

## Supplementary Online Content

Weidhaas JB, Harris J, Schae D, et al. The *KRAS*-variant and cetuximab response in head and neck squamous cell cancer: a secondary analysis of a randomized clinical trial. *JAMA Oncol*. Published online December 22, 2016. doi:10.1001/jamaoncol.2016.5478

**eTable 1.** Pretreatment Characteristics by Whether or Not *KRAS* Genotype Is Known

**eTable 2.** Pretreatment Characteristics by *KRAS* Genotype and Assigned Treatment

**eTable 3.** TGF $\beta$ 1 by p16 and *KRAS*-Variant Status

**eTable 4.** Grade 3-4 Treatment-Related [1] Radiation Mucositis by *KRAS*-Variant and Assigned Treatment

**eTable 5.** Grade 3-4 Treatment-Related [1] Skin Reaction Inside Portal [2] by *KRAS*-Variant and Assigned Treatment

**eTable 6.** Grade 3-4 Treatment-Related [1] Skin Reaction Outside Portal [2] by *KRAS*-Variant and Assigned Treatment

**eFigure 1.** CONSORT Flow Diagram RTOG 0522

**eFigure 2.** Distant Metastasis

**eFigure 3.** Local Regional Failure

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

**eTable 1.** Pretreatment Characteristics by Whether or Not *KRAS* Genotype Is Known

	KRAS genotype known		p-value
	Yes (n=413)	No (n=478)	
Assigned treatment			1.00 <sup>43</sup>
No cetuximab	207 (50.1%)	240 (50.2%)	
Cetuximab	206 (49.9%)	238 (49.8%)	
Age (years)			0.02 [3]
Mean	57.5	56.3	
Std. Dev.	7.88	8.36	
Median	58	56	
Min - Max	31 - 77	34 - 79	
Q1 - Q3	52 - 63	50 - 62	
Gender			0.76 <sup>43</sup>
Male	366 (88.6%)	420 (87.9%)	
Female	47 (11.4%)	58 (12.1%)	
Race			0.13 <sup>43</sup>
White	382 (92.5%)	428 (89.5%)	
Non-white	31 (7.5%)	50 (10.5%)	
Zubrod performance status			0.09 <sup>43</sup>
0	260 (63.0%)	327 (68.4%)	
1	153 (37.0%)	151 (31.6%)	
Smoking history: pack-years [1]	(n=367)	(n=404)	0.93 [3]
Mean	27.4	27.8	
Std. Dev.	27.50	28.75	
Median	23.5	20.7	
Min - Max	0 - 162	0 - 150	
Q1 - Q3	1 - 42	0.1 - 44.9	

**eTable 1.** Pretreatment Characteristics by Whether or Not *KRAS* Genotype Is Known

	KRAS genotype known		p-value
	Yes (n=413)	No (n=478)	
Primary site			0.24 <sup>43</sup>
Oropharynx	298 (72.2%)	327 (68.4%)	
Hypopharynx/larynx	115 (27.8%)	151 (31.6%)	
p16 status (oropharynx only)	(n=188)	(n=133)	0.37 <sup>43</sup>
p16-negative	54 (28.7%)	32 (24.1%)	
p16-positive	134 (71.3%)	101 (75.9%)	
T stage			0.33 [3]
T2	170 (41.2%)	181 (37.9%)	
T3	149 (36.1%)	180 (37.7%)	
T4	94 (22.8%)	117 (24.5%)	
N stage			0.79 [3]
N0	46 (11.1%)	53 (11.1%)	
N1	36 (8.7%)	45 (9.4%)	
N2a	37 (9.0%)	41 (8.6%)	
N2b	139 (33.7%)	154 (32.2%)	
N2c	137 (33.2%)	159 (33.3%)	
N3	18 (4.4%)	26 (5.4%)	

Std. Dev. = standard deviation; Q1 = first quartile; Q3 = third quartile.

[1] A pack-year is defined as the equivalent of smoking one pack of cigarettes a day for 1 year.

<sup>43</sup> Fisher's exact test.

[3] Wilcoxon rank-sum test.

**eTable 2.** Pretreatment Characteristics by *KRAS* Genotype and Assigned Treatment

	Non-variant (TT)		<i>KRAS</i> -variant (GG/TG)	
	No Cetuximab (n=169)	Cetuximab (n=174)	No Cetuximab (n=38)	Cetuximab (n=32)
Age (years)	<b>p=0.05</b>		p=0.22	
Mean	56.7	58.5	57.6	55.6
Standard deviation	8.19	7.59	8.29	6.81
Median	57	59	58	54.5
Min - Max	31 - 77	41 - 76	38 - 75	42 - 69
Q1 - Q3	52 - 62	53 - 64	53 - 63	51 - 61
Gender	p=0.31		p=0.44	
Male	146 (86.4%)	157 (90.2%)	33 (86.8%)	30 (93.8%)
Female	23 (13.6%)	17 ( 9.8%)	5 (13.2%)	2 (6.3%)
Ethnicity	p=0.69		<b>p=0.04</b>	
White	157 (92.9%)	159 (91.4%)	38 (100.0%)	28 (87.5%)
Non-white	12 (7.1%)	15 (8.6%)	0 (0.0%)	4 (12.5%)
Zubrod performance status	p=0.74		p=1.00	
0	109 (64.5%)	109 (62.6%)	23 (60.5%)	19 (59.4%)
1	60 (35.5%)	65 (37.4%)	15 (39.5%)	13 (40.6%)
Smoking history: pack-years [1]	p=0.69		p=0.14	
	(n=150)	(n=154)	(n=35)	(n=28)
Mean	26.5	26.7	35.1	26.8
Standard deviation	26.08	29.24	26.52	26.10
Median	27.25	17.8	34	20.5
Min - Max	0 - 150	0 - 162	0 - 90	0 - 110
Q1 - Q3	1.35 - 40	0 - 42	4.5 - 51	3 - 40.35
Primary site	p=0.47		p=0.79	
Oropharynx	118 (69.8%)	128 (73.6%)	29 (76.3%)	23 (71.9%)
Hypopharynx/larynx	51 (30.2%)	46 (26.4%)	9 (23.7%)	9 (28.1%)

**eTable 2.** Pretreatment Characteristics by *KRAS* Genotype and Assigned Treatment

	Non-variant (TT)		<i>KRAS</i> -variant (GG/TG)	
	No Cetuximab (n=169)	Cetuximab (n=174)	No Cetuximab (n=38)	Cetuximab (n=32)
p16 status (all sites)	p=0.59		p=0.14	
	(n=108)	(n=118)	(n=22)	(n=23)
p16-negative	50 ( 46.3%)	50 ( 42.4%)	13 ( 59.1%)	8 ( 34.8%)
p16-positive	58 ( 53.7%)	68 ( 57.6%)	9 ( 40.9%)	15 ( 65.2%)
T stage	p=0.39		p=0.24	
T2	64 ( 37.9%)	74 ( 42.5%)	16 ( 42.1%)	16 ( 50.0%)
T3	64 ( 37.9%)	62 ( 35.6%)	11 ( 28.9%)	12 ( 37.5%)
T4	41 ( 24.3%)	38 ( 21.8%)	11 ( 28.9%)	4 ( 12.5%)
N stage	p=0.07		p=0.12	
N0	11 ( 6.5%)	23 ( 13.2%)	5 ( 13.2%)	7 ( 21.9%)
N1	19 ( 11.2%)	14 ( 8.0%)	1 ( 2.6%)	2 ( 6.3%)
N2a	11 ( 6.5%)	19 ( 10.9%)	4 ( 10.5%)	3 ( 9.4%)
N2b	57 ( 33.7%)	58 ( 33.3%)	12 ( 31.6%)	12 ( 37.5%)
N2c	63 ( 37.3%)	54 ( 31.0%)	13 ( 34.2%)	7 ( 21.9%)
N3	8 ( 4.7%)	6 ( 3.4%)	3 ( 7.9%)	1 ( 3.1%)

Q1 = first quartile; Q3 = third quartile.

[1] A pack-year is defined as the equivalent of smoking one pack of cigarettes a day for 1 year.

[P-values for age, pack-years, T stage, and N stage are from Wilcoxon rank-sum test.

P-values for gender, race, Zubrod performance status, primary site, and p16 status are from Fisher's exact test.

**eTable 3.** TGFB1 by p16 and *KRAS*-Variant Status

	n	Min	Q1	Median	Q3	Max
p16-negative, <i>KRAS</i> -non-variant	91	2757.51	10155.76	18989.05	28145.41	121030.02
p16-positive, <i>KRAS</i> -non-variant	117	2261.42	7740.52	15284.42	32292.91	119449.13
p16-negative, <i>KRAS</i> -variant	20	5034.35	13106.36	23254.16	43662.46	97677.11
p16-positive, <i>KRAS</i> -variant	23	5070.55	10152.63	20083.48	53024.57	85081.77

(p=0.34 by Kruskal-Wallis test)

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**eTable 4.** Grade 3-4 Treatment-Related [1] Radiation Mucositis by *KRAS*-Variant and Assigned Treatment

<i>KRAS</i>	Assigned Treatment	Patients	Events	Odds Ratio (95% Confidence Interval)
Non-variant	No cetuximab	169	64 (37.9%)	Reference
	Cetuximab	174	88 (50.6%)	1.68 (1.09-2.58) p=0.02
Variant	No cetuximab	38	18 (47.4%)	Reference
	Cetuximab	32	16 (50.0%)	1.11 (0.43-2.85) p=0.83
Total		413	186 (45.0%)	interaction p=0.43

Odds ratios estimated from logistic regression model with covariates *KRAS* (variant vs. Non-variant), treatment (cetuximab vs. no cetuximab) and the interaction of *KRAS* and treatment.

[1] Definitely, probably, or possibly related to protocol treatment.

**eTable 5.** Grade 3-4 Treatment-Related [1] Skin Reaction Inside Portal [2] by *KRAS*-Variant and Assigned Treatment

<i>KRAS</i>	Assigned Treatment	Patients	Events	Odds Ratio (95% Confidence Interval)
Non-variant	No cetuximab	169	19 (11.2%)	Reference
	Cetuximab	174	38 (21.8%)	2.21 (1.21-4.01) p=0.01
Variant	No cetuximab	38	7 (18.4%)	Reference
	Cetuximab	32	5 (15.6%)	0.82 (0.23-2.89) p=0.76
Total		413	69 (16.7%)	interaction p=0.16

Odds ratios estimated from logistic regression model with covariates *KRAS* (variant vs. Non-variant), treatment (cetuximab vs. no cetuximab) and the interaction of *KRAS* and treatment.

[1] Definitely, probably, or possibly related to protocol treatment.

[2] Dermatitis radiation NOS; Radiation recall syndrome.



**eTable 6.** Grade 3-4 Treatment-Related [1] Skin Reaction Outside Portal [2] by *KRAS*-Variant and Assigned Treatment

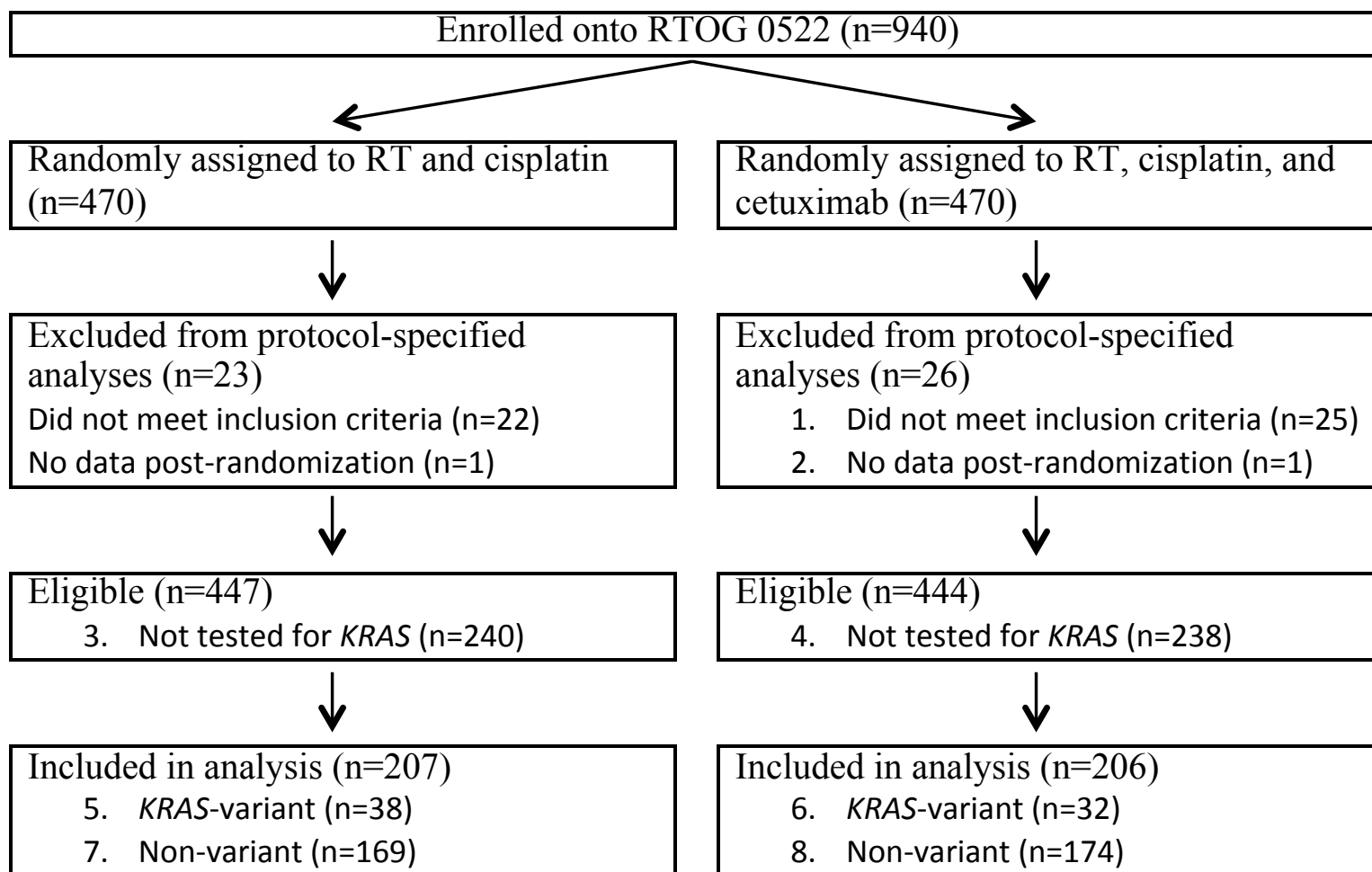
<i>KRAS</i>	Assigned Treatment	Patients	Events	Odds Ratio (95% Confidence Interval)
Non-variant	No cetuximab	169	1 (0.6%)	Reference
	Cetuximab	174	40 (23.0%)	50.15 (6.81-369.54) p<0.001
Variant	No cetuximab	38	1 (2.6%)	Reference
	Cetuximab	32	6 (18.8%)	8.54 (0.97-75.20) p=0.05
Total		413	48 (11.6%)	interaction p=0.24

Odds ratios estimated from logistic regression model with covariates *KRAS* (variant vs. Non-variant), treatment (cetuximab vs. no cetuximab) and the interaction of *KRAS* and treatment.

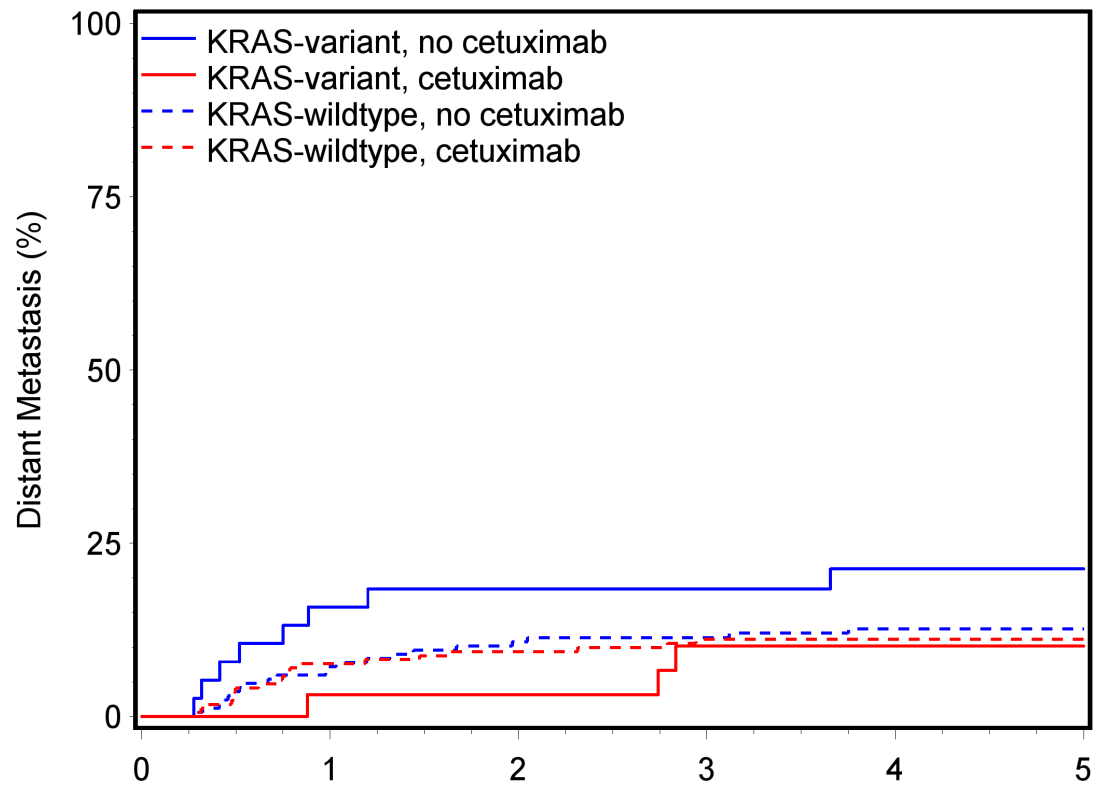
[1] Definitely, probably, or possibly related to protocol treatment.

[2] Pruritis; Dermatitis exfoliative NOS; Acne NOS; Nail disorder NOS.

**eFigure 1. CONSORT Flow Diagram RTOG 0522**

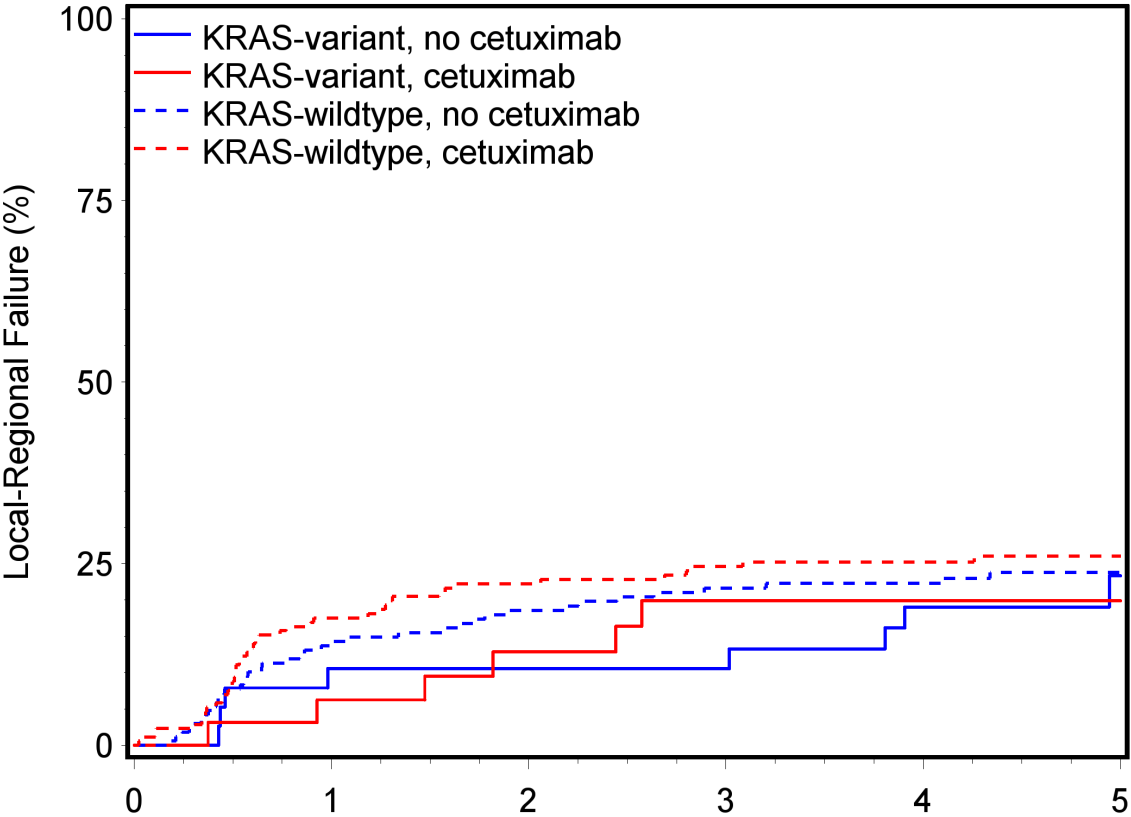


## eFigure 2. Distant metastasis



No. at Risk	Years after Randomization					
	0	1	2	3	4	5
var, no cetux	38	25	23	23	16	11
var, cetux	32	28	23	17	14	8
wt, no cetux	169	127	109	97	88	38
wt. cetux	174	122	108	99	86	52

**eFigure 3. Local Regional Failure**



No. at Risk	Years after Randomization					
	0	1	2	3	4	5
var, no cetux	38	25	23	23	16	11
var, cetux	32	28	23	17	14	8
wt, no cetux	169	127	109	97	88	38
wt. cetux	174	122	108	99	86	52

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