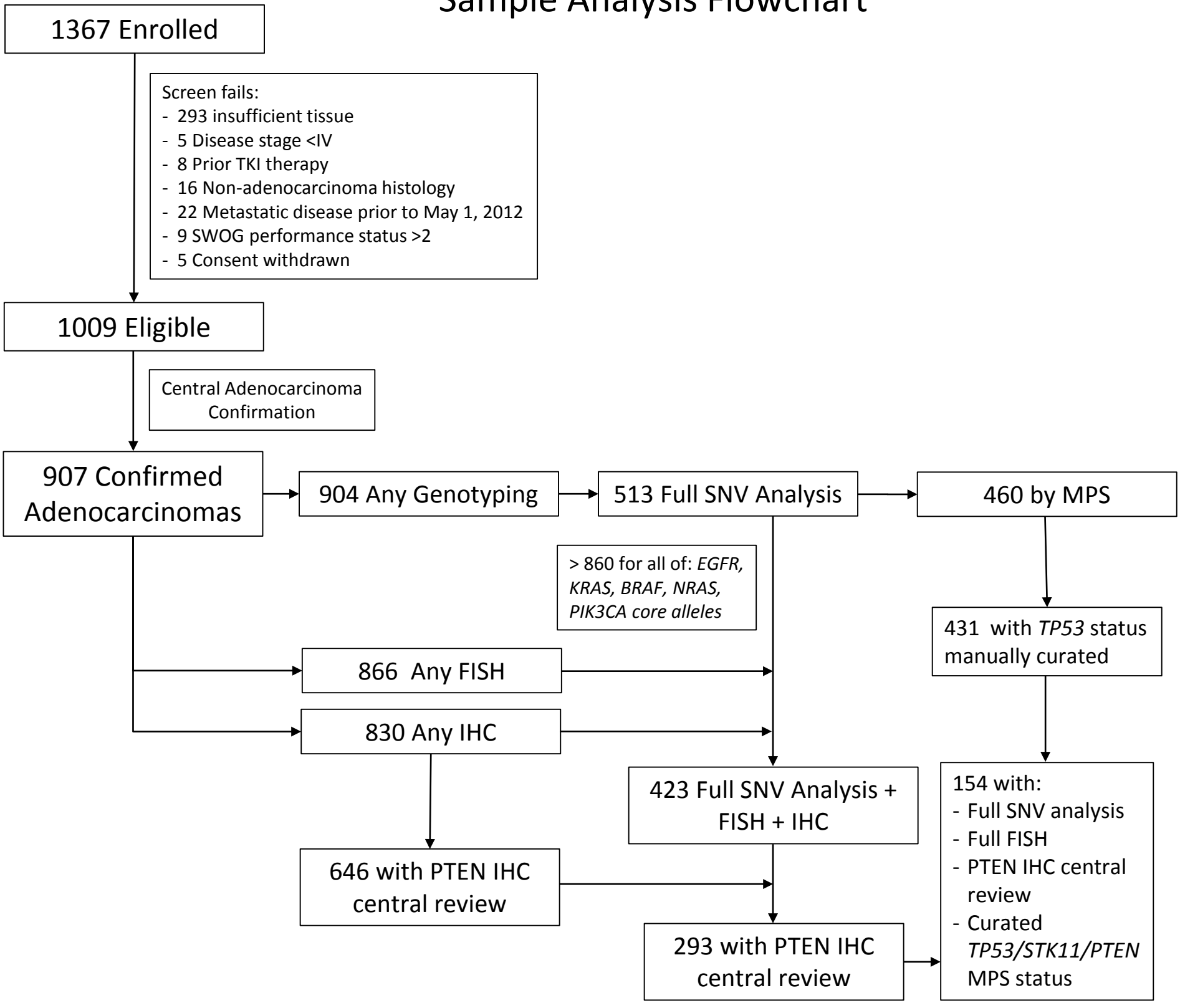
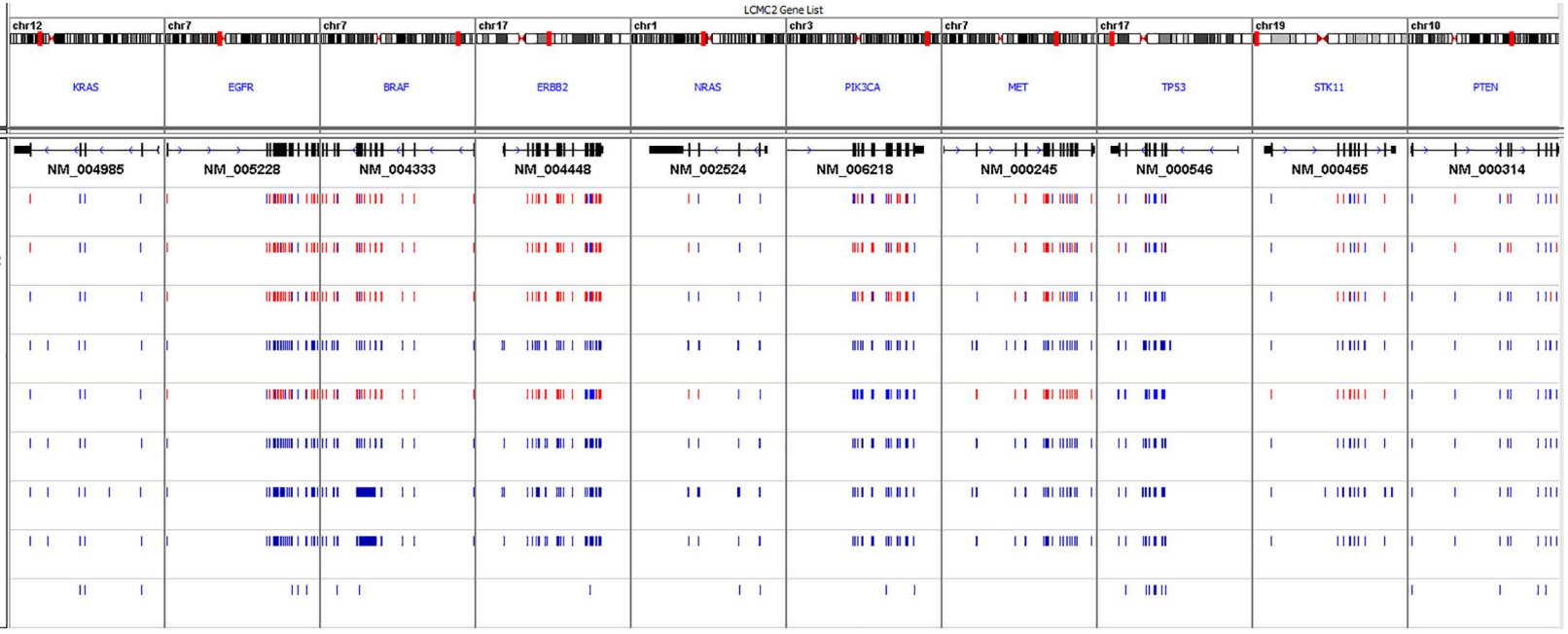
Supplemental Figure 1

Sample Analysis Flowchart

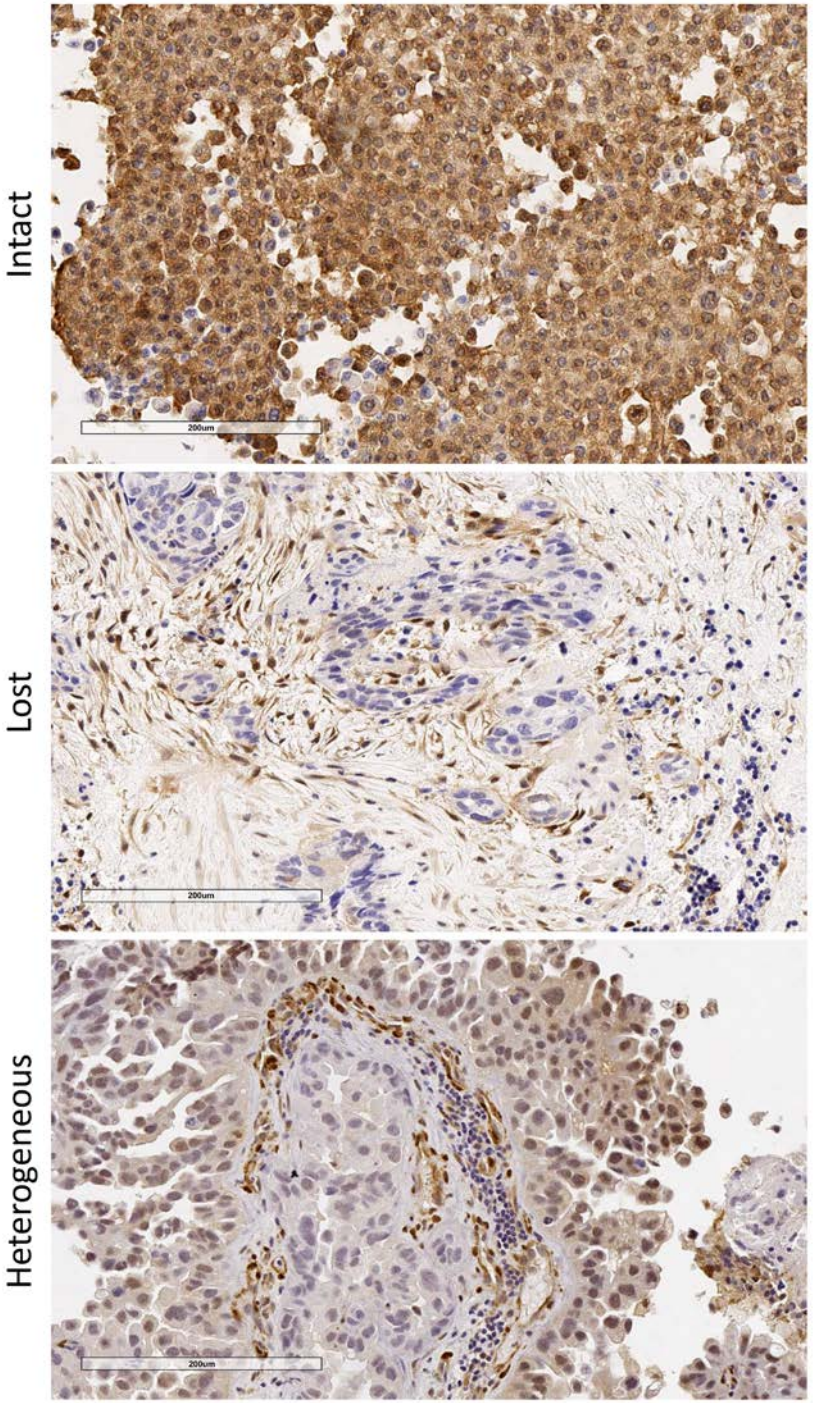


Supplemental Figure 2

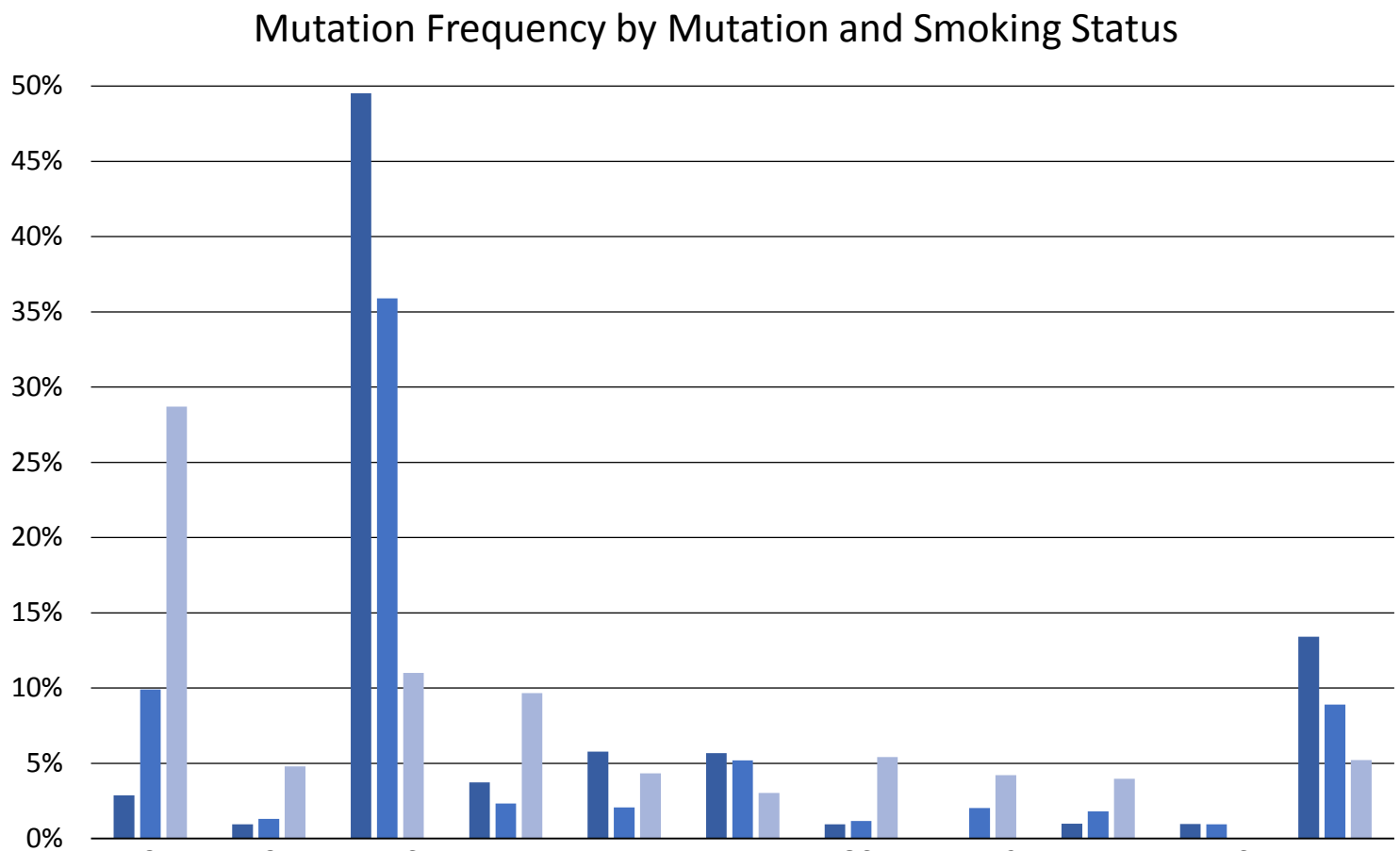


Supplemental Figure 3

PTEN Immunohistochemistry analysis of LCMC II samples.

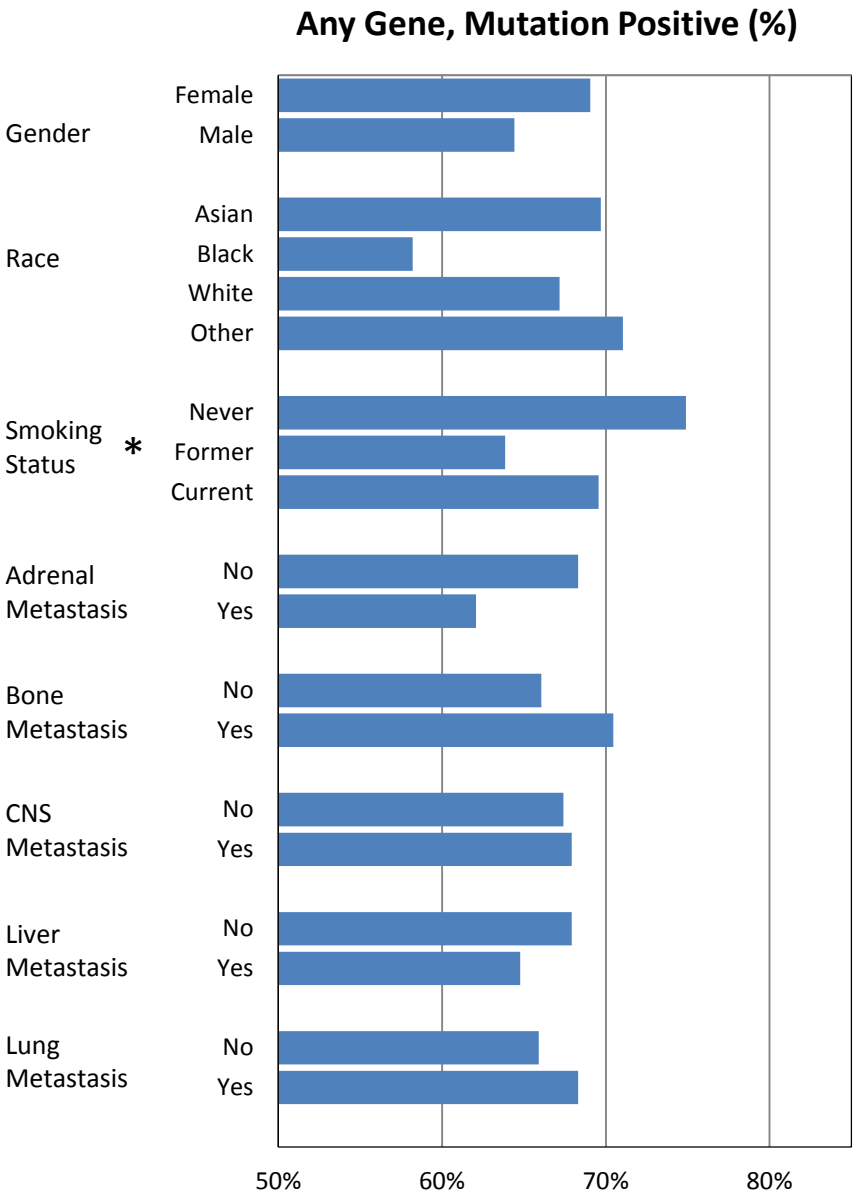


Supplemental Figure 4



	sEGFR	oEGFR	KRAS	ALKr	veBRAF	METamp	ROS1r	ERBB2	RETr	NRAS	PTEN
Current Smoker (n = 115)	2.9%	1.0%	49.5%	3.7%	5.8%	5.7%	1.0%	0.0%	1.0%	1.0%	13.4%
Former Smoker (n = 556)	9.9%	1.3%	35.9%	2.3%	2.1%	5.2%	1.2%	2.0%	1.8%	0.9%	8.9%
Never Smoker (n= 219)	28.7%	4.8%	11.0%	9.7%	4.3%	3.0%	5.4%	4.2%	4.0%	0.0%	5.2%
P value	<0.001	0.009	<0.001	<0.001	0.064	0.488	0.001	0.099	0.14	0.374	0.058

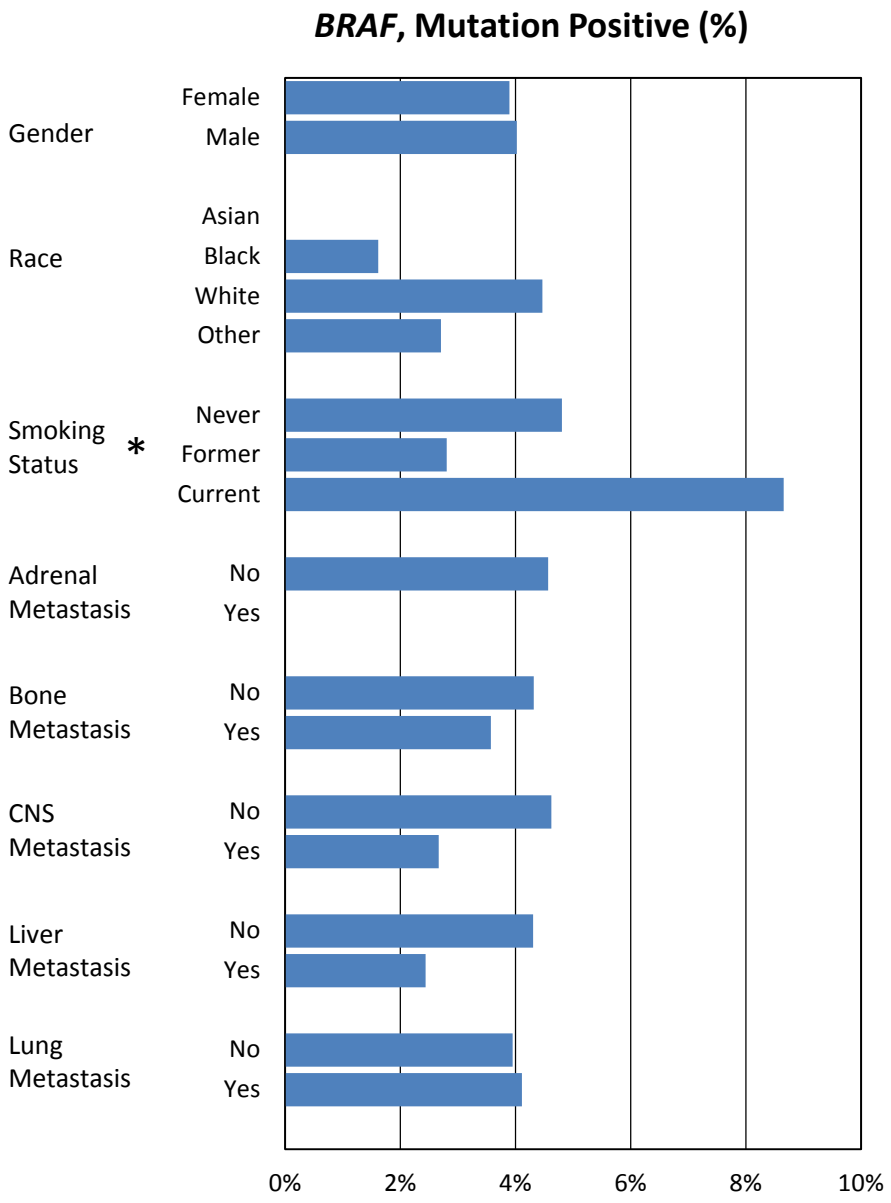
Supplemental Figure 5



Gene: Any* (n=944)**

Variable	N	WT (n=299)	Mut (n=605)	P
Sex	904			0.14
Female		51% (151)	56% (337)	
Male		49% (148)	44% (268)	
Race	904			0.27
Amer Indian/Alaska Native		0% (0)	0% (3)	
Asian		3% (10)	4% (23)	
Black/African American		9% (28)	6% (39)	
Native Hawaii/Pacific Isl.		0% (1)	0% (0)	
White		80% (239)	81% (489)	
Not disclosed		7% (21)	8% (51)	
Smoker	890			**0.01**
Current		12% (35)	13% (80)	
Former		69% (201)	59% (355)	
Never		19% (55)	27% (164)	
Stage at diagnosis	887			0.06
I		12% (36)	8% (49)	
II		9% (26)	6% (34)	
III		11% (34)	11% (65)	
IV		68% (200)	75% (443)	
Adrenal metastasis	863			0.24
No		88% (246)	91% (530)	
Yes		12% (33)	9% (54)	
Bone metastasis	871			0.20
No		73% (206)	68% (401)	
Yes		27% (78)	32% (186)	
Brain metastasis	869			0.89
No		73% (205)	72% (424)	
Yes		27% (77)	28% (163)	
Liver metastasis	864			0.55
No		89% (249)	90% (527)	
Yes		11% (31)	10% (57)	
Lung metastasis	882			0.45
No		46% (134)	44% (259)	
Yes		54% (155)	56% (334)	
Histopathologic subtype	788			0.57
Acinar predominant		29% (77)	35% (182)	
Lepidic predominant		2% (5)	2% (11)	
Micropapillary predom.		0% (0)	0% (1)	
Mucinous		1% (2)	1% (4)	
Papillary predominant		1% (2)	0% (2)	
Solid predominant		68% (180)	62% (322)	
Age at diagnosis	887			**0.04**
(Q1, **median**, Q3)		57.8 65.3 71.0	56.1 63.1 69.9	

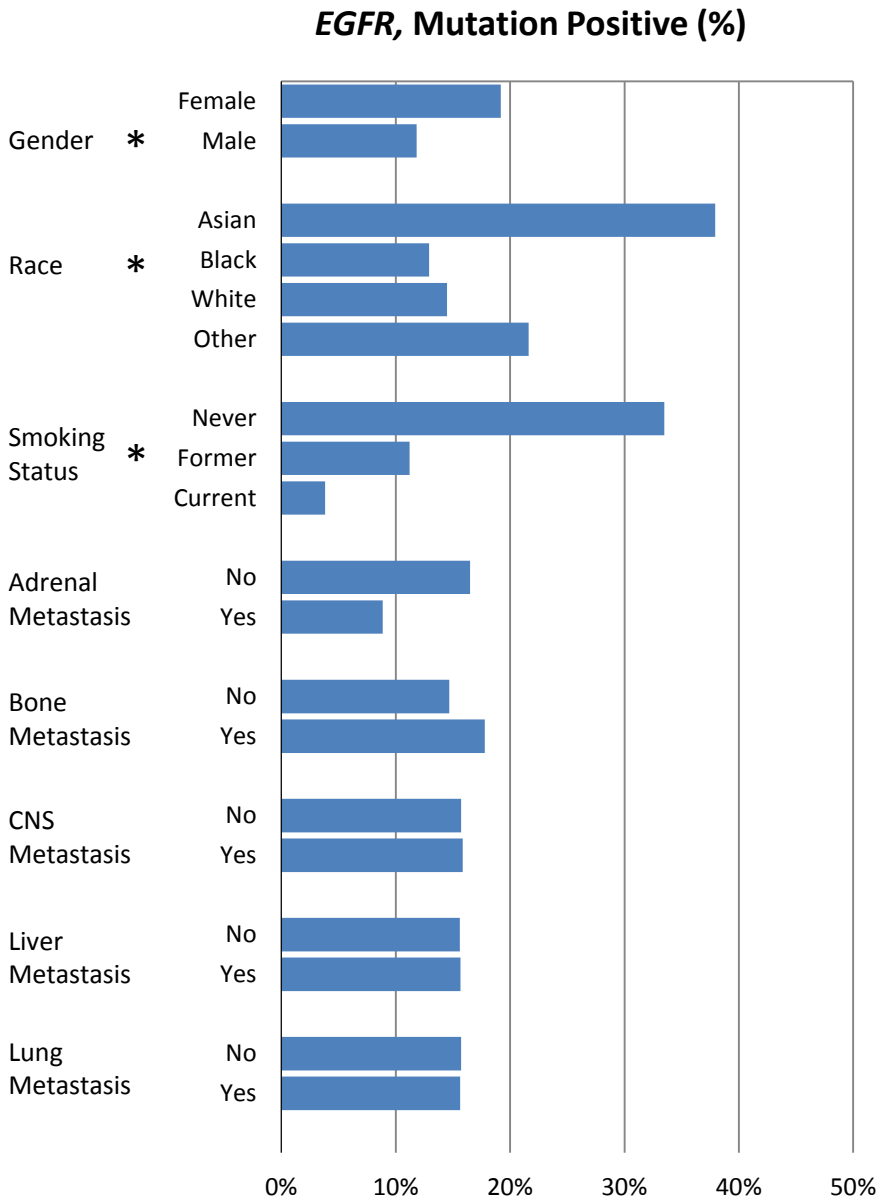
Supplemental Figure 5



Gene: *BRAF* (n=860)

Variable	N	WT (n=826)	Mut (n=34)	P
Sex	904			0.93
Female		54% (444)	53% (18)	
Male		46% (382)	47% (16)	
Race	904			0.7
Amer Indian/Alaska Native		0% (3)	0% (0)	
Asian		4% (30)	0% (0)	
Black/African American		7% (61)	3% (1)	
Native Hawaii/Pacific Isl.		0% (1)	0% (0)	
White		80% (663)	91% (31)	
Not disclosed		8% (68)	6% (2)	
Smoker	890			**0.02**
Current		12% (95)	26% (9)	
Former		64% (520)	44% (15)	
Never		24% (198)	29% (10)	
Stage at diagnosis	887			0.92
I		10% (80)	12% (4)	
II		7% (55)	9% (3)	
III		11% (90)	9% (3)	
IV		72% (585)	71% (24)	
Adrenal metastasis	863			0.05
No		90% (711)	100% (34)	
Yes		10% (79)	0% (0)	
Bone metastasis	871			0.62
No		70% (554)	74% (25)	
Yes		30% (243)	26% (9)	
Brain metastasis	869			0.21
No		73% (578)	82% (28)	
Yes		27% (219)	18% (6)	
Liver metastasis	864			0.42
No		90% (711)	94% (32)	
Yes		10% (80)	6% (2)	
Lung metastasis	882			0.90
No		45% (365)	44% (15)	
Yes		55% (443)	56% (19)	
Histopathologic subtype	788			0.07
Acinar predominant		34% (244)	21% (6)	
Lepidic predominant		2% (16)	0% (0)	
Micropapillary predom.		0% (1)	0% (0)	
Mucinous		1% (5)	4% (1)	
Papillary predominant		0% (3)	4% (1)	
Solid predominant		63% (458)	71% (20)	
Age at diagnosis	887			0.59
(Q1, **median**, Q3)		56.4 63.8 70.4	58.7 63.5 70.1	

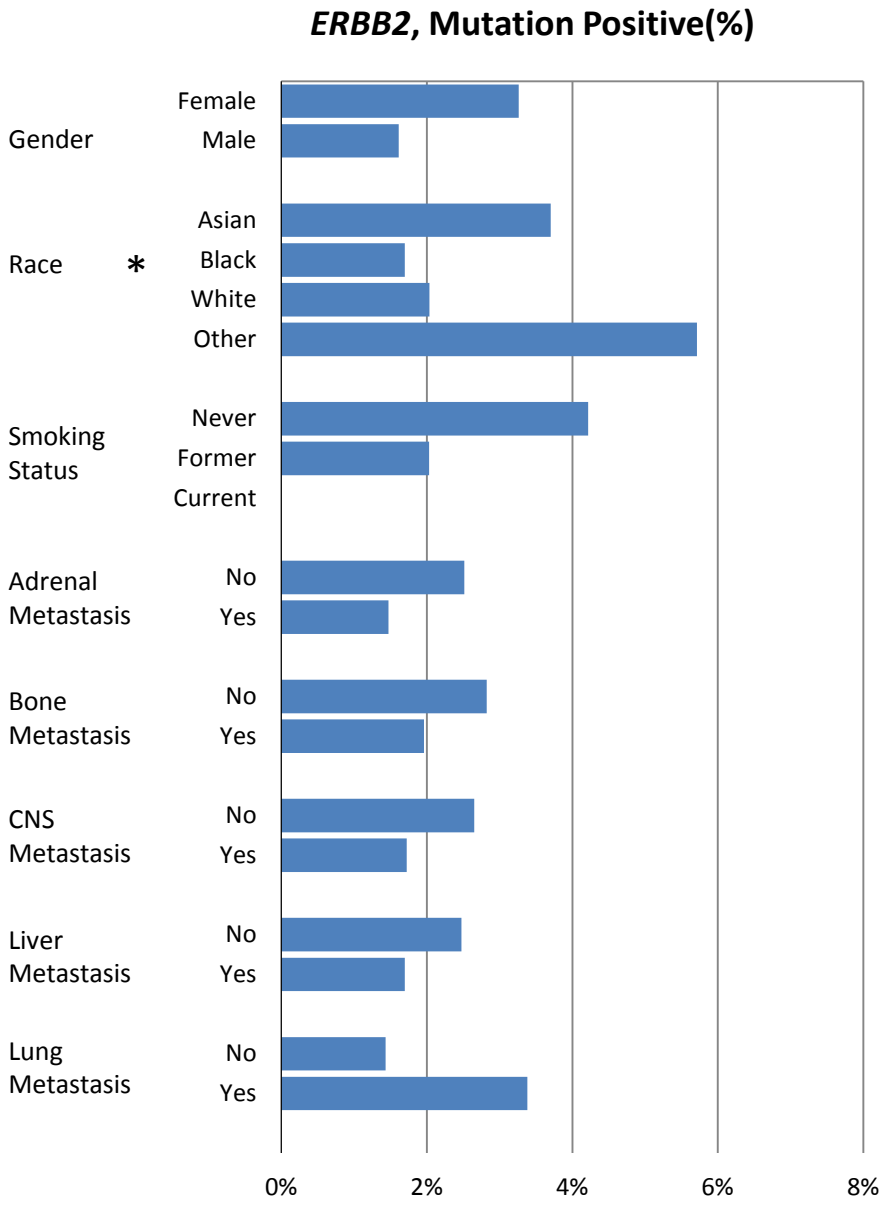
Supplemental Figure 5



Gene: *EGFR* (n=862)

Variable	N	WT (n=726)	Mut (n=136)	P
Sex	904			**0.003**
Female		52% (375)	65% (89)	
Male		48% (351)	35% (47)	
Race	904			**0.009**
Amer Indian/Alaska Native		0% (3)	0% (0)	
Asian		2% (18)	8% (11)	
Black/African American		7% (54)	6% (8)	
Native Hawaii/Pacific Isl.		0% (1)	0% (0)	
White		82% (596)	74% (101)	
Not disclosed		7% (54)	12% (16)	
Smoker	890			**<0.001**
Current		14% (101)	3% (4)	
Former		66% (475)	45% (60)	
Never		19% (139)	52% (70)	
Stage at diagnosis	887			**0.002**
I		11% (79)	4% (5)	
II		8% (54)	2% (3)	
III		11% (82)	8% (11)	
IV		70% (499)	85% (112)	
Adrenal metastasis	863			0.08
No		90% (623)	95% (123)	
Yes		10% (72)	5% (7)	
Bone metastasis	871			0.26
No		70% (494)	65% (85)	
Yes		30% (208)	35% (45)	
Brain metastasis	869			1
No		73% (510)	73% (95)	
Yes		27% (191)	27% (36)	
Liver metastasis	864			1
No		90% (627)	90% (116)	
Yes		10% (70)	10% (13)	
Lung metastasis	882			1
No		45% (322)	45% (60)	
Yes		55% (389)	55% (72)	
Histopathologic subtype	788			0.48
Acinar predominant		32% (203)	41% (47)	
Lepidic predominant		2% (14)	2% (2)	
Micropapillary predom.		0% (1)	0% (0)	
Mucinous		1% (5)	1% (1)	
Papillary predominant		1% (4)	0% (0)	
Solid predominant		65% (415)	57% (65)	
Age at diagnosis	887			0.17
(Q1, **median**, Q3)		56.7 63.8 70.7	55.3 63.0 68.8	

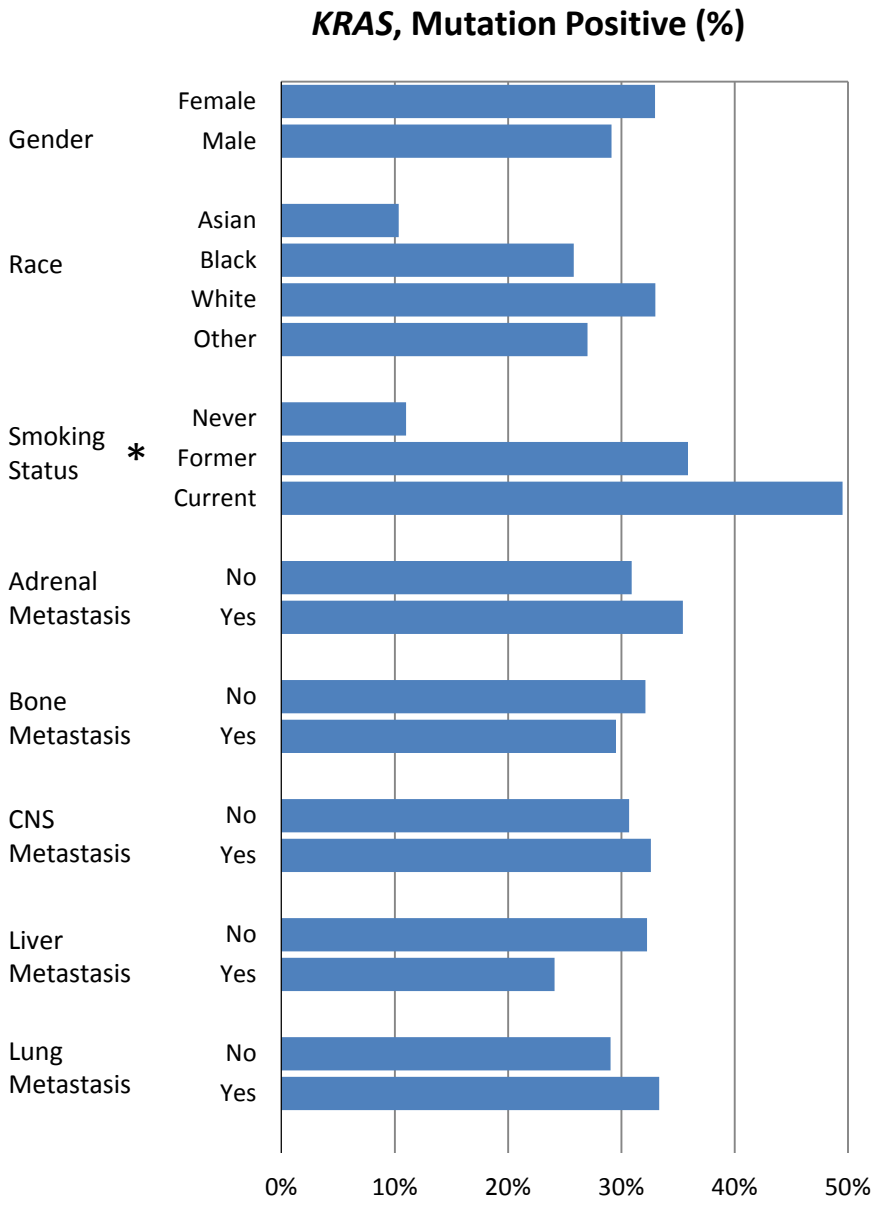
Supplemental Figure 5



Gene: *ERBB2* (n=647)

Variable	N	WT (n=631)	Mut (n=16)	P
Sex	904			0.18
Female		52% (326)	69% (11)	
Male		48% (305)	31% (5)	
Race	904			**0.02**
Amer Indian/Alaska Native		0% (2)	6% (1)	
Asian		4% (26)	6% (1)	
Black/African American		9% (58)	6% (1)	
Native Hawaii/Pacific Isl.		0% (1)	0% (0)	
White		76% (481)	62% (10)	
Not disclosed		10% (63)	19% (3)	
Smoker	890			0.1
Current		13% (80)	0% (0)	
Former		62% (386)	53% (8)	
Never		25% (159)	47% (7)	
Stage at diagnosis	887			0.26
I		8% (51)	19% (3)	
II		5% (32)	6% (1)	
III		12% (76)	0% (0)	
IV		74% (459)	75% (12)	
Adrenal metastasis	863			0.6
No		89% (543)	93% (14)	
Yes		11% (67)	7% (1)	
Bone metastasis	871			0.52
No		67% (413)	75% (12)	
Yes		33% (200)	25% (4)	
Brain metastasis	869			0.5
No		72% (441)	80% (12)	
Yes		28% (171)	20% (3)	
Liver metastasis	864			0.71
No		90% (552)	93% (14)	
Yes		10% (58)	7% (1)	
Lung metastasis	882			0.12
No		44% (275)	25% (4)	
Yes		56% (343)	75% (12)	
Histopathologic subtype	788			0.82
Acinar predominant		31% (169)	50% (6)	
Lepidic predominant		2% (11)	0% (0)	
Micropapillary predom.		0% (1)	0% (0)	
Mucinous		1% (6)	0% (0)	
Papillary predominant		0% (2)	0% (0)	
Solid predominant		65% (357)	50% (6)	
Age at diagnosis	887			0.43
(Q1, **median**, Q3)		56.6 63.0 69.5	54.7 68.0 71.9	

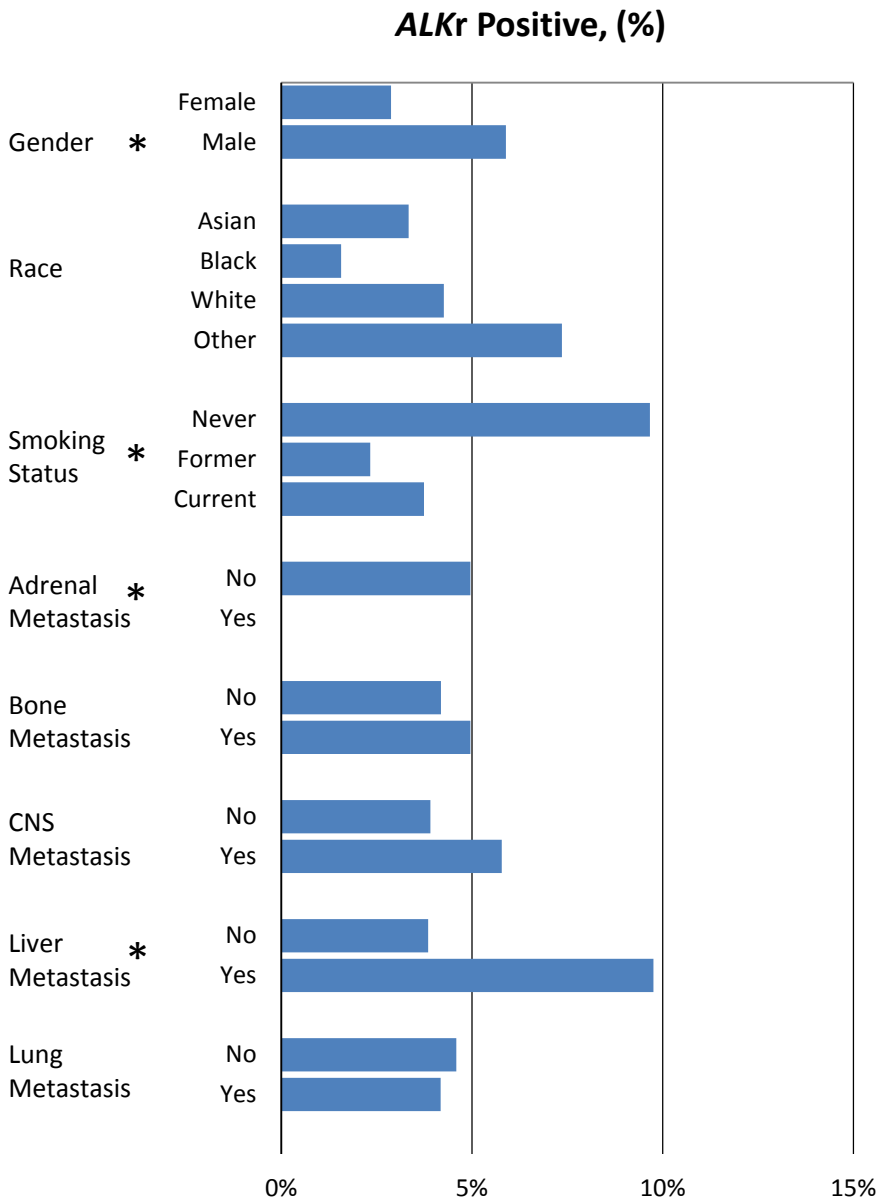
Supplemental Figure 5



Gene: *KRAS* (n=862)

Variable	N	WT (n=593)	Mut (n=269)	P
Sex	904			0.23
Female		52% (311)	57% (153)	
Male		48% (282)	43% (116)	
Race	904			0.05
Amer Indian/Alaska Native		0% (1)	1% (2)	
Asian		4% (26)	1% (3)	
Black/African American		8% (46)	6% (16)	
Native Hawaii/Pacific Isl.		0% (1)	0% (0)	
White		79% (467)	86% (230)	
Not disclosed		9% (52)	7% (18)	
Smoker	890			**<0.001**
Current		9% (53)	19% (52)	
Former		59% (343)	72% (192)	
Never		32% (186)	9% (23)	
Stage at diagnosis	887			0.77
I		10% (56)	11% (28)	
II		6% (37)	8% (20)	
III		11% (62)	12% (31)	
IV		73% (428)	70% (184)	
Adrenal metastasis	863			0.41
No		91% (516)	89% (231)	
Yes		9% (51)	11% (28)	
Bone metastasis	871			0.46
No		69% (393)	71% (186)	
Yes		31% (179)	29% (75)	
Brain metastasis	869			0.6
No		73% (420)	72% (186)	
Yes		27% (153)	28% (74)	
Liver metastasis	864			0.13
No		89% (504)	92% (240)	
Yes		11% (63)	8% (20)	
Lung metastasis	882			0.18
No		47% (271)	42% (111)	
Yes		53% (308)	58% (154)	
Histopathologic subtype	788			0.06
Acinar predominant		31% (160)	37% (90)	
Lepidic predominant		1% (7)	4% (9)	
Micropapillary predom.		0% (1)	0% (0)	
Mucinous		1% (5)	0% (1)	
Papillary predominant		1% (3)	0% (1)	
Solid predominant		66% (338)	58% (142)	
Age at diagnosis	887			0.18
(Q1, **median**, Q3)		55.9 63.6 70.1	57.4 63.9 71.0	

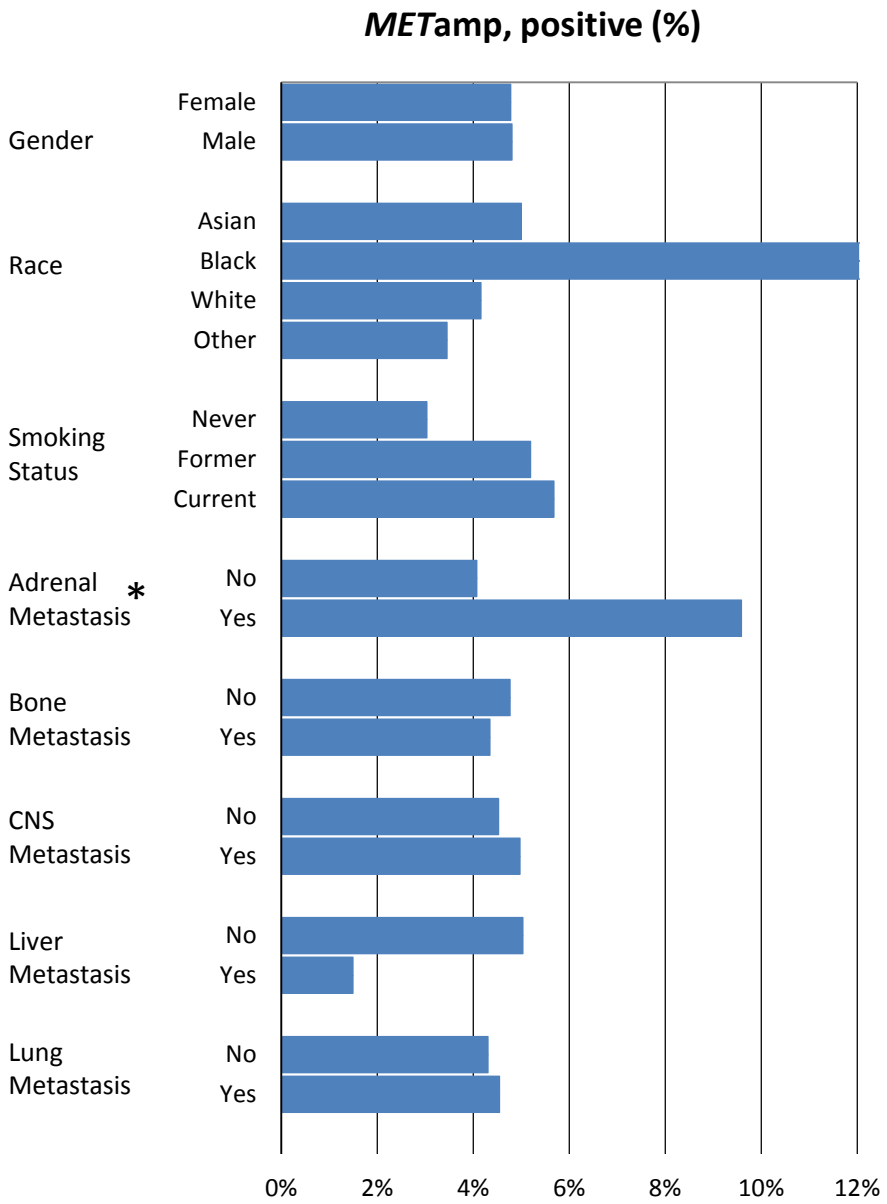
Supplemental Figure 5



Gene: *ALK* (rearrangement) (n=843)

Variable	N	WT (n=807)	Mut (n=36)	P
Sex	904			**0.03**
Female		54% (439)	36% (13)	
Male		46% (368)	64% (23)	
Race	904			0.67
Amer Indian/Alaska Native		0% (2)	0% (0)	
Asian		4% (29)	3% (1)	
Black/African American		8% (63)	3% (1)	
Native Hawaii/Pacific Isl.		0% (1)	0% (0)	
White		7% (60)	14% (5)	
Not disclosed		81% (652)	81% (29)	
Smoker	890			**<0.001**
Current		13% (103)	11% (4)	
Former		63% (504)	33% (12)	
Never		24% (187)	56% (20)	
Stage at diagnosis	887			**0.02**
I		10% (79)	0% (0)	
II		7% (58)	0% (0)	
III		11% (88)	23% (8)	
IV		72% (570)	77% (27)	
Adrenal metastasis	863			**0.04**
No		89% (690)	100% (36)	
Yes		11% (83)	0% (0)	
Bone metastasis	871			0.62
No		71% (550)	67% (24)	
Yes		29% (230)	33% (12)	
Brain metastasis	869			0.25
No		73% (566)	64% (23)	
Yes		27% (212)	36% (13)	
Liver metastasis	864			**0.01**
No		90% (700)	78% (28)	
Yes		10% (74)	22% (8)	
Lung metastasis	882			0.78
No		45% (354)	47% (17)	
Yes		55% (436)	53% (19)	
Histopathologic subtype	788			0.91
Acinar predominant		33% (231)	29% (8)	
Lepidic predominant		2% (16)	0% (0)	
Micropapillary predom.		0% (1)	0% (0)	
Mucinous		1% (6)	0% (0)	
Papillary predominant		1% (4)	0% (0)	
Solid predominant		63% (447)	71% (20)	
Age at diagnosis	887			**<0.001**
(Q1, **median**, Q3)		56.9 63.9 70.5	45.8 55.6 61.7	

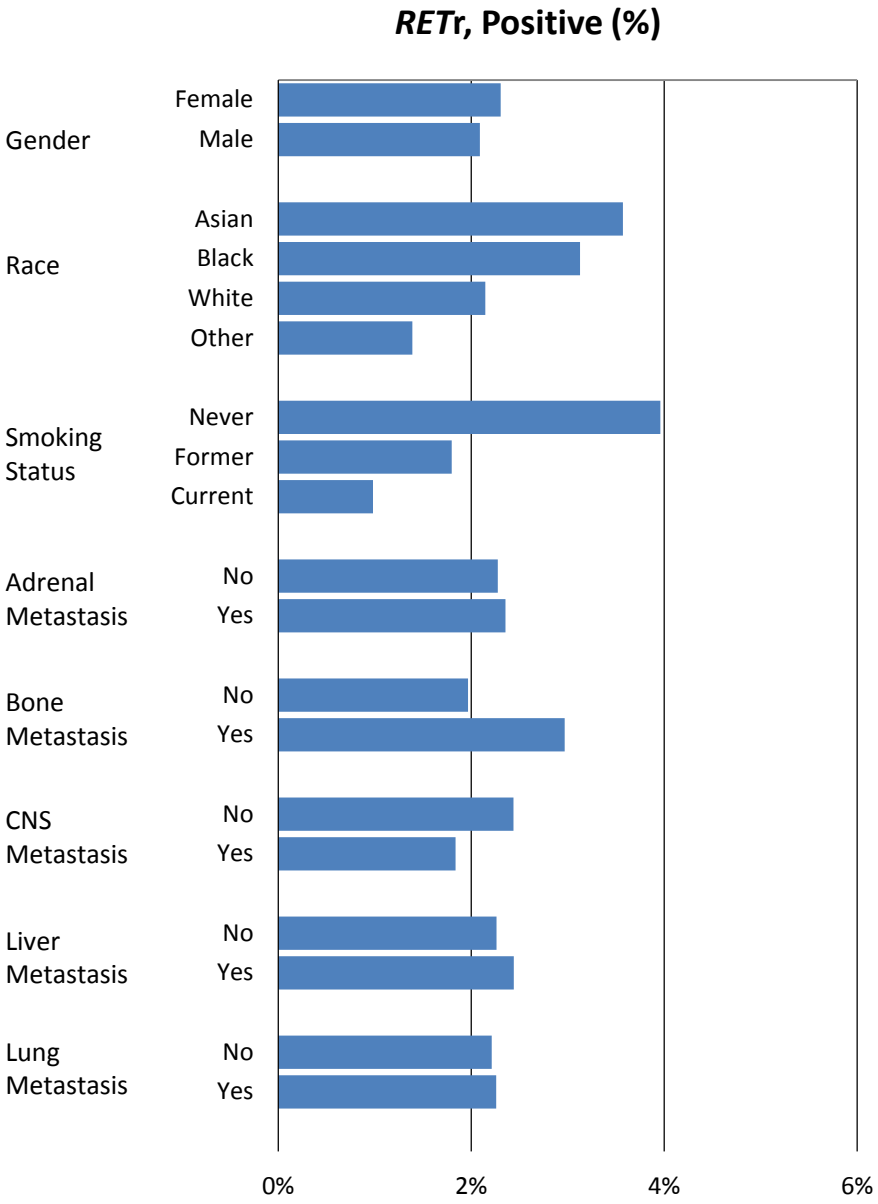
Supplemental Figure 5



Gene: MET (amplification) (n=689)

Variable	N	WT (n=656)	Mut (n=33)	P
Sex	904			1
Female		52% (339)	52% (17)	
Male		48% (317)	48% (16)	
Race	904			0.11
Amer Indian/Alaska Native		0% (2)	0% (0)	
Asian		3% (19)	3% (1)	
Black/African American		8% (51)	21% (7)	
Native Hawaii/Pacific Isl.		0% (0)	0% (0)	
White		81% (530)	70% (23)	
Not disclosed		8% (54)	6% (2)	
Smoker	890			0.49
Current		13% (83)	16% (5)	
Former		62% (402)	69% (22)	
Never		25% (160)	16% (5)	
Stage at diagnosis	887			0.81
I		8% (49)	9% (3)	
II		7% (45)	6% (2)	
III		11% (72)	6% (2)	
IV		74% (479)	79% (26)	
Adrenal metastasis	863			**0.04**
No		90% (565)	77% (24)	
Yes		10% (66)	23% (7)	
Bone metastasis	871			0.81
No		69% (440)	71% (22)	
Yes		31% (198)	29% (9)	
Brain metastasis	869			0.81
No		73% (464)	71% (22)	
Yes		27% (172)	29% (9)	
Liver metastasis	864			0.19
No		90% (566)	97% (30)	
Yes		10% (66)	3% (1)	
Lung metastasis	882			0.88
No		45% (289)	43% (13)	
Yes		55% (357)	57% (17)	
Histopathologic subtype	788			0.55
Acinar predominant		33% (185)	17% (4)	
Lepidic predominant		2% (9)	0% (0)	
Micropapillary predom.		0% (1)	0% (0)	
Mucinous		1% (4)	0% (0)	
Papillary predominant		1% (4)	0% (0)	
Solid predominant		64% (359)	83% (20)	
Age at diagnosis	887			0.46
(Q1, **median**, Q3)		56.8 63.6 70.2	55.7 62.2 69.9	

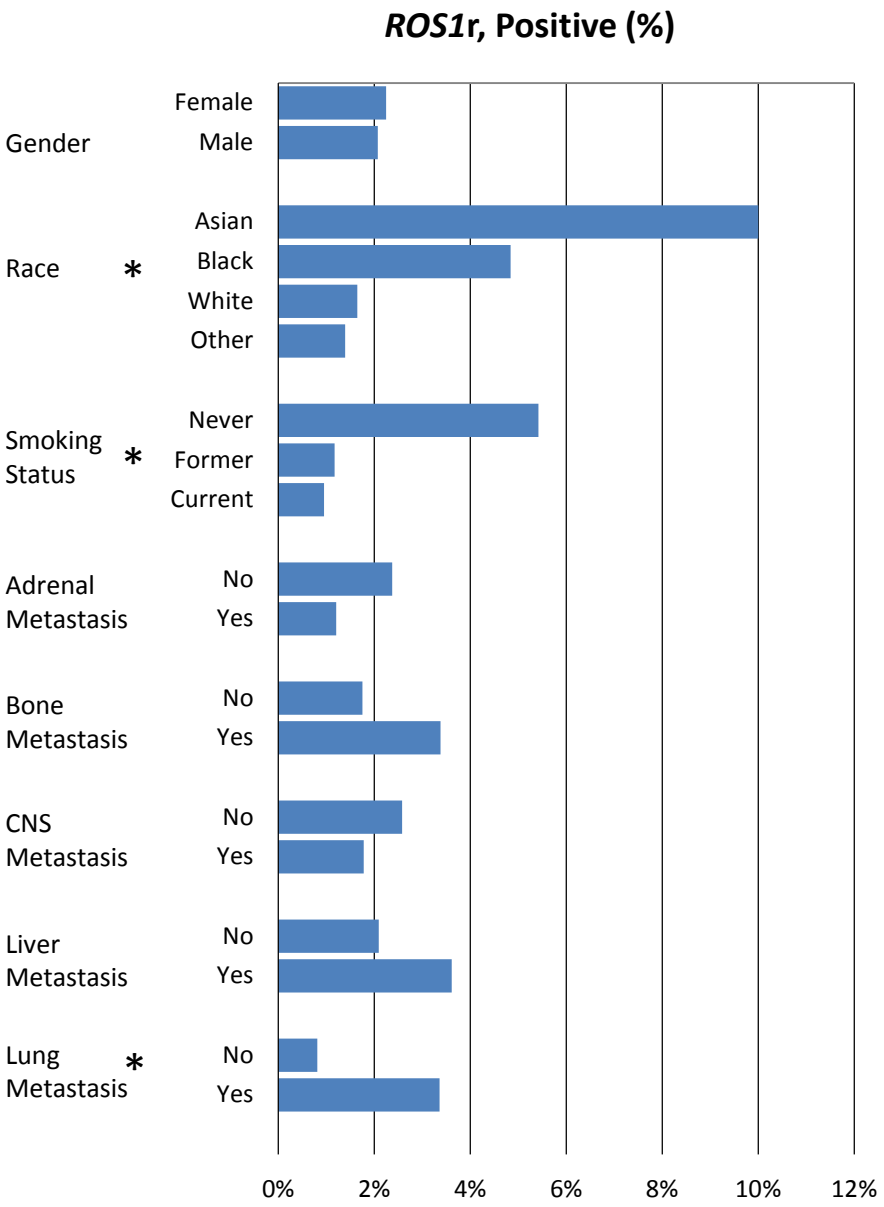
Supplemental Figure 5



Gene: *RET* (rearrangement) (n=817)

Variable	N	WT (n=799)	Mut (n=18)	P
Sex	904			0.83
Female		53% (424)	56% (10)	
Male		47% (375)	44% (8)	
Race	904			0.98
Amer Indian/Alaska Native		0% (2)	0% (0)	
Asian		3% (27)	6% (1)	
Black/African American		8% (62)	11% (2)	
Native Hawaii/Pacific Isl.		0% (1)	0% (0)	
White		80% (639)	78% (14)	
Not disclosed		9% (68)	6% (1)	
Smoker	890			0.14
Current		13% (101)	6% (1)	
Former		63% (492)	50% (9)	
Never		25% (194)	44% (8)	
Stage at diagnosis	887			0.43
I		10% (77)	11% (2)	
II		7% (52)	11% (2)	
III		12% (92)	0% (0)	
IV		72% (568)	78% (14)	
Adrenal metastasis	863			0.96
No		89% (688)	89% (16)	
Yes		11% (83)	11% (2)	
Bone metastasis	871			0.39
No		71% (549)	61% (11)	
Yes		29% (229)	39% (7)	
Brain metastasis	869			0.61
No		72% (561)	78% (14)	
Yes		28% (214)	22% (4)	
Liver metastasis	864			0.92
No		90% (692)	89% (16)	
Yes		10% (80)	11% (2)	
Lung metastasis	882			0.96
No		45% (354)	44% (8)	
Yes		55% (433)	56% (10)	
Histopathologic subtype	788			0.90
Acinar predominant		33% (233)	21% (3)	
Lepidic predominant		2% (15)	0% (0)	
Micropapillary predom.		0% (1)	0% (0)	
Mucinous		1% (5)	0% (0)	
Papillary predominant		0% (3)	0% (0)	
Solid predominant		63% (439)	79% (11)	
Age at diagnosis	887			0.49
(Q1, **median**, Q3)		56.7 63.6 70.4	58.7 65.1 73.2	

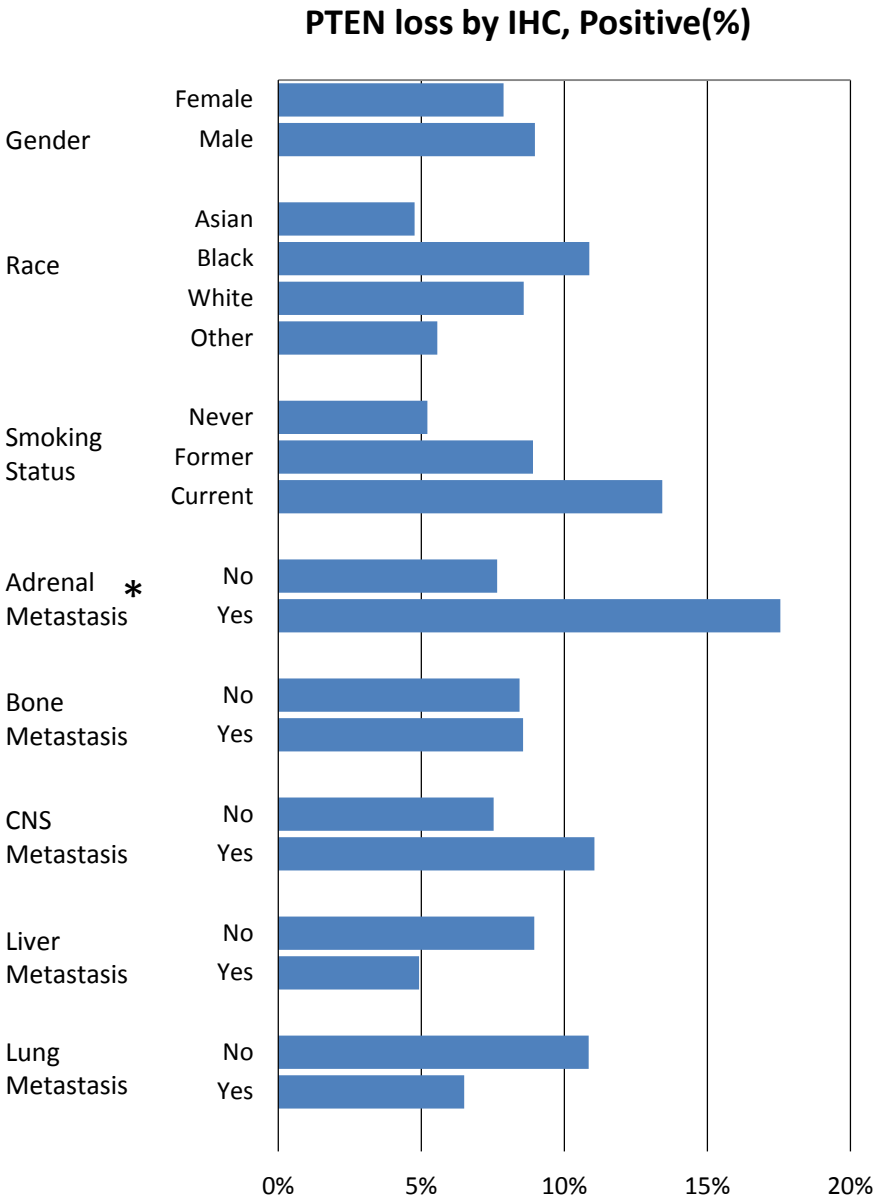
Supplemental Figure 5



Gene: *ROS1* (rearrangement) (n=832)

Variable	N	WT (n=814)	Mut (n=18)	P
Sex	904			0.87
Female		54% (436)	56% (10)	
Male		46% (378)	44% (8)	
Race	904			**0.04**
Amer Indian/Alaska Native		0% (2)	0% (0)	
Asian		3% (27)	17% (3)	
Black/African American		7% (59)	17% (3)	
Native Hawaii/Pacific Isl.		0% (1)	0% (0)	
White		81% (657)	61% (11)	
Not disclosed		8% (68)	6% (1)	
Smoker	890			**0.001**
Current		13% (104)	6% (1)	
Former		63% (506)	33% (6)	
Never		24% (192)	61% (11)	
Stage at diagnosis	887			0.59
I		10% (79)	0% (0)	
II		7% (53)	6% (1)	
III		12% (93)	12% (2)	
IV		72% (579)	82% (14)	
Adrenal metastasis	863			0.5
No		90% (700)	94% (17)	
Yes		10% (82)	6% (1)	
Bone metastasis	871			0.15
No		71% (561)	56% (10)	
Yes		29% (229)	44% (8)	
Brain metastasis	869			0.59
No		72% (567)	78% (14)	
Yes		28% (221)	22% (4)	
Liver metastasis	864			0.38
No		90% (703)	83% (15)	
Yes		10% (80)	17% (3)	
Lung metastasis	882			**0.01**
No		46% (366)	17% (3)	
Yes		54% (432)	83% (15)	
Histopathologic subtype	788			**<0.001**
Acinar predominant		33% (230)	35% (6)	
Lepidic predominant		2% (15)	0% (0)	
Micropapillary predom.		0% (0)	6% (1)	
Mucinous		1% (5)	0% (0)	
Papillary predominant		1% (4)	0% (0)	
Solid predominant		64% (450)	59% (10)	
Age at diagnosis	887			**0.03**
(Q1, **median**, Q3)		56.7 63.8 70.5	51.0 57.8 67.4	

Supplemental Figure 5

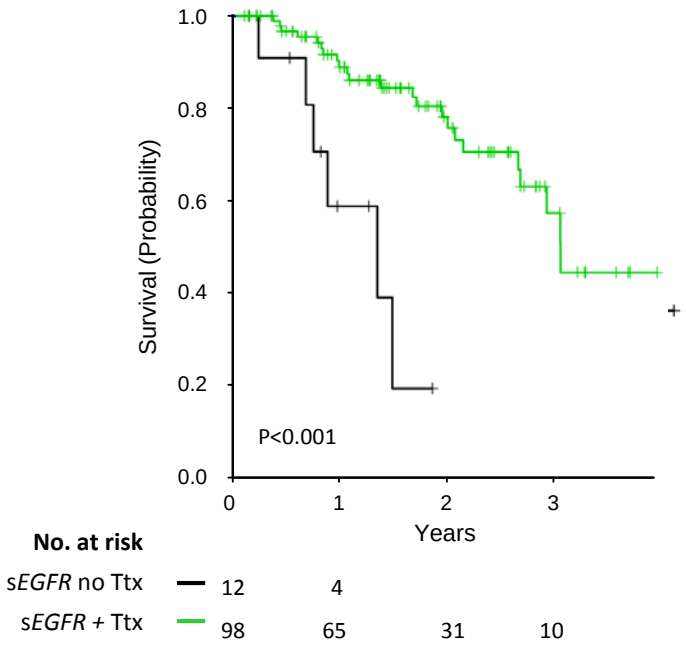


Gene: PTEN (IHC loss) (n=646)

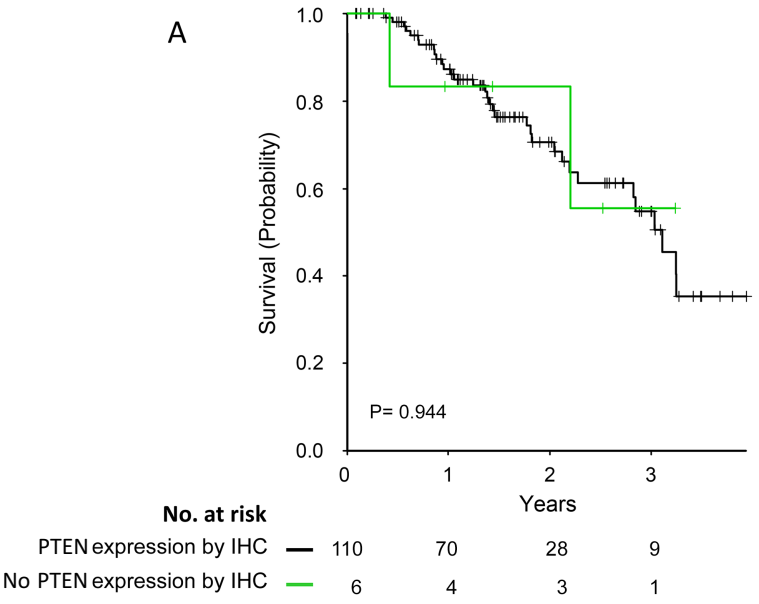
Variable	N	WT (n=592)	Mut (n=54)	P
Sex	904			0.62
Female		55% (328)	52% (28)	
Male		45% (264)	48% (26)	
Race	904			0.92
Amer Indian/Alaska Native		0% (2)	0% (0)	
Asian		3% (20)	2% (1)	
Black/African American		7% (41)	9% (5)	
Native Hawaii/Pacific Isl.		0% (1)	0% (0)	
White		81% (480)	83% (45)	
Not disclosed		8% (48)	6% (3)	
Smoker	890			0.08
Current		12% (71)	20% (11)	
Former		60% (348)	63% (34)	
Never		28% (164)	17% (9)	
Stage at diagnosis	887			**0.03**
I		11% (65)	2% (1)	
II		8% (44)	4% (2)	
III		11% (63)	20% (11)	
IV		71% (413)	74% (40)	
Adrenal metastasis	863			**0.01**
No		92% (519)	81% (43)	
Yes		8% (47)	19% (10)	
Bone metastasis	871			0.96
No		70% (402)	70% (37)	
Yes		30% (171)	30% (16)	
Brain metastasis	869			0.16
No		73% (418)	64% (34)	
Yes		27% (153)	36% (19)	
Liver metastasis	864			0.29
No		90% (509)	94% (50)	
Yes		10% (58)	6% (3)	
Lung metastasis	882			0.05
No		45% (263)	59% (32)	
Yes		55% (317)	41% (22)	
Histopathologic subtype	788			0.11
Acinar predominant		33% (175)	15% (7)	
Lepidic predominant		2% (12)	0% (0)	
Micropapillary predom.		0% (1)	0% (0)	
Mucinous		1% (3)	0% (0)	
Papillary predominant		1% (3)	0% (0)	
Solid predominant		63% (336)	85% (39)	
Age at diagnosis	887			0.92
(Q1, **median**, Q3)		56.2 63.5 70.7	57.3 64.7 68.9	

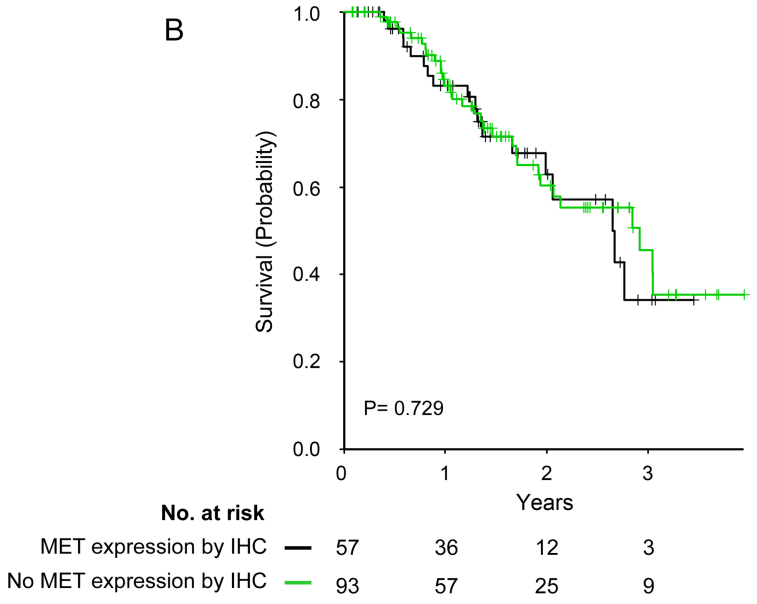
Supplemental Figure 6

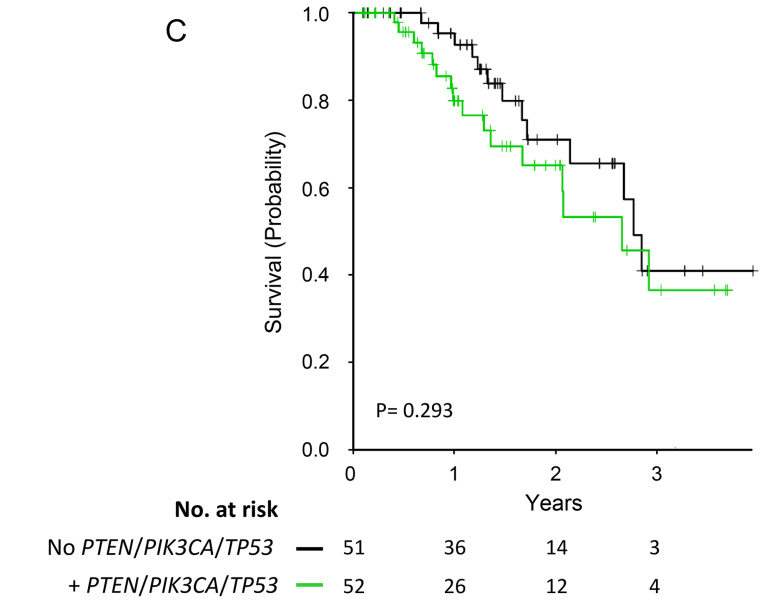
s*EGFR* survival comparison according to targeted treatment (Ttx) or not.



Supplemental Figure 7







Comparison of survival in the targeted therapy cohort according to presence or absence of several molecular features

Supplemental Figure 8

Survival comparisons according to presence or absence of TP53 mutation.