

Supplementary Online Content

Kichenadasse G, Miners JO, Mangoni AA, Rowland A, Hopkins A, Sorich MJ. Association between body mass index and overall survival with immune checkpoint inhibitor therapy for advanced non–small cell lung cancer. *JAMA Oncol*. Published online December 26, 2019. doi:10.1001/jamaoncol.2019.5241

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

eTable 1. Baseline Characteristics of Atezolizumab Treated Patients.

	Total No. 1,434	18.5 - 24.9 No. 705	25.0 - 29.9 No. 490	≥30.0 No. 239	P-value
Study					0.90
BIRCH	611 (43%)	301 (43%)	214 (44%)	96 (40%)	
FIR	122 (9%)	61 (9%)	44 (9%)	17 (7%)	
OAK	563 (39%)	274 (39%)	188 (38%)	101 (42%)	
POPLAR	138 (10%)	69 (10%)	44 (9%)	25 (10%)	
Age (years)	64 (57 - 70)	64 (56 - 70)	64 (58 - 71)	63 (57 - 70)	0.093
Sex					< 0.001
Male	890 (62%)	388 (55%)	344 (70%)	158 (66%)	
Female	544 (38%)	317 (45%)	146 (30%)	81 (34%)	
Race					< 0.001
White	1,132 (79%)	519 (74%)	407 (83%)	206 (86%)	
Asian	210 (15%)	146 (21%)	51 (10%)	13 (5%)	
Other	60 (4%)	30 (4%)	18 (4%)	12 (5%)	
Missing	32 (2%)	10 (1%)	14 (3%)	8 (3%)	
ECOG PS					0.067
0	507 (35%)	228 (32%)	188 (38%)	91 (38%)	
1	919 (64%)	474 (67%)	297 (61%)	148 (62%)	
2	6 (<1%)	2 (<1%)	4 (1%)	0 (0%)	
Missing	2 (<1%)	1 (<1%)	1 (<1%)	0 (0%)	
Histology					0.16
Non-squamous	1,033 (72%)	515 (73%)	358 (73%)	160 (67%)	
Squamous	401 (28%)	190 (27%)	132 (27%)	79 (33%)	
Tumor sites					0.13
<3	724 (50%)	349 (50%)	241 (49%)	134 (56%)	
≥3	676 (47%)	338 (48%)	240 (49%)	98 (41%)	
Missing	34 (2%)	18 (3%)	9 (2%)	7 (3%)	
Liver tumor site	273 (19%)	148 (21%)	82 (17%)	43 (18%)	0.17
Bone tumor site	406 (28%)	220 (31%)	126 (26%)	60 (25%)	0.058
Brain tumor site	65 (5%)	40 (6%)	20 (4%)	5 (2%)	0.055
Prior treatments ¹					0.53
0	157 (11%)	79 (11%)	54 (11%)	24 (10%)	
1	847 (59%)	402 (57%)	294 (60%)	151 (63%)	
2	430 (30%)	224 (32%)	142 (29%)	64 (27%)	
Smoking history					0.022
Never	250 (17%)	136 (19%)	73 (15%)	41 (17%)	
Previous	1,012 (71%)	470 (67%)	365 (74%)	177 (74%)	
Current	172 (12%)	99 (14%)	52 (11%)	21 (9%)	
PD-L1 expression					0.91
Negative	491 (34%)	240 (34%)	166 (34%)	85 (36%)	
Positive	938 (65%)	462 (66%)	322 (66%)	154 (64%)	
Missing	5 (<1%)	3 (<1%)	2 (<1%)	0 (0%)	
Lactate dehydrogenase					0.78
≤ ULN	843 (59%)	412 (58%)	284 (58%)	147 (62%)	
> ULN	547 (38%)	268 (38%)	191 (39%)	88 (37%)	
Missing	44 (3%)	25 (4%)	15 (3%)	4 (2%)	
Neutrophil to lymphocyte ratio					0.004
<3	491 (34%)	214 (30%)	177 (36%)	100 (42%)	
≥3	863 (60%)	450 (64%)	283 (58%)	130 (54%)	
Missing	80 (6%)	41 (6%)	30 (6%)	9 (4%)	
C Reactive Protein (mg/L)					< 0.001
Median (IQR)	14 (4 - 42)	15 (4 - 48)	13 (5 - 45)	11 (4 - 32)	
Missing	43 (3%)	26 (4%)	9 (2%)	8 (3%)	

Data are median (IQR) or number of patients (%). P values per Fisher test for categorical data and Wilcoxon test for continuous data. ¹Number of prior treatments in the locally advanced or metastatic setting

eTable 2. Cox proportional hazards regression analysis for overall survival/progression free survival for atezolizumab treated patients across trials

Variables	Overall Survival - HR (95% CI)				
	All trials	BIRCH	FIR	OAK	POPLAR
BMI (Kg/m ²)					
25.0-29.9	0.80 (0.67-0.96)	0.78 (0.56-1.09)	0.30 (0.09-0.96)	0.90 (0.69-1.16)	0.32 (0.16-0.67)
≥ 30	0.69 (0.54-0.87)	0.58 (0.35-0.95)	0.13 (0.01-1.23)	0.83 (0.60-1.14)	0.37 (0.18-0.75)
Age (years)	1.0 (0.99-1.01)	1.01 (0.99-1.03)	0.97 (0.97-1.08)	1.00 (0.99-1.01)	1.00 (0.97-1.03)
Female sex	1.02 (0.85-1.23)	1.17 (0.85-1.60)	0.68 (0.19-2.47)	1.02 (0.78-1.33)	0.77 (0.42-1.42)
Race					
Asian	0.81 (0.63-1.04)	1.61 (1.00-2.58)	2.78 (0.74-10.5)	0.69 (0.50-0.95)	0.40 (0.16-1.01)
Other	1.18 (0.82-1.69)	1.48 (0.73-3.00)	0.24 (0.02-2.66)	1.07 (0.65-1.78)	1.07 (0.41-2.27)
ECOG PS	1.42 (1.18-1.70)	1.50 (1.07-2.10)	2.08 (0.76-5.69)	1.38 (1.08-1.76)	1.30 (0.71-2.40)
Squamous histology	1.15 (0.96-1.38)	1.05 (0.76-1.45)	1.34 (0.40-4.47)	1.26 (0.97-1.63)	0.90 (0.51-1.60)
Count of tumor sites	1.52 (1.29-1.79)	1.24 (0.91-1.69)	1.14 (0.44-2.95)	1.73 (1.17-2.18)	1.03 (0.56-1.90)
Number of prior treatments	1.10 (0.95-1.27)	1.09 (0.89-1.34)	0.76 (0.21-2.79)	1.06 (0.82-1.36)	0.74 (0.43-1.28)
Smoking history					

Previous	0.77 (0.61-0.98)	0.72 (0.47-1.09)	0.69 (0.23-2.01)	0.77 (0.55-1.09)	0.97 (0.42-2.24)
Current	0.79 (0.58-1.10)	0.80 (0.42-1.51)	0.52 (0.11-2.79)	0.73 (0.46-1.16)	0.82 (0.29-2.82)
PD-L1 high	0.59 (0.47-0.74)	N/A	NA	0.56 (0.43-0.73)	0.61 (0.34-1.09)
High LDH at baseline	1.39 (1.18-1.64)	1.57 (1.15-2.13)	1.42 (0.47-4.26)	1.36 (1.08-1.70)	1.79 (1.02-3.14)
Log CRP	1.42 (1.33-1.52)	1.59 (1.40-1.80)	1.43 (1.00-2.05)	1.34 (1.23-1.47)	1.62 (1.30-2.03)
Neutrophil Lymphocyte Ratio > 3	1.52 (1.25-1.85)	1.79 (1.19-2.70)	3.02(0.56-16.3)	1.42 (1.10-1.84)	1.48 (0.81-2.70)
Progression free survival - HR (95% CI)					
BMI (Kg/m ²)					
25.0-29.9	0.88(0.77-1.02)	0.84 (0.67-1.05)	0.50 (0.19-1.31)	1.00 (0.81-1.24)	0.68 (0.41-1.12)
≥ 30	0.87 (0.72-1.04)	0.77 (0.57-1.03)	0.52 (0.13-2.07)	1.09 (0.83-1.429)	0.52 (0.29-0.94)
Age (years)	0.99 (0.99-1.00)	0.99 (0.98-1.01)	1.00 (0.97-1.04)	0.99 (0.98-1.00)	1.00 (0.97-1.02)
Female sex	0.99 (0.86-1.14)	1.01 (0.82-1.26)	0.93 (0.36-2.36)	0.94 (0.75-1.17)	1.20 (0.75-1.92)
Race					
Asian	1.12 (0.93-1.35)	1.34 (0.97-1.84)	2.89 (0.88-9.44)	1.02 (0.78-1.31)	0.80 (0.43-1.49)
Other	1.15 (0.85-1.57)	1.72 (0.95-3.15)	1.55 (0.27-8.83)	0.94 (0.61-1.46)	0.84 (0.40-1.77)
EOCG PS	1.12 (0.98-1.28)	1.08 (0.87-1.33)	1.04 (0.48-2.25)	1.02 (0.84-1.24)	1.54 (0.97-2.43)
Squamous histology	1.09 (0.95-1.26)	1.10 (0.88-1.38)	0.89 (0.34-2.29)	1.09 (0.87-1.37)	1.02 (0.65-1.60)
Count of tumor sites	1.20 (1.06-1.37)	0.98 (0.79-1.21)	1.07 (0.49-2.34)	1.41 (1.16-1.71)	1.39 (0.82-2.23)

Number of prior treatments	0.97 (0.87-1.08)	1.00 (0.88-1.15)	0.76 (0.24-2.37)	0.87 (0.70-1.08)	0.84 (0.54-1.32)
Smoking history					
Previous	0.69 (0.58-0.83)	0.65 (0.49-0.87)	1.21 (0.46-3.15)	0.64 (0.49-0.85)	0.77 (0.44-1.38)
Current	0.59 (0.46-0.76)	0.61 (0.40-0.93)	1.11 (0.28-4.44)	0.52 (0.35-0.77)	0.50 (0.23-1.09)
PD-L1 high	0.70 (0.58-0.85)	NA	NA	0.68 (0.55-0.84)	0.70 (0.46-1.08)
High LDH at baseline	1.33 (1.16-1.51)	1.46 (1.18-1.80)	2.21 (0.92-5.30)	1.28 (1.06-1.55)	1.05 (0.68-1.63)
Log CRP	1.15 (1.09-1.21)	1.20 (1.11-1.30)	1.44 (1.06-1.95)	1.11 (1.03-1.20)	1.13 (0.95-1.35)
Neutrophil Lymphocyte Ratio > 3	1.19 (1.03-1.37)	1.16 (0.92-1.46)	0.65 (0.19-2.24)	1.23 (1.00-1.51)	1.42 (0.90-2.24)

CI= confidence interval, HR= Hazard ratio, NA = not applicable as only high PDL1 patients included

eTable 3. Sex-specific association between BMI and overall survival for patients with advanced NSCLC treated with atezolizumab.

	Events/Patients	Median, months (95% CI)	Univariable HR (95% CI) ¹
Women			
BMI 18.5-24.9	155/317	13.3 (10.1-16.3)	1 (reference)
BMI 25.0-29.9	59/146	15.0 (14.1-NR)	0.74 (0.55-0.99)
BMI ≥ 30	27/81	NR	0.57 (0.38-0.86)
Men			
BMI 18.5-24.9	206/388	10.0 (8.2-13.5)	1 (reference)
BMI 25.0-29.9	165/344	13.2 (12.1-16.0)	0.80 (0.65-0.98)
BMI ≥ 30	73/158	14.9 (11.8-20.7)	0.65 (0.50-0.85)

CI=confidence interval, HR=hazard ratio, NR=not reached

¹stratified for study

eTable 4: Cause of death by trials

Cause	N (%)				
	All trials (n = 742)	BIRCH (n = 223)	FIR (n = 60)	OAK (n = 383)	POPLAR (n = 76)
Cancer related	673 (91%)	200 (90%)	50 (83%)	357 (93%)	66 (87%)
Non-cancer related	69 (9%)	23 (10%)	10 (17%)	26 (7%)	10 (13%)

eTable 5: Cause of deaths by BMI groups

Cause of deaths	BMI groups (Kg/m ²) N (%) P = 0.44				
	Total (n = 742)	18-5-24.9 (n = 361)	25.0-29.9 (n = 224)	≥30 (n = 100)	Missing (n = 57)
Cancer related	673 (91%)	326 (90%)	201 (90%)	94 (94%)	52 (91%)
Non-cancer related	69 (9%)	35 (9.7%)	23 (10%)	6 (6%)	5 (8.8%)

eTable 6. Pooled adverse events related to atezolizumab across all trials

Adverse events	BMI groups (Kg/m ²) N (%)				P value
	Total (n = 1411)	18-5-24.9 (n = 693)	25.0-29.9 (n = 480)	≥30 (n = 238)	
TRAEs	911 (64%)	450 (65%)	307 (64%)	154 (65%)	0.92
TRAEs (grade 3 or more)	178 (13%)	83 (12%)	67 (14%)	28 (12%)	0.66
irAEs (all grades)	390 (27%)	177 (26%)	138 (29%)	75 (32%)	0.73

eTable 7. Baseline characteristics of docetaxel treated patients.

	Total No. 676	18.5 - 24.9 No. 353	25.0 - 29.9 No. 221	>= 30.0 No. 102	P-value
Study					0.055
OAK	548 (81%)	294 (83%)	180 (81%)	74 (73%)	
POPLAR	128 (19%)	59 (17%)	41 (19%)	28 (27%)	
Age (years)	63 (57 - 69)	62 (56 - 70)	65 (58 - 69)	62 (56 - 68)	0.064
Sex					0.53
Male	419 (62%)	212 (60%)	143 (65%)	64 (63%)	
Female	257 (38%)	141 (40%)	78 (35%)	38 (37%)	
Race					< 0.001
White	497 (74%)	234 (66%)	169 (76%)	94 (92%)	
Asian	124 (18%)	87 (25%)	33 (15%)	4 (4%)	
Other	35 (5%)	21 (6%)	11 (5%)	3 (3%)	
Missing	20 (3%)	11 (3%)	8 (4%)	1 (1%)	
ECOG PS					0.72
0	250 (37%)	126 (36%)	84 (38%)	40 (39%)	
1	425 (63%)	227 (64%)	137 (62%)	61 (60%)	
Missing	1 (<1%)	0 (0%)	0 (0%)	1 (1%)	
Histology					0.17
Non-squamous	484 (72%)	263 (75%)	154 (70%)	67 (66%)	
Squamous	192 (28%)	90 (25%)	67 (30%)	35 (34%)	
Tumor sites					0.015
<3	266 (39%)	123 (35%)	92 (42%)	51 (50%)	
≥3	410 (61%)	230 (65%)	129 (58%)	51 (50%)	
Liver tumor site	145 (21%)	80 (23%)	48 (22%)	17 (17%)	0.45
Bone tumor site	207 (31%)	112 (32%)	71 (32%)	24 (24%)	0.24
Brain tumor site	66 (10%)	42 (12%)	17 (8%)	7 (7%)	0.16
Prior treatments¹					0.38
1	499 (74%)	258 (73%)	160 (72%)	81 (79%)	
2	177 (26%)	95 (27%)	61 (28%)	21 (21%)	
Smoking history					0.12
Never	110 (16%)	68 (19%)	30 (14%)	12 (12%)	
Previous	457 (68%)	225 (64%)	161 (73%)	71 (70%)	
Current	109 (16%)	60 (17%)	30 (14%)	19 (19%)	
PD-L1 expression					0.76
Negative	457 (68%)	242 (69%)	150 (68%)	65 (64%)	
Positive	216 (32%)	110 (31%)	71 (32%)	35 (34%)	
Missing	3 (<1%)	1 (<1%)	0 (0%)	2 (2%)	
Lactate dehydrogenase					0.76
≤ ULN	371 (55%)	193 (55%)	120 (54%)	58 (57%)	
> ULN	287 (42%)	152 (43%)	96 (43%)	39 (38%)	
Missing	18 (3%)	8 (2%)	5 (2%)	5 (5%)	
Neutrophil to lymphocyte ratio					0.97
<3	247 (37%)	128 (36%)	82 (37%)	37 (36%)	
≥3	418 (62%)	219 (62%)	139 (63%)	60 (59%)	
Missing	11 (2%)	6 (2%)	0 (0%)	5 (5%)	
C Reactive Protein (mg/L)					0.55
Median (IQR)	13 (4 - 38)	14 (4 - 39)	11 (4 - 36)	13 (5 - 31)	
Missing	7 (1%)	3 (1%)	2 (1%)	2 (2%)	

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

¹Number of prior treatments in the locally advanced or metastatic setting

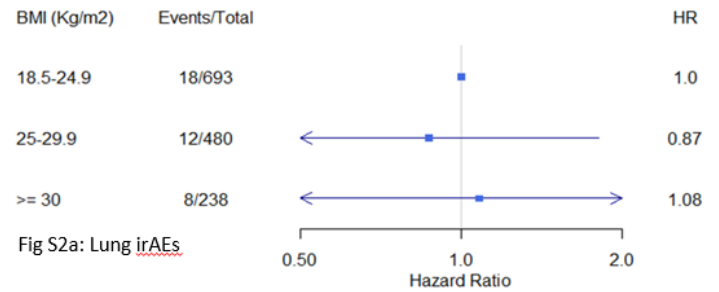
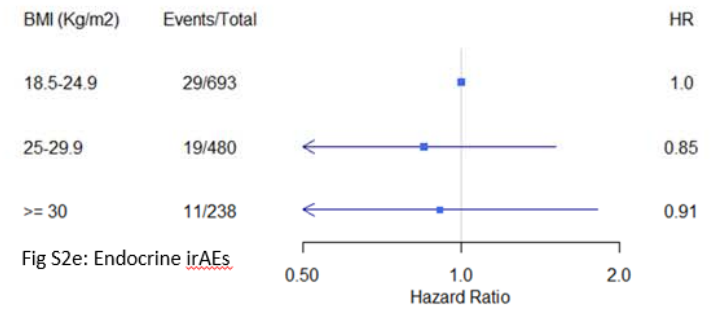
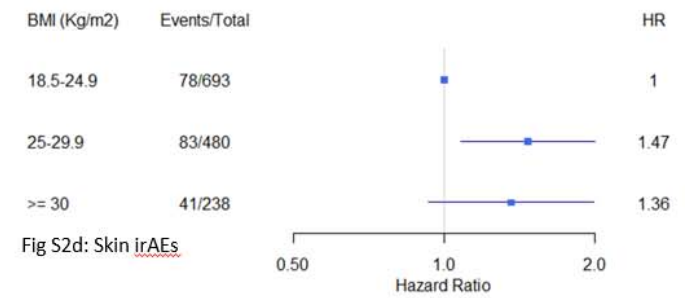
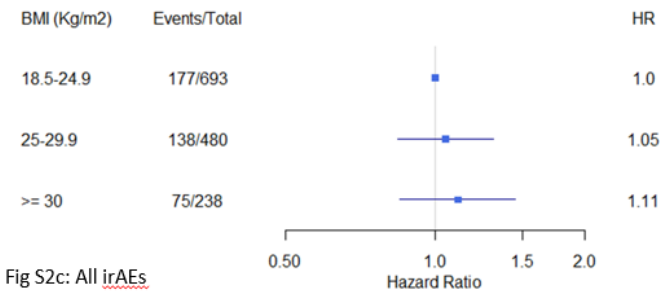
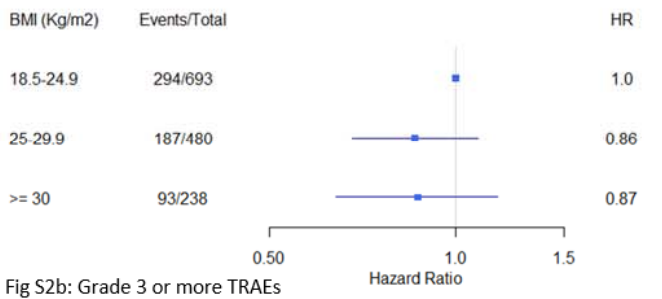
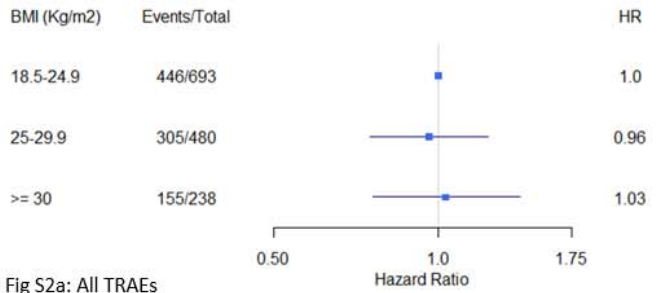
eTable 8. Baseline characteristics of the pooled intention-to-treat populations of the OAK and POPLAR trials excluding participants with missing or underweight BMI.

	Total No. 1,419	Docetaxel No. 712	Atezolizumab No. 707
Study			
OAK	1,144 (81%)	577 (81%)	567 (80%)
POPLAR	275 (19%)	135 (19%)	140 (20%)
Age (years)	63 (56 - 69)	63 (57 - 69)	63 (56 - 69)
Sex			
Male	886 (62%)	438 (62%)	448 (63%)
Female	533 (38%)	274 (38%)	259 (37%)
Race			
White	1,036 (73%)	522 (73%)	514 (73%)
Asian	263 (19%)	130 (18%)	133 (19%)
Other	73 (5%)	38 (5%)	35 (5%)
Missing	47 (3%)	22 (3%)	25 (4%)
ECOG PS			
0	524 (37%)	267 (38%)	257 (36%)
1	893 (63%)	444 (62%)	449 (64%)
Missing	2 (<1%)	1 (<1%)	1 (<1%)
Histology			
Non-squamous	1,027 (72%)	514 (72%)	513 (73%)
Squamous	392 (28%)	198 (28%)	194 (27%)
Tumor sites			
<3	594 (42%)	282 (40%)	312 (44%)
≥3	825 (58%)	430 (60%)	395 (56%)
Liver tumor site	299 (21%)	151 (21%)	148 (21%)
Bone tumor site	430 (30%)	218 (31%)	212 (30%)
Brain tumor site	126 (9%)	72 (10%)	54 (8%)
Prior treatments¹			
1	1,041 (73%)	529 (74%)	512 (72%)
2	378 (27%)	183 (26%)	195 (28%)
Smoking history			
Never	251 (18%)	122 (17%)	129 (18%)
Previous	959 (68%)	476 (67%)	483 (68%)
Current	209 (16%)	114 (16%)	95 (13%)
BMI (Kg/m²)			
18.5-24.9	720 (51%)	377 (53%)	343 (49%)
25.0-29.9	467 (33%)	229 (32%)	238 (34%)
≥ 30	232 (16%)	106 (15%)	126 (18%)
PD-L1 expression			
Negative	978 (69%)	483 (68%)	495 (70%)
Positive	432 (30%)	225 (32%)	207 (29%)
Missing	9 (1%)	4(1%)	5 (1%)
Lactate dehydrogenase			
≤ ULN	777(55%)	372 (55%)	405 (57%)
> ULN	560 (39%)	287 (40%)	273 (39%)
Missing	82 (6%)	53 (7%)	29 (4%)
Neutrophil to lymphocyte ratio			
<3	515 (37%)	247 (35%)	268 (38%)
≥3	837 (59%)	419 (59%)	418 (59%)
Missing	67 (5%)	46 (6%)	21 (3%)
C Reactive Protein (mg/L)			
Median (IQR)	14 (4 - 41)	13 (4 - 38)	15 (5 - 43)
Missing	58 (4%)	42 (6%)	16 (2%)

Data are median (IQR) or number of patients (%).

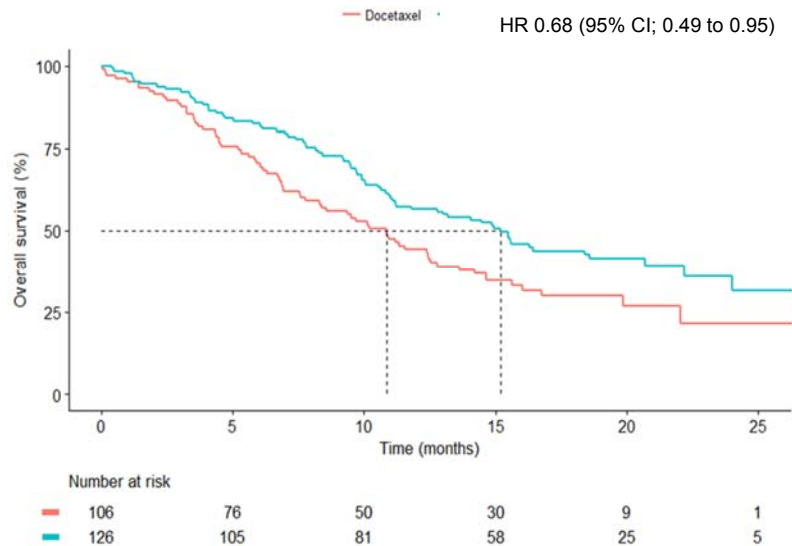
¹Number of prior treatments in the locally advanced or metastatic setting

eFigure 1: Forest plots for adverse events from atezolizumab

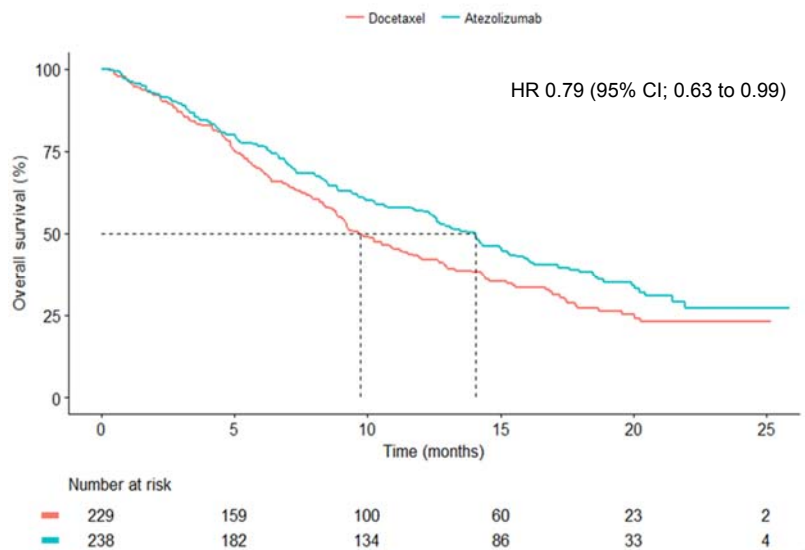


eFigure 2: OS as per BMI categories for pooled OAK and POPLAR trials

A) BMI ≥ 30 kg/m²



B) BMI 25-29.9 kg/m²



C) BMI 18.5-24.9 kg/m²

