

## Supplementary materials

**Table S1** Clinical, biological, and pathological characteristics of the 77 HNSCC patients who were treated with cetuximab in the first-line recurrent and/or metastatic setting, and their associations with PFS

Characteristics	n (%)	Progression <sup>c</sup>	HR <sup>d</sup>	95% CI (HR)	PFS <sup>e</sup>
Total	77 (100.0)	72			
Age at diagnosis					
< 60 years	42 (54.5)	40	1		0.51
≥ 60 years	35 (45.5)	32	1.17	[0.73; 1.87]	
Gender					
Female	18 (23.4)	14	1		0.74
Male	59 (76.6)	58	1.11	[0.61; 2]	
Tobacco <sup>a</sup>					
No	8 (89.0)	6	1		0.38
Yes	65 (11.0)	63	1.45	[0.63; 3.37]	
Alcohol <sup>b</sup>					
No	24 (43.6)	21	1		0.93
Yes	31 (56.4)	31	0.97	[0.55; 1.72]	
HPV status					
Negative	71 (92.2)	66	1		0.32
Positive	6 (7.8)	6	1.53	[0.66; 3.57]	
AJCC stage					
Stage I–II	13 (16.9)	11	1		0.16
Stage III	12 (15.6)	11	1.57	[0.68; 3.63]	
Stage IV	52 (67.5)	50	1.88	[0.97; 3.62]	
Tumor location					
Oral cavity	28 (36.4)	24	1		0.47
Oropharynx	27 (35.0)	27	1.30	[0.74; 2.26]	
Larynx	10 (13.0)	10	1.95	[0.91; 4.14]	
Hyopharynx	7 (9.1)	7	1.30	[0.56; 3.04]	
Other	5 (6.5)	4	1.76	[0.61; 5.14]	

<sup>a</sup>Information available for 73 patients; <sup>b</sup>information available for 55 patients; <sup>c</sup>progression data collected until June 2016; <sup>d</sup>HR estimated by non-adjusted Cox proportional hazards model; <sup>e</sup>P value of the log-rank test. AJCC; American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; HNSCC, head and neck squamous cell carcinoma; HPV; human papillomavirus; PFS, progression-free survival.

**Table S2** Clinical, biological, and pathological characteristics of the 38 HNSCC patients who were treated with cetuximab combined with radiotherapy, and their associations with PFS

Characteristics	n (%)	Progression <sup>c</sup>	HR <sup>d</sup>	95% CI (HR)	PFS <sup>e</sup>
Total	38 (100.0)	25			
Age at diagnosis					
< 60 years	11 (28.9)	7	1		0.89
≥ 60 years	27 (71.1)	18	0.94	[0.39; 2.25]	
Gender					
Female	8 (21.1)	4	1		0.13
Male	30 (78.9)	21	2.25	[0.77; 6.58]	
Tobacco <sup>a</sup>					
No	7 (18.9)	2	1		<b>0.03</b>
Yes	30 (81.1)	22	4.34	[1.02; 18.55]	
Alcohol <sup>b</sup>					
No	13 (40.6)	7	1		0.19
Yes	19 (59.4)	14	1.82	[0.73; 4.52]	
HPV status					
Negative	29 (76.3)	22	1		<b>0.01</b>
Positive	9 (23.7)	3	0.23	[0.07; 0.78]	
AJCC stage					
Stage I–II	3 (7.9)	3	1		<b>&lt;0.001</b>
Stage III	12 (31.6)	6	0.02	[0; 0.16]	
Stage IV	23 (60.5)	16	0.04	[0.01; 0.23]	
Tumor location					
Oral cavity	5 (13.2)	5	1		0.58
Oropharynx	23 (60.5)	14	0.53	[0.19; 1.47]	
Larynx	5 (13.2)	2	0.31	[0.06; 1.61]	
Hypopharynx	1 (2.6)	1	0.61	[0.07; 5.25]	
Other	4 (10.5)	3	0.85	[0.20; 3.57]	

<sup>a</sup>Information available for 37 patients; <sup>b</sup>information available for 32 patients; <sup>c</sup>progression data collected until June 2016; <sup>d</sup>HR estimated by non-adjusted Cox proportional hazards model; <sup>e</sup>P value of the log-rank test. AJCC; American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; HNSCC, head and neck squamous cell carcinoma; HPV; human papillomavirus; PFS, progression-free survival.

**Table S3** Clinical, biological, and pathological characteristics of the HNSCC patients, compared between those treated with cetuximab in the locally advanced setting versus in an R/M setting

Characteristics	Cetuximab in first line recurrent and/or metastatic setting (group 1) (%)	RT + cetuximab (group 2) (%)	<i>P</i> <sup>c</sup>
Total	77 (100.0)	38 (100.0)	
Age			
< 60 years	42 (54.5)	11 (28.9)	<b>0.01</b>
≥ 60 years	35 (45.5)	27 (71.1)	
Gender			
Male	59 (76.6)	30 (78.9)	0.78
Female	18 (23.4)	8 (21.1)	
Tobacco <sup>a</sup>			
Yes	65 (89.0)	30 (81.1)	0.25
No	8 (11.0)	7 (18.9)	
Alcohol <sup>b</sup>			
Yes	31 (56.4)	19 (59.4)	0.78
No	24 (43.6)	13 (40.6)	
HPV status			
Positive	6 (7.8)	9 (23.7)	<b>0.04</b>
Negative	71 (92.2)	29 (76.3)	
AJCC stage			
Stage I–II	13 (16.9)	3 (7.9)	0.09
Stage III	12 (15.6)	12 (31.6)	
Stage IV	52 (67.5)	23 (60.5)	
Tumor location			
Oral cavity	28 (36.4)	5 (13.2)	<b>0.03</b>
Oropharynx	27 (35.0)	23 (60.5)	
Larynx	10 (13)	5 (13.2)	
Hypopharynx	7 (9.1)	1 (2.6)	
Other	5 (6.5)	4 (10.5)	

<sup>a</sup>Information available for 110 patients (73 patients for group 1, 37 for group 2); <sup>b</sup>information available for 87 patients (55 patients for group 1, 32 for group 2); <sup>c</sup>Yates's  $\chi^2$  test. AJCC; American Joint Committee on Cancer; CT, chemotherapy; CI, confidence interval; HR, hazard ratio; HNSCC, head and neck squamous cell carcinoma; HPV; human papillomavirus; PFS, progression-free survival; R/M, recurrent and/or metastatic; RT, radiotherapy.

**Table S4** Mutational profiles of the 115 HNSCC samples

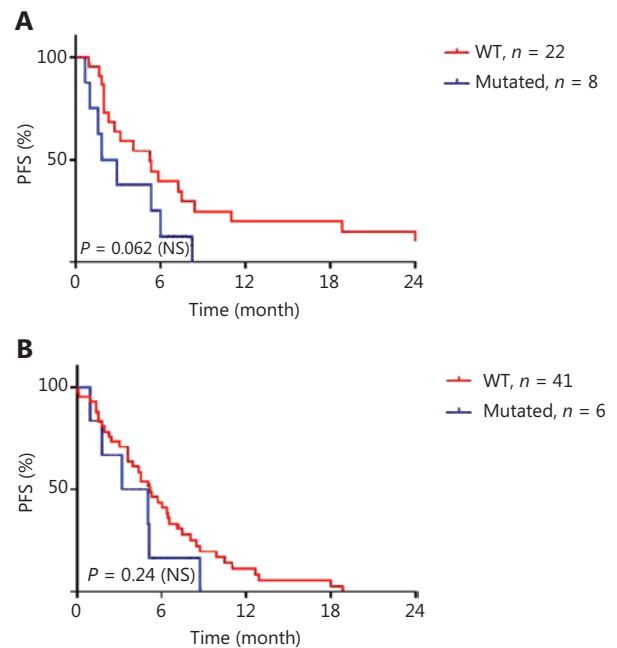
Gene	Exon	Mutation status	Number of mutated samples
<i>PIK3CA</i>	9	p.E545K; c.1633G>A	5
		p.E542K; c.1624G>A	3
	20	p.H1047R; c.3140A>G	4
<i>KRAS</i>	2	p.G12C; c.34G>T	1
	4	p.A146V; c.437C>T	1
<i>HRAS</i>	2	p.G12D; c.35G>A	1
		p.G12S; c.34G>A	1
	3	p.Q61R; c.182A>G	1
		p.Q61L; c.182A>T	1

HNSCC, head abd neck squamous cell carcinoma.

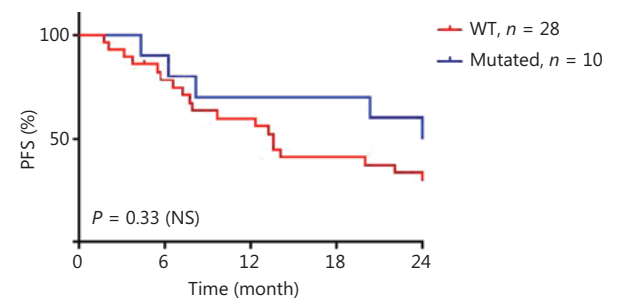
**Table S5** Relationship between global resistance biomarker status and the clinical, biological, and pathological parameters among the 77 HNSCC patients treated with cetuximab in first-line recurrent and/or metastatic setting

Characteristics	Tumors with a resistance biomarker (%)	Tumors without a resistance biomarker (%)	<i>P</i> <sup>c</sup>
Total	14 (18.2)	63 (81.8)	
Age			
< 60 years	4 (28.6)	38 (60.3)	<b>0.03</b>
≥ 60 years	10 (71.4)	25 (39.7)	
Gender			
Male	11 (78.6)	48 (76.2)	0.85
Female	3 (21.4)	15 (23.8)	
Tobacco <sup>a</sup>			
Yes	11 (91.7)	54 (88.5)	0.75
No	1 (8.3)	7 (11.5)	
Alcohol <sup>b</sup>			
Yes	6 (54.5)	25 (56.8)	0.89
No	5 (45.5)	19 (43.2)	
HPV status			
Positive	3 (21.4)	3 (4.8)	0.12 <sup>c</sup>
Negative	11 (78.6)	60 (95.2)	
AJCC stage			
Stage I–II	1 (7.1)	12 (19.0)	0.28 <sup>c</sup>
Stage III	1 (7.1)	11 (17.5)	
Stage IV	12 (85.7)	40 (63.5)	
Tumor location			
Oral cavity	4 (28.6)	24 (38.1)	0.15
Oropharynx	5 (35.7)	22 (34.9)	
Larynx	1 (7.1)	9 (14.3)	
Hypopharynx	1 (7.1)	6 (9.5)	
Other	3 (21.4)	2 (3.2)	

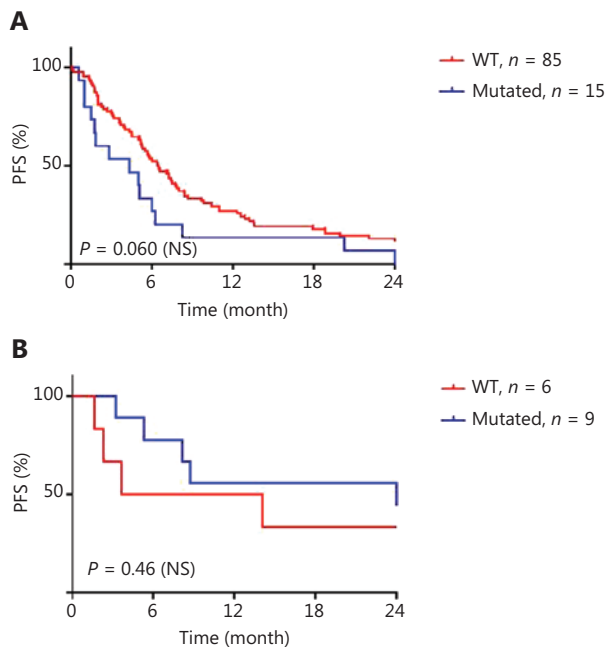
<sup>a</sup>Information available for 73 patients; <sup>b</sup>information available for 55 patients; <sup>c</sup>Yates's  $\chi^2$  test. AJCC; American Joint Committee on Cancer; HNSCC, head and neck squamous cell carcinoma; HPV; human papillomavirus.



**Figure S1** Progression-free-survival (PFS) in a first-line recurrence and/or metastatic setting, comparing patients with and without a biomarker of resistance (*PIK3CA* mutation, *RAS* mutation, or loss of PTEN protein expression). (A) Patients treated with cetuximab alone. (B) Patients treated with cetuximab + chemotherapy.



**Figure S2** Progression-free-survival (PFS) in group 2 (cetuximab + radiotherapy), comparing patients with and without a biomarker of resistance (*PIK3CA* mutation, *RAS* mutation, or loss of PTEN protein expression).



**Figure S3** Progression-free-survival (PFS) in patients with and without a biomarker of resistance (PIK3CA mutation, RAS mutation, or loss of PTEN protein expression). (A) human papillomavirus (HPV) negative patients. (B) HPV positive patients.