Supplementary results

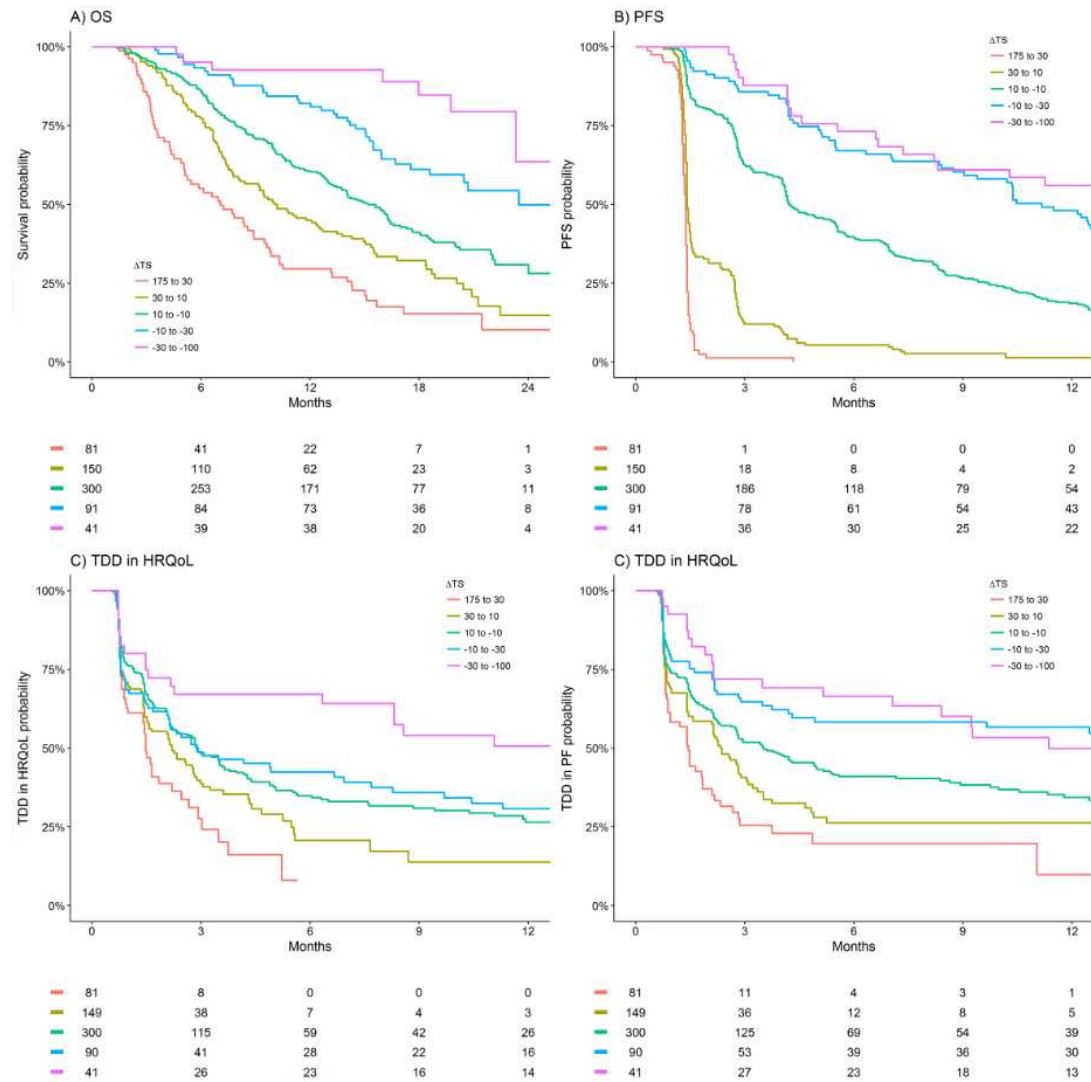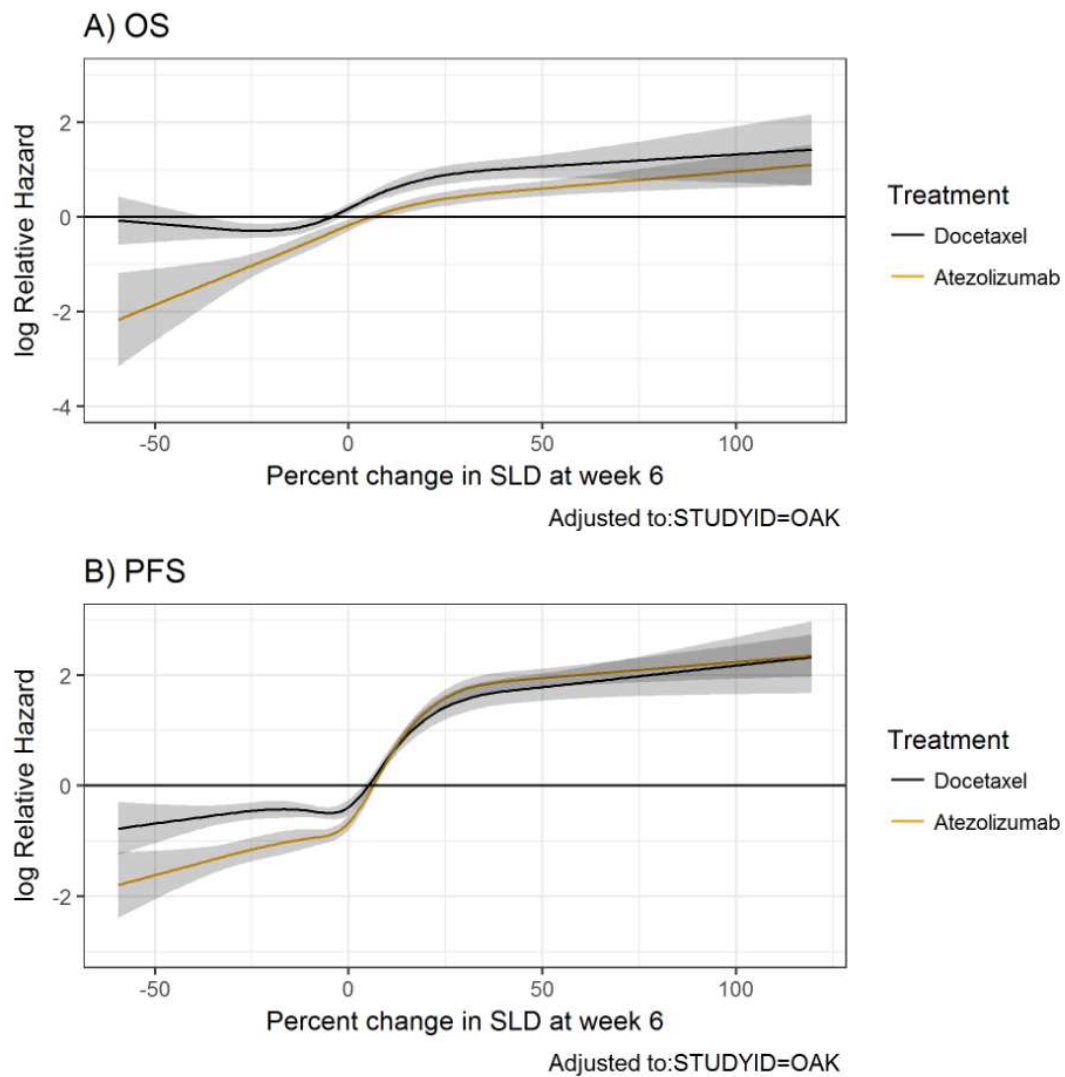**Figure S1: Kaplan Meier estimates of OS, PFS, TDD in HRQoL and PF by ΔTS (%) for atezolizumab treated patients from OAK and POPLAR**

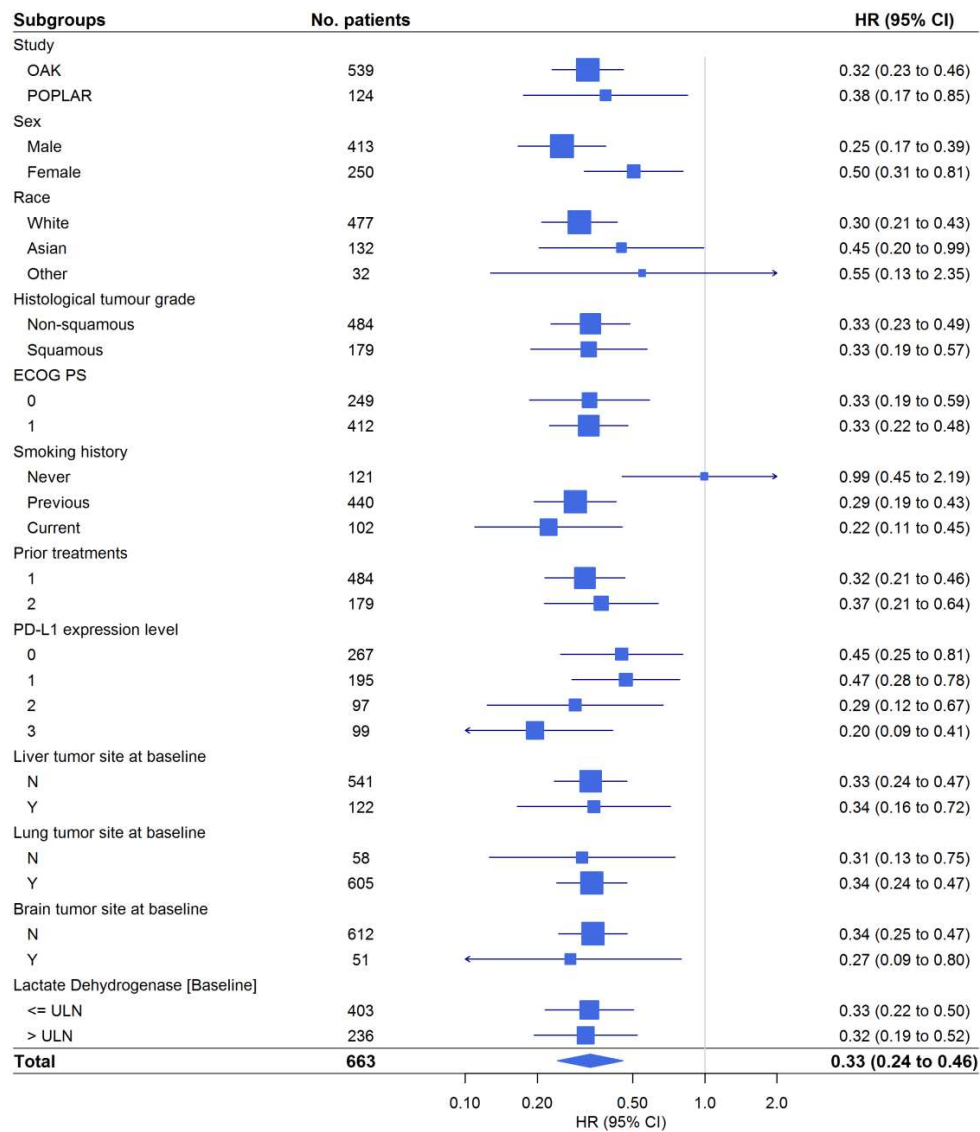**Figure S2: Relationship (log Relative Hazard ±95%CI) between ΔTS with OS and PFS for patients from OAK and POPLAR. AIC defined a restricted cubic spline of 4 knots for OS, and 5 knots for PFS.**

Table S1: Univariable and multivariable association between ΔTS and OS, PFS, TDD in HRQoL and PF for patients treated with atezolizumab from BIRCH and FIR

	ΔTS	N	Univariable Analysis		Multivariable Analysis [a]	
			HR (95%CI)	P	HR (95%CI)	P
OS	175 to 30	56	2.32 (1.43-3.77)		2.17 (1.30-3.62)	
	30 to 10	147	2.43 (1.74-3.41)		2.27 (1.59-3.24)	
	10 to -10	282	Reference	<0.001	Reference	<0.001
	-10 to -30	108	0.65 (0.39-1.08)		0.64 (0.37-1.10)	
	-30 to -100	75	0.42 (0.21-0.83)		0.45 (0.22-0.91)	
PFS	175 to 30	56	6.92 (5.02-9.54)		7.14 (5.07-10.1)	
	30 to 10	147	2.92 (2.33-3.66)		3.06 (2.41-3.88)	
	10 to -10	282	Reference	<0.001	Reference	<0.001
	-10 to -30	108	0.57 (0.43-0.76)		0.62 (0.46-0.84)	
	-30 to -100	75	0.40 (0.28-0.59)		0.40 (0.27-0.59)	
TDD in HRQoL	175 to 30	55	1.24 (0.84-1.83)		1.32 (0.88-1.98)	
	30 to 10	147	1.44 (1.12-1.85)		1.53 (1.18-1.98)	
	10 to -10	282	Reference	<0.001	Reference	<0.001
	-10 to -30	107	0.73 (0.54-0.98)		0.77 (0.57-1.05)	
	-30 to -100	75	0.55 (0.38-0.80)		0.57 (0.39-0.85)	
TDD in PF	175 to 30	55	1.29 (0.84-1.98)		1.14 (0.73-1.79)	
	30 to 10	147	1.58 (1.21-2.07)		1.53 (1.16-2.03)	
	10 to -10	282	Reference	<0.001	Reference	<0.001
	-10 to -30	107	0.85 (0.62-1.16)		0.85 (0.62-1.19)	
	-30 to -100	75	0.66 (0.45-0.97)		0.65 (0.44-0.97)	

CI = confidence interval, HR = hazard ratio, OS = overall survival, ΔTS = early changes in tumour size
[a] multivariable analysis adjusted for baseline ECOG PS, age, sex, race, smoking status, histology, count of prior treatments, PDL1 expression, serum LDH levels and the presence of liver, lung or brain lesions

Subgroups	No. patients	HR (95% CI)
Study		
OAK	539	0.32 (0.23 to 0.46)
POPLAR	124	0.38 (0.17 to 0.85)
Sex		
Male	413	0.25 (0.17 to 0.39)
Female	250	0.50 (0.31 to 0.81)
Race		
White	477	0.30 (0.21 to 0.43)
Asian	132	0.45 (0.20 to 0.99)
Other	32	0.55 (0.13 to 2.35)
Histological tumour grade		
Non-squamous	484	0.33 (0.23 to 0.49)
Squamous	179	0.33 (0.19 to 0.57)
ECOG PS		
0	249	0.33 (0.19 to 0.59)
1	412	0.33 (0.22 to 0.48)
Smoking history		
Never	121	0.99 (0.45 to 2.19)
Previous	440	0.29 (0.19 to 0.43)
Current	102	0.22 (0.11 to 0.45)
Prior treatments		
1	484	0.32 (0.21 to 0.46)
2	179	0.37 (0.21 to 0.64)
PD-L1 expression level		
0	267	0.45 (0.25 to 0.81)
1	195	0.47 (0.28 to 0.78)
2	97	0.29 (0.12 to 0.67)
3	99	0.20 (0.09 to 0.41)
Liver tumor site at baseline		
N	541	0.33 (0.24 to 0.47)
Y	122	0.34 (0.16 to 0.72)
Lung tumor site at baseline		
N	58	0.31 (0.13 to 0.75)
Y	605	0.34 (0.24 to 0.47)
Brain tumor site at baseline		
N	612	0.34 (0.25 to 0.47)
Y	51	0.27 (0.09 to 0.80)
Lactate Dehydrogenase [Baseline]		
<= ULN	403	0.33 (0.22 to 0.50)
> ULN	236	0.32 (0.19 to 0.52)
Total	**663**	**0.33 (0.24 to 0.46)**

HR (95% CI)

Figure S3: Effect of ETS on OS by pre-treatment characteristic subgroups for patients treated with atezolizumab from OAK and POPLAR
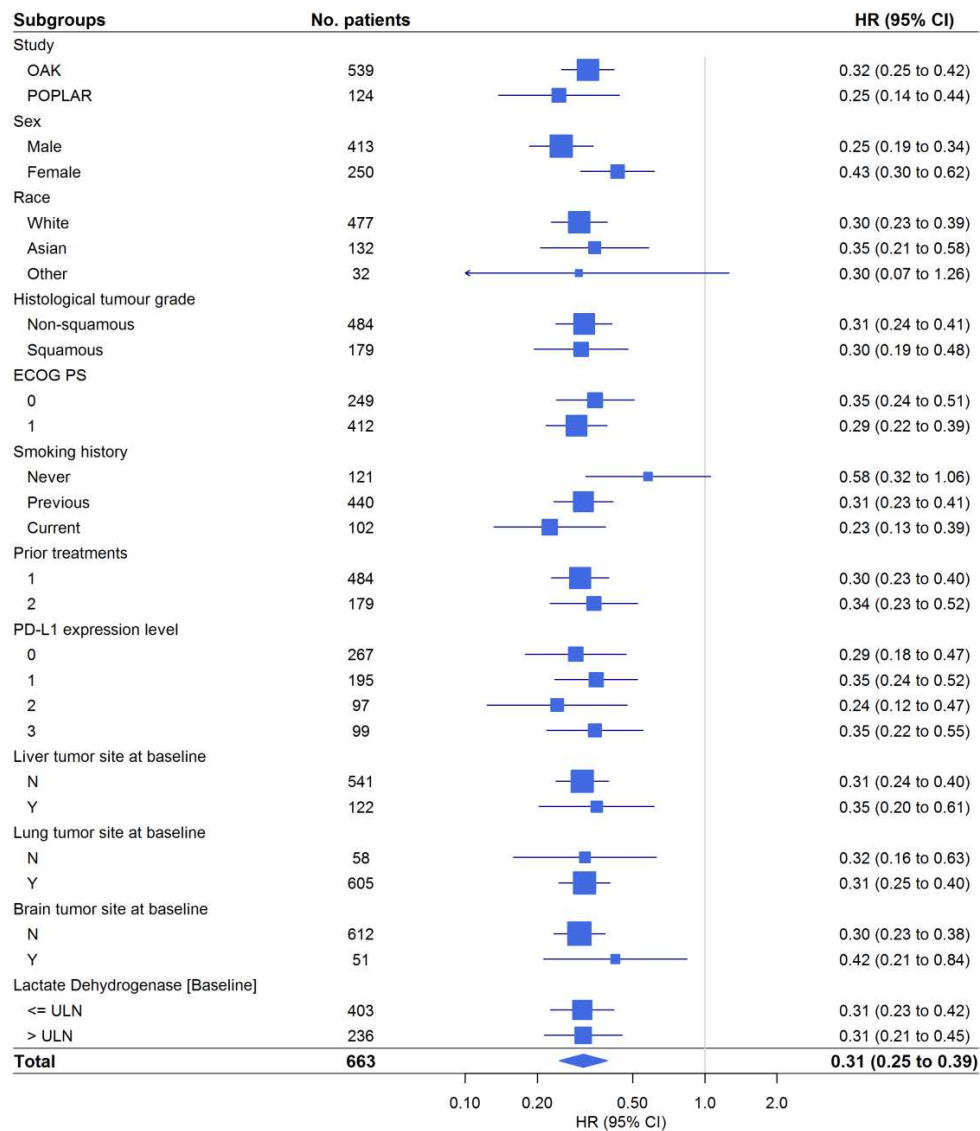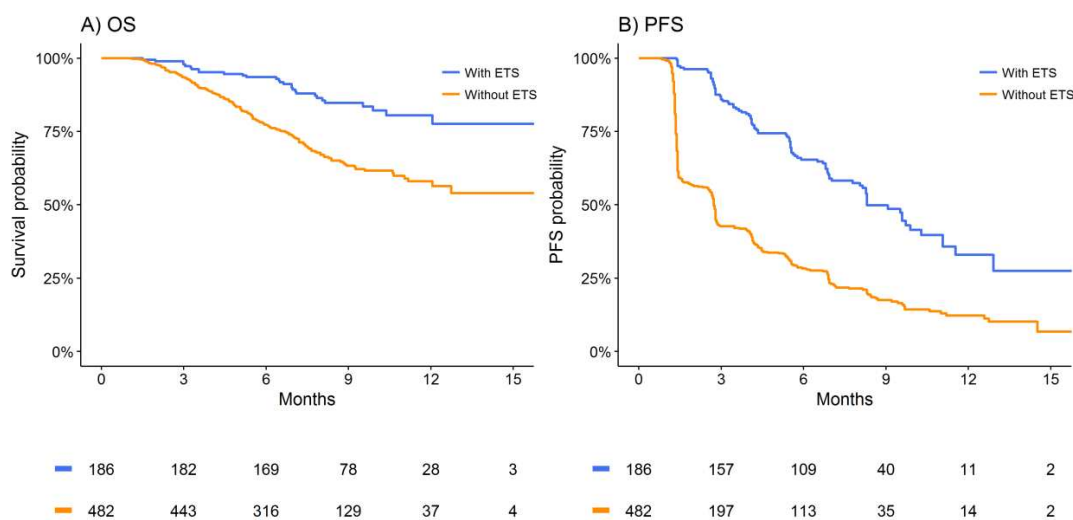
Figure S4: Effect of ETS on PFS by pre-treatment characteristic subgroups for patients treated with atezolizumab from OAK and POPLAR

Table S2: Univariable and multivariable association between ETS status (with and without) and OS / PFS for patients treated with atezolizumab from BIRCH and FIR.

	ETS	Probability (%) at 15-months (95%CI)	N	Univariable Analysis HR (95%CI)	P	c	N	Multivariable Analysis a HR (95%CI)	P	c
OS	No	54 (47-62)	482	.	<0.001	0.58	457	.	<0.001	0.72
	Yes	78 (69-87)	186	0.37 (0.25-0.56)			177	0.40 (0.26-0.61)		
PFS	No	7 (3-17)	482	.	<0.001	0.62	457	.	<0.001	0.69
	Yes	27 (17-44)	186	0.35 (0.28-0.44)			177	0.37 (0.29-0.47)		

CI = confidence interval, HR = hazard ratio
a multivariable analysis adjusted for baseline ECOG PS, age, sex, race, smoking status, histology, count of prior treatments, PDL1 expression, serum LDH levels and the presence of liver, lung or brain lesions

Figure S5: Kaplan Meier estimates of OS and PFS by ETS status for atezolizumab treated patients from BIRCH and FIR

Table S3: Univariable and multivariable association between ETS status (with and without) at week 12 with OS and PFS for patients treated with atezolizumab from OAK and POPLAR.

	ETS	N	Univariable Analysis HR (95%CI)	P	c	N	Multivariable Analysis a HR (95%CI)	P	c
OS	No	338	.	<0.001	0.60	314	.	<0.001	0.68
	Yes	170	0.41 (0.31-0.56)			157	0.39 (0.28-0.54)		
PFS	No	338	.	<0.001	0.62	314	.	<0.001	0.66
	Yes	170	0.37 (0.30-0.46)			157	0.38 (0.30-0.48)		

CI = confidence interval, HR = hazard ratio
a multivariable analysis adjusted for baseline ECOG PS, age, sex, race, smoking status, histology, count of prior treatments, PDL1 expression, serum LDH levels and the presence of liver, lung or brain lesions

Table S4: Univariable and multivariable association between ETS status (with and without) at week 12 with OS and PFS for patients treated with atezolizumab from BIRCH and FIR.

	ETS	N	Univariable Analysis HR (95%CI)	P	c	N	Multivariable Analysis a HR (95%CI)	P	c
OS	No	296	.	<0.001	0.63	282	.	<0.001	0.74
	Yes	236	0.33 (0.21-0.53)			223	0.38 (0.23-0.63)		
PFS	No	296	.	<0.001	0.66	282	.	<0.001	0.70
	Yes	236	0.29 (0.23-0.36)			223	0.31 (0.24-0.39)		

CI = confidence interval, HR = hazard ratio
a multivariable analysis adjusted for baseline ECOG PS, age, sex, race, smoking status, histology, count of prior treatments, PDL1 expression, serum LDH levels and the presence of liver, lung or brain lesions

Table S5: Summary of pre-treatment characteristics of atezolizumab and docetaxel treated participants of OAK and POPLAR by ETS status

	Atezolizumab			Docetaxel		
	Without ETS No. 528	With ETS No. 135	P-value	Without ETS No. 413	With ETS No. 198	P-value
Study			0.81			0.58
OAK	428 (81%)	111 (82%)		333 (81%)	164 (83%)	
POPLAR	100 (19%)	24 (18%)		80 (19%)	34 (17%)	
Age (years)	63 (57 - 69)	62 (55 - 71)	0.92	62 (56 - 68)	64 (57 - 71)	0.15
Sex			1			0.48
Male	329 (62%)	84 (62%)		242 (59%)	122 (62%)	
Female	199 (38%)	51 (38%)		171 (41%)	76 (38%)	
Race			0.53			< 0.001
White	377 (71%)	100 (74%)		315 (76%)	118 (60%)	
Asian	107 (20%)	25 (19%)		56 (14%)	63 (32%)	
Other	28 (5%)	4 (3%)		28 (7%)	9 (5%)	
Missing	16 (3%)	6 (4%)		14 (3%)	8 (4%)	
Smoking history			< 0.001			0.024
Never	108 (20%)	13 (10%)		56 (14%)	44 (22%)	
Previous	350 (66%)	90 (67%)		281 (68%)	125 (63%)	
Current	70 (13%)	32 (24%)		76 (18%)	29 (15%)	
Histological tumour grade			0.83			0.021
Non-squamous	384 (73%)	100 (74%)		285 (69%)	155 (78%)	
Squamous	144 (27%)	35 (26%)		128 (31%)	43 (22%)	
ECOG PS			0.55			0.72
0	195 (37%)	54 (40%)		159 (38%)	80 (40%)	
1	331 (63%)	81 (60%)		253 (61%)	118 (60%)	
Missing	2 (<1%)	0 (0%)		1 (<1%)	0 (0%)	
Prior treatments			0.45			0.49
1	389 (74%)	95 (70%)		309 (75%)	143 (72%)	
2	139 (26%)	40 (30%)		104 (25%)	55 (28%)	
Days since metastatic diagnosis	316 (568 -196)	328 (560 - 196)	0.34	287 (451 - 178)	376 (616 - 238)	0.003
Months since initial diagnosis	14 (27 - 8)	14 (23 - 9)	0.86	12 (22 - 8)	15 (27 - 9)	0.01
Stage at initial diagnosis			1			0.16
IA	16 (3%)	4 (3%)		9 (2%)	7 (4%)	
IB	19 (4%)	4 (3%)		14 (3%)	10 (5%)	
IIA	13 (2%)	3 (2%)		15 (4%)	1 (1%)	
IIB	32 (6%)	7 (5%)		9 (2%)	8 (4%)	
IIIA	64 (12%)	19 (14%)		55 (13%)	20 (10%)	
IIIB	67 (13%)	17 (13%)		56 (14%)	28 (14%)	
IVA	146 (28%)	37 (27%)		119 (29%)	55 (28%)	
IVB	162 (31%)	39 (29%)		132 (32%)	67 (34%)	
Missing	9 (2%)	5 (4%)		4 (1%)	2 (1%)	
Stage			1			0.44
Locally advanced	33 (6%)	8 (6%)		24 (6%)	8 (4%)	
Metastatic Disease	495 (94%)	127 (94%)		389 (94%)	190 (96%)	
Count of tumour sites	3 (2 - 4)	2 (2 - 3)	0.019	3 (2 - 4)	3 (2 - 4)	0.29
Liver tumour site at baseline	103 (20%)	19 (14%)	0.17	82 (20%)	35 (18%)	0.58
Lung tumour site at baseline	490 (93%)	115 (85%)	0.009	383 (93%)	183 (92%)	0.87
Brain tumour site at baseline	38 (7%)	13 (10%)	0.37	43 (10%)	16 (8%)	0.38
Lactate Dehydrogenase			0.61			0.052
<= ULN	323 (61%)	80 (59%)		220 (53%)	124 (63%)	
> ULN	185 (35%)	51 (38%)		179 (43%)	71 (36%)	
Missing	20 (4%)	4 (3%)		14 (3%)	3 (2%)	
PD-L1 expression level			< 0.001			0.7
0	237 (45%)	30 (22%)		175 (42%)	82 (41%)	
1	152 (29%)	43 (32%)		104 (25%)	58 (29%)	
2	79 (15%)	18 (13%)		75 (18%)	31 (16%)	
3	56 (11%)	43 (32%)		58 (14%)	26 (13%)	
Missing	4 (1%)	1 (1%)		1 (<1%)	1 (1%)	
EGFR mutation status			0.088			0.007
Negative	361 (68%)	102 (76%)		304 (74%)	131 (66%)	
Positive	57 (11%)	7 (5%)		26 (6%)	26 (13%)	
T790M	1 (<1%)	0 (0%)		0 (0%)	0 (0%)	
Missing	109 (21%)	26 (19%)		83 (20%)	41 (21%)	
KRAS mutation status			0.7			0.38
Negative	122 (23%)	40 (30%)		82 (20%)	45 (23%)	
Positive	39 (7%)	10 (7%)		37 (9%)	14 (7%)	
Missing	367 (70%)	85 (63%)		294 (71%)	139 (70%)	
EMLA-ALK rearrangement			0.58			1
Negative	263 (50%)	70 (52%)		172 (42%)	95 (48%)	
Positive	4 (1%)	0 (0%)		2 (<1%)	1 (1%)	
Missing	261 (49%)	65 (48%)		239 (58%)	102 (52%)	

Data are median (IQR) or number of patients (%). P values per Fisher test for categorical data and Wilcoxon test for continuous data.

Median follow-up was 9 [95%CI: 8-9] months within the cohort of 668 advanced NSCLC patients treated with atezolizumab from BIRCH and FIR.

Table S6: Summary of pre-treatment characteristics of atezolizumab and docetaxel treated participants of BIRCH and FIR by ETS status

| | Atezolizumab | | |
	Without ETS No. 482	With ETS No. 186	P-value
Study			0.91
BIRCH	398 (83%)	153 (82%)	
FIR	84 (17%)	33 (18%)	
Age (years)	64 (58 - 71)	67 (58 - 73)	0.17
Sex			0.43
Male	276 (57%)	113 (61%)	
Female	206 (43%)	73 (39%)	
Race			0.57
White	404 (84%)	158 (85%)	
Asian	53 (11%)	18 (10%)	
Other	16 (3%)	9 (5%)	
Missing	9 (2%)	1 (1%)	
Smoking history			0.089
Never	86 (18%)	21 (11%)	
Previous	346 (72%)	141 (76%)	
Current	50 (10%)	24 (13%)	
Histological tumour grade			0.63
Non-squamous	348 (72%)	138 (74%)	
Squamous	134 (28%)	48 (26%)	
ECOG PS			< 0.001
0	160 (33%)	87 (47%)	
1	321 (67%)	95 (51%)	
2	0 (0%)	4 (2%)	
Missing	1 (<1%)	0 (0%)	
Prior treatments			0.007
0	86 (18%)	54 (29%)	
1	234 (49%)	80 (43%)	
2	162 (34%)	52 (28%)	
Days since metastatic diagnosis			0.058
Median (IQR)	350 (718 - 138)	252 (629 - 86)	
Missing	1 (<1%)	0 (0%)	
Months since initial diagnosis			0.26
Median (IQR)	20 (34 - 10)	19 (36 - 9)	
Missing	84 (17%)	33 (18%)	
Stage at initial diagnosis			0.39
IA	21 (4%)	16 (9%)	
IB	32 (7%)	9 (5%)	
IIA	27 (6%)	10 (5%)	
IIB	29 (6%)	11 (6%)	
IIIA	78 (16%)	34 (18%)	
IIIB	53 (11%)	12 (6%)	
IV	47 (10%)	18 (10%)	
IVA	78 (16%)	33 (18%)	
IVB	105 (22%)	38 (20%)	
Missing	12 (2%)	5 (3%)	
Stage			0.38
Locally advanced	22 (5%)	5 (3%)	
Metastatic Disease	460 (95%)	181 (97%)	
Count of tumor sites			0.32
Median (IQR)	2 (2 - 3)	2 (2 - 3)	
Missing	19 (4%)	5 (3%)	
Liver tumor site at baseline	89 (18%)	21 (11%)	0.027
Lung tumor site at baseline	259 (54%)	92 (49%)	0.34
Brain tumor site at baseline	6 (1%)	2 (1%)	1
Lactate Dehydrogenase			0.78
<= ULN	305 (63%)	119 (64%)	
> ULN	162 (34%)	59 (32%)	
Missing	15 (3%)	8 (4%)	
PD-L1 expression level			< 0.001
2	287 (60%)	70 (38%)	
3	195 (40%)	116 (62%)	
EGFR mutation status			0.41
Negative	225 (47%)	74 (40%)	
Positive	32 (7%)	6 (3%)	
T790M	3 (1%)	0 (0%)	
Missing	222 (46%)	106 (57%)	
KRAS mutation status			1
Negative	98 (20%)	35 (19%)	
Positive	50 (10%)	17 (9%)	
Missing	334 (69%)	134 (72%)	
EMLA-ALK rearrangement			0.73
Negative	282 (59%)	110 (59%)	
Positive	8 (2%)	2 (1%)	
Missing	192 (40%)	74 (40%)	

Data are median (IQR) or number of patients (%). P values per Fisher test for categorical data and Wilcoxen test for continuous data.

Table S7: Summary of BOR for atezolizumab and docetaxel treated participants from OAK and POPLAR by ETS status

	Atezolizumab			Docetaxel		
	Without ETS No. 528	With ETS No. 135	P-value	Without ETS No. 413	With ETS No. 198	P-value
Best overall response (study primary definition)			<0.001			<0.001
PD	276 (52%)	16 (12%)		168 (41%)	23 (12%)	
SD	228 (43%)	37 (27%)		208 (50%)	97 (49%)	
PR	18 (3%)	75 (56%)		19 (5%)	73 (37%)	
CR	1 (<1%)	7 (5%)		1 (<1%)	0 (0%)	
Missing	5 (1%)	0 (0%)		17 (4%)	5 (3%)	

Data are median (IQR) or number of patients (%). P values per Fisher test for categorical data and Wilcoxon test for continuous data.
PD – progressive disease, SD – stable disease, PR- partial response, CR – complete response

Table S8: Summary of BOR for atezolizumab treated participants from BIRCH and FIR by ETS status

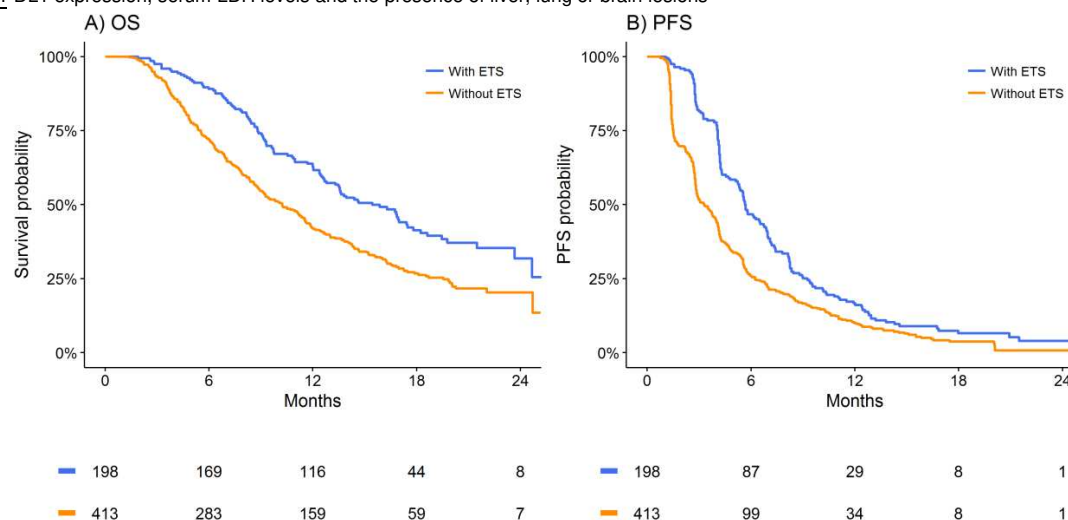|	Atezolizumab		
	Without ETS No. 482	With ETS No. 186	P-value
Best overall response (study primary definition)			<0.001
PD	219 (45%)	15 (8%)	
SD	213 (44%)	63 (34%)	
PR	34 (7%)	98 (53%)	
CR	1 (<1%)	8 (4%)	
Missing	15 (3%)	2 (1%)	

Data are median (IQR) or number of patients (%). P values per Fisher test for categorical data and Wilcoxon test for continuous data.
PD – progressive disease, SD – stable disease, PR- partial response, CR – complete response

Table S9: Univariable and multivariable association between ETS status and OS and PFS, for patients treated with docetaxel from OAK and POPLAR

	ETS	Probability (%) at 24-months (95%CI)	N	Univariable Analysis HR (95%CI)	P	N	Multivariable Analysis [a] HR (95%CI)	P
OS	No	20 (16-26)	413	.	<0.001	385	.	<0.001
	Yes	32 (23-44)	198	0.61 (0.49-0.76)		187	0.65 (0.51-0.82)	
PFS	No	1 (0-5)	413	.	<0.001	385	.	<0.001
	Yes	4 (2-10)	198	0.61 (0.51-0.74)		187	0.64 (0.53-0.78)	

CI = confidence interval, HR = hazard ratio, mOS: median overall survival in months
[a] multivariable analysis adjusted for baseline ECOG PS, age, sex, race, smoking status, histology, count of prior treatments, PDL1 expression, serum LDH levels and the presence of liver, lung or brain lesions

Figure S6: Kaplan Meier estimates of OS and PFS by ETS status for docetaxel treated patients from OAK and POPLAR

Table S10: Summary of pre-treatment characteristics of atezolizumab treated participants who did not experience ETS yet achieved a BOR of complete or partial within OAK, POPLAR, BIRCH or FIR

	No. 54
Study	
OAK	15 (28%)
POPLAR	4 (7%)
BIRCH	29 (54%)
FIR	6 (11%)
Age (years)	64 (59 – 70)
Sex	
Male	25 (46%)
Female	29 (54%)
Race	
White	48 (89%)
Asian	4 (7%)
Other	1 (2%)
Missing	1 (2%)
Smoking history	
Never	4 (7%)
Previous	44 (81%)
Current	6 (11%)
Histological tumour grade	
Non-squamous	40 (74%)
Squamous	14 (26%)
ECOG PS	
0	18 (33%)
1	36 (67%)
Prior treatments	
0	5 (9%)
1	31 (57%)
2	18 (33%)
Days since metastatic diagnosis	464 (816 – 229)
Months since initial diagnosis	
Median (IQR)	21 (42 – 11)
Missing	6 (11%)
Stage at initial diagnosis	
IA	1 (2%)
IB	3 (6%)
IIA	2 (4%)
IIB	7 (13%)
IIIA	9 (17%)
IIIB	10 (19%)
IV	3 (6%)
IVA	8 (15%)
IVB	9 (17%)
Missing	2 (4%)
Stage	
Locally advanced	1 (2%)
Metastatic Disease	53 (98%)
Count of tumor sites	
Median (IQR)	2 (2 – 3)
Missing	1 (2%)
Liver tumor site at baseline	6 (11%)
Lung tumor site at baseline	36 (67%)
Brain tumor site at baseline	54 (100%)
Lactate Dehydrogenase	
<= ULN	41 (76%)
> ULN	12 (22%)
Missing	1 (2%)
PD-L1 expression level	
0	9 (17%)
1	3 (6%)
2	22 (41%)
3	20 (37%)
EGFR mutation status	
Negative	27 (50%)
Positive	4 (7%)
Missing	23 (43%)
KRAS mutation status	
Negative	8 (15%)
Positive	5 (9%)
Missing	41 (76%)
EMLA-ALK rearrangement	
Negative	32 (59%)
Missing	22 (41%)

Data are median (IQR) or number of patients (%). P values per Fisher test for categorical data and Wilcoxen test for continuous data.