

Table S1a – *TP53* mutation distribution by effect and type grouped into categories for predicted effect on the protein

<b>Biomarker</b>	<b>Mutation effect</b>	<b>n</b>	<b>%</b>
<i>TP53</i>	Wild Type	129	51.2
	Mutated	121	48.8
Conservation	0 – Silent (and WT)	133	54.1
	1 – Deleterious	78	31.7
	2 – Neutral	1	0.4
	4 – Non missense	34	13.8
Transactivation	0 – Silent MT or WT	133	54.1
	1 – Non Functional	73	29.7
	2 – Functional/Partially functional	6	2.4
	4 – NA	34	13.8
Structure	0 – Silent (and WT)	133	54.7
	1 – Missense mutations in DNA-binding domain	44	18.1
	2 – Missense mutations outside DNA-binding domain	32	13.2
	4 – Non-missense	34	14.0
Type	0 – Wild Type	130	53.3
	1 – CpGs sites	6	2.5
	2 – A:T > xxx	24	9.8
	3 – All G>T	36	14.8
	4 – G>A or G>C not a CpG sites	27	11.1
	5 - Other	21	8.6
Deleterious	0 – Wild type and silent mutations	133	53.8
	1 – Deleterious	82	33.2
	2 – Non-deleterious	32	13.0

<sup>s</sup> Hardy Weinberg equilibrium test validated

<b>Variable (missing)</b>	<b>Items</b>	<b>Wild type (n = 130)</b>		<b>3 – All G &gt; T (n = 36)</b>		<b>P value<sup>s</sup></b>
		<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	
Gender	Male	108	83.1	30	83.3	0.78
	Female	22	16.9	6	16.7	
Age	< 60	41	31.5	15	41.7	0.16
	[60 – 65]	16	12.3	7	19.4	
	[65 – 70]	24	18.5	9	25.0	
	≥ 70	49	37.7	5	13.9	
Smoking status * (1)	Current smoker	78	60.5	25	69.4	0.60
	Former smoker	44	34.1	10	27.8	
	Never smoker	7	5.4	1	2.8	
Age at smoking initiation (2)	< 16	51	41.8	14	41.2	0.29
	[16 – 18]	20	16.4	3	8.8	
	[18 – 20]	22	18.0	4	11.8	
	≥ 20	29	23.8	13	38.2	
Smoking duration (3) in years	< 30	15	12.4	6	17.7	0.67
	[30 – 40]	36	29.8	11	32.4	
	[40 – 50]	33	27.3	12	35.3	
	≥ 50	37	30.6	5	14.7	

Packs year (3)	< 20	20	15.6	4	11.4	0.24
	[20 – 40]	41	32.0	18	51.4	
	[40 – 50]	22	17.2	5	14.3	
	≥ 50	45	35.2	8	22.9	
Cigarette type (4)	Filter	53	44.2	16	45.7	0.78
	Mixed	38	31.7	9	25.7	
	Non Filter & Rolled	29	24.2	10	28.6	
Years since quit smoking** (1)	[2 – 6]	9	20.5	1	10.0	0.54
	[6 – 13]	14	31.8	3	30.0	
	[13 – 20 ]	8	18.2	5	50.0	
	≥ 20	13	29.6	1	10.0	

\* Current smokers were smokers in the last 2 years before interview

\*\* Among patients who ever smoked and quit (former smokers)

\$ Mantel Haenzsel Chi square controlling for centre

**Table S1b – Association between *TP53* mutation and clinical variables**

Variable (missing)	Items	Wild type (n = 129)		Mutated (n = 121)		P value <sup>\$</sup>
		n	%	n	%	
Gender	Male	107	82,9	103	85,1	0.8936
	Female	22	17,1	18	14,9	
Age	< 60	40	31	49	40,5	0.6034
	[60-65]	49	38	33	27,3	
	[65-70]	16	12,4	14	11,6	
	≥ 70	24	18,6	25	20,7	
Education level (10)	No/Primary Level	93	76,2	88	74,6	0.7154
	High educated	29	23,8	30	25,4	
Histology	Adenocarcinoma	85	65,9	48	39,7	<.0001
	Squamous Cell Carcinoma	41	31,8	69	57	
	Others	3	2,3	4	3,3	
Asbestos exposure (2)	Non	100	78,7	91	75,2	0.8007
	Yes	27	21,3	30	24,8	
pT (1)	T1	39	30,5	37	30,6	0.9810
	T2	76	59,4	74	61,2	
	T3	8	6,3	7	5,8	
	T4	5	3,9	3	2,5	
pN (1)	N0	89	69,5	84	69,4	0.3696
	N1	30	23,4	35	28,9	
	N2	2	1,6	0	0	
	NX	7	5,5	2	1,7	
Past pulmonary illness (2)	No	50	39,4	60	49,6	0.1505
	Yes	77	60,6	61	50,4	
Smoking status * (1)	Current smoker	77	60,2	75	62	0.8287
	Former smoker	44	34,4	42	34,7	
	Never smoker	7	5,5	4	3,3	

\$ Mantel Haenzsel Chi square controlling for centre

**Table S1c - Association between *TP53* mutation and smoking variables**

Variable (missing)	Items	Wild type (n = 129)		Mutated (n = 121)		P value <sup>§</sup>
		n	%	n	%	
Smoking duration (2) in years	< 30	15	12.5	20	17.2	0.3690
	[30-40]	35	29.2	35	30.2	
	[40-50]	33	27.5	39	33.6	
	≥ 50	37	30.8	22	19.0	
Age at smoking initiation (1)	< 16	50	41.3	41	35.3	0.7771
	[16-18]	20	16.5	21	18.1	
	[18-20]	22	18.2	26	22.4	
	≥ 20	29	24.0	28	24.1	
Packs year (3)	< 20	20	15.8	18	15.0	0.7647
	[20-40]	41	32.3	48	40.0	
	[40-50]	22	17.3	22	18.3	
	≥ 50	44	34.7	32	26.7	
Years since quit smoking **	[2 – 6]	9	20.5	4	9.5	0.7084
	[6 – 13]	14	31.8	14	33.3	
	[13 – 20]	8	18.2	13	31.0	
	≥ 20	13	29.6	11	26.2	
Cigarette type (4)	Filtered	52	43.7	52	45.2	0.5528
	Mixed	38	31.9	29	25.2	
	Non Filtered/Rolled	29	24.4	34	29.6	
Family history of Lung/HN cancer (6)	No Lung/HN cancer	96	76,8	83	69,7	0.1620
	Lung/HN cancer	29	23,2	36	30,3	
Personal history of Lung/HN cancer (2)	No Lung/HN cancer	118	92,9	107	88,4	0.4381
	Lung/HN cancer	9	7,1	14	11,6	

\* Current smokers were smokers in the last 2 years before interview

\*\* Among patients who ever smoked and quit (former smoker)

§ Mantel Haenzsel Chi square controlling for centre

**Table S2a – Clinical risk factors of *TP53* mutation**

Variable (missing)	Items	Wild type (n=135)		Mutated (n=124)		P**
		n	%	n	%	
Gender (1)	Female	21	15,7	19	15,3	0.9241
	Male	113	84,3	105	84,7	
Age	<60	40	29,6	51	41,1	0.4672
	[60-65]	16	11,9	14	11,3	
	[65-70]	25	18,5	24	19,4	
	≥70	54	40	35	28,2	
Education age (22)	<14	17	13,9	22	19,1	0.2665
	[14-16]	48	39,3	41	35,7	
	[16-18]	19	15,6	25	21,7	
	≥18	38	31,1	27	23,5	
Past cancer (6)	No	112	85,5	96	78,7	0.1972
	Yes	19	14,5	26	21,3	
Asbestos exposure (6)	No	90	68,7	84	68,9	0.6270
	Unsure	14	10,7	8	6,6	

	Yes	27	20,6	30	24,6	
Past pulmonary illness (6)	None	51	38,9	59	48,4	0.2018
	At least one	80	61,1	63	51,6	
Family history of Lung/HN cancer (10)	Lung/HNCancer	29	22,5	37	30,8	0.1103
	No Lung/HNCancer	100	77,5	83	69,2	
Family history of cancer (10)	Cancer	62	48,1	66	55	0.1650
	No cancer	67	51,9	54	45	
Smoking status (1)	Current Smoker	20	14,9	27	21,8	0.5288
	Former Smoker	106	79,1	93	75	
	Never Smoker	8	6	4	3,2	
Cigarette type (10)	Filtered	52	43	53	45,7	0.6311
	Mixed	39	32,2	30	25,9	
	Non Filtered/Rolled	30	24,8	33	28,4	
Years since quit smoking (46)	<1	20	19,8	27	27	0.5433
	[1-2]	18	17,8	21	21	
	[2-10]	32	31,7	21	21	
	≥10	31	30,7	31	31	
Smoking initiation age (7)	<15	30	24,4	27	23,1	0.5674
	[15-16]	21	17,1	14	12	
	[16-18]	21	17,1	22	18,8	
	≥ 18	51	41,5	54	46,2	
Packs year (8)	<25	34	26,2	29	24	0.5484
	[25-40]	28	21,5	37	30,6	
	[40-55]	34	26,2	27	22,3	
	≥ 55	34	26,2	28	23,1	
Smoking duration (8)	<30	24	18,5	23	19	0.3587
	[30-40]	34	26,2	36	29,8	
	[40-50]	33	25,4	39	32,2	
	≥ 50	39	30	23	19	
<b>Histology</b>	Adenocarcinoma	91	67,4	48	38,7	<b>&lt;.0001</b>
	Squamous Cell Carcinoma	43	31,9	69	55,6	
	Other	1	0,7	7	5,6	
pT (1)	T1	41	30,6	37	29,8	0.9071
	T2	79	59	77	62,1	
	T3	9	6,7	7	5,6	
	T4	5	3,7	3	2,4	
pN (1)	N0	94	70,1	85	68,5	0.9875
	N1, N2, Nx	40	30,9	39	31,5	
Stage (1 + 9 Nx*)	Stage I	90	70,9	82	67,2	0.6485
	Stage II	28	22,0	32	26,2	
	Stage III	9	7,1	8	6,6	

\* 9 stages unknown because of undetermined pN

\*\* Conditional logistic regression with centre stratification

**Table S2b - Clinical risk factors of *KRAS* mutation**

Variable (missing)	Items	Wild type (n=203)		Mutated (n=46)		P value
		n	%	n	%	
Gender	Male	172	84,7	38	82,6	0.81
	Female	31	15,3	8	17,4	
Age	< 60	73	36	14	30,4	0.77
	[60-65]	26	12,8	5	10,9	
	[65-70]	38	18,7	12	26,1	
	≥ 70	66	32,5	15	32,6	
Past pulmonary illness (2)	No	88	43,6	21	46,7	0.77
	Yes	114	56,4	24	53,3	
Asbestos exposure (2)	Non	154	76,2	36	80	0.82
	Yes	48	23,8	9	20	
pN (1)	N0	140	69,3	33	71,7	0.60
	N1, N2, NX	62	30,7	13	28,3	
pT (1)	T1	68	33,7	9	19,6	0.10
	T2, T3, T4	134	66,3	37	80,4	
Histology	SCC / Others	110	54,2	5	10,9	<b>&lt;.0001</b>
	ADK	93	45,8	41	89,1	
Smoking status * (1)	Current smoker	128	63,4	24	52,2	0.08
	Former smoker	64	31,7	21	45,7	
	Never smoker	10	5	1	2,2	
Smoking duration (2) in years	< 30	27	14.1	9	20.0	0.29
	[30-40]	54	28.3	14	31.1	
	[40-50]	63	33.0	10	22.2	
	≥ 50	47	24.6	12	26.7	
Age at smoking initiation	< 16	75	39.1	17	37.8	0.95
	[16-18]	32	16.7	9	20.0	
	[18-20]	36	18.8	9	20.0	
	≥ 20	49	25.5	10	22.2	
Packs year (1)	< 20	28	13.9	10	21.7	0.64
	[20-40]	74	36.8	15	32.6	
	[40-50]	36	17.9	8	17.4	
	≥ 50	63	31.3	13	28.3	
Years since quit smoking **	[2 – 6]	11	17.2	2	9.5	0.71
	[6 – 13]	22	34.4	6	28.6	
	[13 – 20]	15	23.4	5	23.8	
	≥ 20	16	25.0	8	38.1	
Cigarette type (4)	Filtered	79	42	24	53,3	0.23
	Mixed	58	30,9	9	20	
	Non Filtered/Rolled	51	27,1	12	26,7	
Family history of Lung/HN cancer (5)	No Lung/HN cancer	146	73,4	33	73,3	0.92
	Lung/HN cancer	53	26,6	12	26,7	
Personal history of Lung/HN cancer (2)	No Lung/HN cancer	183	90,6	41	91,1	0.49
	Lung/HN cancer	19	9,4	4	8,9	

\* Current smoker were smoker in the last 2 years before interview

\*\* Among patients who ever smoked and quit (Former smoker)

§ Mantel Haenzsel Chi square controlling for centre

**Table S2c - Clinical risk factors of *EGFR* mutation (on 120 ADC patients)**

Variable (missing)	Items	Wild type (n=113)		Mutated (n=17)		P value
		n	%	n	%	
Gender	Male	92	81.4	11	64.7	0.35
	Female	21	18.6	6	35.3	
Age	< 60	41	36.3	5	29.4	0.21
	[60-65]	15	13.3	2	11.8	
	[65-70]	19	16.8	6	35.3	
	≥ 70	38	33.6	4	23.5	
Past pulmonary illness	No	55	48.7	8	47.1	0.72
	Yes	58	51.3	9	52.9	
Asbestos exposure	Non	89	78.8	14	82.4	0.93
	Yes	24	21.2	3	17.7	
pN (1)	N0	83	73.5	11	68.8	0.95
	N1, N2, NX	30	26.6	5	31.3	
pT (1)	T1	36	31.9	5	31.3	0.87
	T2, T3, T4	77	68.1	11	68.8	
Smoking status*	Current smoker	64	56.6	8	47.1	0.11
	Former smoker	43	38.1	5	29.4	
	Never smoker	6	5.3	4	23.5	
Smoking duration (1) In years	< 30	21	19.8	4	30.8	0.49
	[30-40]	33	31.1	2	15.4	
	[40-50]	29	27.4	3	23.1	
	≥ 50	23	21.7	4	30.8	
Age at smoking initiation	≥ 16	59	55.1	8	61.5	0.87
	< 16	48	44.9	5	38.5	
Packs year (1)	≤ 40	61	54.5	13	76.5	0.15
	> 40	51	45.5	4	23.5	
Years since quit smoking **	≥ 13	24	55.8	3	60.0	0.96
	< 13	19	44.2	2	40.0	
Cigarette type (3)	Filtered	48	45.7	5	41.7	0.97
	Mixed	31	29.5	4	33.3	
	Non Filtered/Rolled	26	24.8	3	25.0	
Family history of Lung/HN cancer (2)	No Lung/HN cancer	80	71.4	10	62.5	0.34
	Lung/HN cancer	32	28.6	6	37.5	
Personal history of Lung/HN cancer	No Lung/HN cancer	103	91.2	16	94.1	0.79
	Lung/HN cancer	10	8.9	1	5.9	
Gender / Smoking status	Others	109	96.5	13	76.5	<b>0.0067</b>
	Never smoker female	4	3.5	4	23.5	

\* Current smoker were smoker in the last 2 years before interview

\*\* Among patients who ever smoked and quit (Former smoker)

§ Mantel Haenzsel Chi square controlling for centre

**Table S3 - Association between *TP53* mutation and P53 expression**

P53 Expression score*	TP53 Mutation		Total
	Wild Type	Mutated	
(0,1,2)	87 37.8 %	43 18.7 %	130 56.5 %
3	29 12.6 %	71 30.9 %	100 43.5 %
<b>Total</b>	116 50.4 %	114 49.6 %	230 100 %

Mantel Haenzel Chi square controlling for centre: P<.0001

\*: p53 immunostaining was expressed as a score summing up the results for intensity and distribution as follows: sum of 0, no staining (score 0); sum of 1 to 3, slight staining (score 1); sum of 4 to 5, moderate staining (score 2); and sum of 6 to 7, marked staining (score 3).

**Table S4 – Clinical risk factors of disease progression**

Variable (missing)	Items	DF (n=162)		PD (n=99)		P*
		n	%	n	%	
Gender (1)	Female	23	14,2	18	18,4	0.1285
Age	> 65	81	50	51	51,5	0.5066
Education duration (22) in years	> 16	54	35,8	37	41,6	0.7591
Professional exposure (6)	Asbestos	35	22	21	21,9	0.5629
Past pulmonary illness (6)	At least one	83	52,2	61	63,5	0.0991
Family history of HN/Lung cancer (10)	HN/Lung cancer	44	28	22	23,4	0.4807
Family history of cancer (10)	Any cancer	79	50,3	47	50	0.7761
Smoking status (1)	Current smoker	36	22,2	13	13,3	0.0634
Cigarette type (10)	Non Filtered	82	55,4	52	56,5	0.7210
Years since quit smoking	< 5	68	42	43	43,4	0.7059
Age at smoking initiation	< 16 years old	74	45,7	37	37,4	0.5271
Packs year (8)	> 40	79	50,3	42	43,3	0.1196
<b>Smoking duration ( 8) in years</b>	<b>&gt;40</b>	<b>88</b>	<b>56,1</b>	<b>42</b>	<b>43,3</b>	<b>0.0224</b>
PLC Histology	Adenocarcinoma	89	54,9	54	54,5	0.5583
	Squamous Cell Carcinoma	70	43,2	40	40,4	0.4535
<b>pT (1)</b>	T2, T3, T4 vs T0, T1	99	61,1	82	83,7	<b>0.0014</b>
<b>pN (1)</b>	N1, N2, Nx vs N0	33	20,4	44	44,9	<b>0.0006</b>
<b>Tumor Stage (1+ 9 Nx**)</b>	Stages II & III vs Stage I	34	21,4	42	45,2	<b>0.0038</b>

\* Fine & Gray hazard model in the setting of competing risk with centre stratification

\*\* 9 stages unknown because of undetermined pN

**Table S5 – Association between disease progression and predicted effect of *TP53* mutation on p53 protein or function.**

Variable	Item	DF		PD		HR (95% CI)	P*	Adj HR (95% CI)	P <sup>§</sup>
		n	%	n	%				
<b>TP53</b>	Wild Type	73	50	56	53,8	1	0.51	1	0.77
	Mutated	73	50	48	46,2	0.88 (0.59 – 1.30)		0.94 (0.63 – 1.40)	
Conservation	Silent	75	51,7	59	58,4	1	0.32	1	0.62
	Deleterious	45	31	33	32,7	0.91 (0.59 – 1.41)		1.00 (0.64 – 1.55)	
	Non missense	25	17,2	9	8,9	0.58 (0.29 – 1.18)		0.71 (0.35 – 1.45)	
Transactivation	Silent/ WT/ Functional	78	53,8	61	60,4	1	0.32	1	0.62
	Non Functional	42	29	31	30,7	0.91 (0.58 – 1.41)		0.98 (0.63 – 1.52)	
	Non missense	25	17,2	9	8,9	0.58 (0.29 – 1.18)		0.70 (0.34 – 1.43)	
Structure	Silent/ WT	74	51,7	59	59	1	0.46	1	0.76
	Missense in DNA-binding domain	24	16,8	20	20	0.94 (0.56 – 1.58)		0.99 (0.59 – 1.66)	
	Missense outside DNA-bind domain	20	14	12	12	0.83 (0.44 – 1.55)		0.86 (0.46 – 1.63)	
	Non missense	25	17,5	9	9	0.57 (0.28 – 1.16)		0.69 (0.34 – 1.41)	
Structure	Silent/ WT/ Non missense	99	69,2	68	68	1	0.93	1	0.98
	Missense	44	30,8	32	32	0.98 (0.64 – 1.50)		0.99 (0.65 – 1.52)	
Type	Others	128	88,9	80	80	1	0.14	1	0.11
	All G > T	16	11,1	20	20	1.45 (0.88 – 2.40)		1.52 (0.92 – 2.51)	
Deleterious	Silent/ WT	74	51,4	59	57,3	1	0.65	1	0.86
	Deleterious	50	34,7	32	31,1	0.83 (0.54 – 1.29)		0.93 (0.59 – 1.44)	
	Non deleterious	20	13,9	12	11,7	0.82 (0.44 – 1.54)		0.85 (0.45 – 1.61)	
<b>KRAS</b>	Wild Type	122	84,7	81	77,1	1	0.21	1	0.43
	Mutated	22	15,3	24	22,9	1.35 (0.85 – 2.15)		1.21 (0.75 – 1.94)	
<b>KRAS/TP53</b>	Otherwise	142	97,9	98	93,3	1	0.07	1	0.22
	Both Mutated	3	2,1	7	6,7	2.08 (0.95 – 4.57)		1.66 (0.74 – 3.76)	
<b>KRAS/TP53</b>	Otherwise	53	36,6	39	37,5	1	0.70	1	0.83
	At least one Mutated	92	63,4	65	62,5	0.93 (0.62 – 1.38)		0.96 (0.64 – 1.44)	
<b>EGFR<sup>E</sup></b>	Wild Type	63	86,3	50	87,7	1	0.57	1	0.80
	Mutated	10	13,7	7	12,3	1.26 (0.56 – 2.83)		1.12 (0.47 – 2.67)	



<b>P53 Expression</b>	0, 1, 2	98	53,8	65	52,4	1		1	
	3	84	46,2	59	47,6	1.02 (0.71 – 1.46)	0.92	1.01 (0.70 – 1.46)	0.97
<b>P53 / TP53</b>	Otherwise	89	66,9	70	72,2	1		1	
	P53 = 3 and TP53 = mutated	44	33,1	27	27,8	0.84 (0.54 – 1.32)	0.46	0.93 (0.59 – 1.47)	0.74

Supplementary Figures

Figure S1 Patterns of mutations, broken down by type of base substitution.

