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Supplementary Table 1. Multivariable Cox model for OS (categorical variable) – Immunotherapy alone subset.

N=393	P-value of variable	HR (95% CI)	P-value of contrasts
BMI	0.686		
Normal weight		reference	
Overweight		1.09 (0.79 - 1.49)	0.601
Obese		1.17 (0.82 - 1.68)	0.390
Gender	0.887		
FEMALE		reference	
MALE		1.02 (0.77 - 1.34)	0.887
BRAF mutation	0.037*		
Wild type		reference	
Mutated		0.56 (0.33 - 0.96)	0.037*
Disease stage	0.129		
M1a+M1b		reference	
M1c+M1d		1.24 (0.94 - 1.64)	0.129
LDH value*	<0.001*		
0		reference	
>=1		1.72 (1.29 - 2.30)	<0.001*
ECOG PS value	<0.001*		
0		reference	
>=1		2.10 (1.46 - 3.03)	<0.001*
Age	0.711	1.00 (0.99 - 1.01)	-
Type of immunotherapy	0.566		
AntiPD1		reference	
Ipilimumab		1.12 (0.76 - 1.67)	0.566

Legend: HR: Hazard Ratio, CI: Confidence Interval

(*): for LDH hypothesis of PH not satisfied

Note 1: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference

Supplementary Table 2. Multivariable Cox model for OS allowing time varying effect for BMI (continuous variable) – Target therapy alone subset.

N=104	P-value of variable	HR (95% CI)	P-value of contrasts
BMI t0	0.188	1.08 (0.97 - 1.20)	-
Time varying effect of BMI	0.031*	0.99 (0.98 – 1.00)	-
Gender	0.893		
FEMALE		reference	
MALE		0.97 (0.61 - 1.55)	0.893
Disease stage	0.160		
M1a+M1b		reference	
M1c+M1d		1.55 (0.84 - 2.84)	0.160
LDH value	0.126		
0		reference	
>=1		1.48 (0.90 - 2.44)	0.126
ECOG PS value	0.008*		
0		Reference	
>=1		2.39 (1.25- 4.57)	0.008*
Age	0.920	1.00 (0.98 - 1.02)	-

Legend: HR: Hazard Ratio, CI: Confidence Interval

Note: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference.

Supplementary Table 3. Multivariable Cox model for OS allowing time varying effect for BMI (categorical variable) – Target therapy alone subset.

N=104	P-value of variable	HR (95% CI)	P-value of contrasts
BMI Overweight (vs normal weight)	0.907	1.03 (0.61 - 1.75)	0.907
BMI Obese (vs normal weight) at t0	0.117	2.40 (0.80 - 7.19)	0.117
Time varying effect of BMI obese (vs normale weight)	0.016*	0.87 (0.78 - 0.97)	-
Gender	0.652		
FEMALE		reference	
MALE		0.89 (0.54 - 1.47)	0.652
Disease stage	0.170		
M1a+M1b		Reference	
M1c+M1d		1.53 (0.83 - 2.83)	0.170
LDH value	0.173		
0		reference	
>=1		1.41 (0.86 - 2.31)	0.173
ECOG PS value	0.002*		
0		reference	
>=1		2.77 (1.44 - 5.33)	0.002*
Age	0.838	1.00 (0.98 - 1.02)	-

Legend: HR: Hazard Ratio, CI: Confidence Interval

Note: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference.

Supplementary Table 4. Multivariable Cox model for OS (continuous variable) – Target therapy followed by immunotherapy subset.

N=113	P-value of variable	HR (95% CI)	P-value of contrasts
BMI	0.896	1.00 (0.96 - 1.05)	-
Type of immunotherapy	0.399		
AntiPD1		reference	
Ipilimumab		1.29 (0.71 - 2.36)	0.399
Gender	0.895		
FEMALE		reference	
MALE		1.03 (0.65 - 1.63)	0.895
Disease stage	0.286		
M1a+M1b		reference	
M1c+M1d		1.31 (0.80 - 2.16)	0.286
LDH value	<0.001*		
0		reference	
>=1		2.98 (1.80 - 4.95)	<0.001*
ECOG PS value	0.294		
0		reference	
>=1		1.43 (0.73 - 2.77)	0.294
Age	0.460	0.99 (0.97 - 1.01)	-

Legend: HR: Hazard Ratio, CI: Confidence Interval

Note: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference.

Supplementary Table 5. Multivariable Cox model for OS (categorical variable) – Target therapy followed by immunotherapy subset.

N=113	P-value of variable	HR (95% CI)	P-value of contrasts
BMI	0.388		
Normal weight		reference	
Overweight		1.46 (0.82 - 2.62)	0.200
Obese		1.10 (0.60 - 2.01)	0.766
Gender	0.870		
FEMALE		reference	
MALE		0.96 (0.60 - 1.55)	0.870
Disease stage	0.258		
M1a+M1b		reference	
M1c+M1d		1.35 (0.80 - 2.25)	0.258
LDH value*	<.001*		
0		reference	
>=1		2.74 (1.63 - 4.63)	<0.001*
ECOG PS value	0.274		
0		reference	
>=1		1.44 (0.75 - 2.79)	0.274
Age	0.263	0.99 (0.97 - 1.01)	-
Type of immunotherapy	0.507		
AntiPD1		reference	
Ipilimumab		1.23 (0.67 - 2.26)	0.507

Legend: HR: Hazard Ratio, CI: Confidence Interval.
 (*) The PH assumption is not fulfilled

Note1: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference. **Note2:** Two underweight subjects were excluded from the analysis

Supplementary Table 6. Multivariable Cox model for OS allowing time varying effect for type of therapy (continuous variable) – *BRAF* mutated subset.

N=281	P-value of variable	HR (95% CI)	P-value of contrasts
BMI	0.108	0.97 (0.94 - 1.01)	-
Gender	0.838		
FEMALE		reference	
MALE		0.97 (0.73 - 1.29)	0.838
Disease stage	0.151		
M1a+M1b		reference	
M1c+M1d		1.26 (0.92 - 1.73)	0.151
LDH value	<0.001*		
0		reference	
>=1		2.26 (1.64 - 3.11)	<0.001*
ECOG PS value	<0.001*		
0		reference	
>=1		2.41 (1.62 - 3.57)	<0.001*
Age	0.289	0.99 (0.98 - 1.01)	-
Type of therapy*	0.003*		
Target		reference	
Immuno		0.47 (0.26 - 0.85)	0.012*
Immuno-Target		0.54 (0.27 - 1.05)	0.071
Target-Immuno		1.15 (0.82 - 1.61)	0.424

Legend: HR: Hazard Ratio, CI: Confidence Interval

(*): for immuno-target and target-immuno the PH assumption is not satisfied

Note: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference.

Supplementary Table 7. Multivariable Cox model for OS allowing time varying effect for type of therapy (categorical variable) – *BRAF* mutated subset.

N=281	P-value of variable	HR (95% CI)	P-value of contrasts
BMI	0.044*		
Normal weight		reference	
Overweight		1.22 (0.87 - 1.71)	0.254
Obese		0.74 (0.49 - 1.13)	0.164
Gender	0.519		
FEMALE		reference	
MALE		0.91 (0.68 - 1.22)	0.519
Disease stage	0.127		
M1a+M1b		reference	
M1c+M1d		1.29 (0.93 - 1.77)	0.127
LDH value	<0.001*		
0		reference	
>=1		2.16 (1.57 - 2.98)	<0.001*
ECOG PS value	<0.001*		
0		reference	
>=1		2.52 (1.70 - 3.75)	<0.001*
Age	0.183	0.99 (0.98 - 1.01)	-
Type of therapy*	0.003*		
Target		reference	
Immuno		0.45 (0.25 - 0.80)	0.007*
Immuno-Target		0.56 (0.28 - 1.09)	0.087
Target-Immuno		1.14 (0.82 - 1.60)	0.439

Legend: HR: Hazard Ratio, CI: Confidence Interval
 (*) for immuno-target and target-immuno the PH assumption is not satisfied

Note1: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference.

Supplementary Table 8. Multivariable Cox model for PFS (continuous variable) – Immunotherapy subset.

N=410	P-value of variable	HR (95% CI)	P-value of contrasts
BMI	0.723	1.00 (0.98 - 1.03)	-
Gender	0.838		
FEMALE		reference	
MALE		1.03 (0.81 - 1.30)	0.838
BRAF mutation	0.909		
Wild type		reference	
Mutated		0.98 (0.70 - 1.37)	0.909
Disease stage	0.546		
M1a+M1b		reference	
M1c+M1d		1.08 (0.85 - 1.37)	0.546
LDH value	<0.001*		
0		reference	
>=1		1.60 (1.23 - 2.09)	<0.001*
ECOG PS value	0.002*		
0		reference	
>=1		1.67 (1.21 - 2.31)	0.002*
Age	0.253	0.99 (0.99 - 1.00)	-
type of immunotherapy	<0.001*		
AntiPD1		reference	
Ipilimumab		2.49 (1.78 - 3.48)	<0.001*

Legend: HR: Hazard Ratio, CI: Confidence Interval

Note: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference.

Supplementary Table 9. Multivariable Cox model for PFS (categorical variable) – Immunotherapy subset.

N=410	P-value of variable	HR (95% CI)	P-value of contrasts
BMI	0.997		
Normal (BMI<25)		reference	
Overweight (BMI [25-30))		1.01 (0.77 - 1.32)	0.957
Obese (BMI>=30)		1.01 (0.74 - 1.39)	0.944
Gender	0.879		
FEMALE		reference	
MALE		1.02 (0.80 - 1.30)	0.879
BRAF mutation	0.946		
Wild type		reference	
Mutated		1.01 (0.72 - 1.42)	0.946
Disease stage	0.799		
M1a+M1b		reference	
M1c+M1d		1.03 (0.81 - 1.31)	0.799
LDH value	<0.001*		
0		reference	
>=1		1.74 (1.33 - 2.27)	<0.001*
ECOG PS value	0.013*		
0		reference	
>=1		1.48 (1.09 - 2.02)	0.013*
Age	0.040*	0.99 (0.98 - 1.00)	0.040*
type of immunotherapy	<0.001*		
AntiPD1		reference	
Ipilimumab		2.50 (1.79 - 3.49)	<0.001*

Legend: HR: Hazard Ratio, CI: Confidence Interval

Note1: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference.

Supplementary Table 10. Multivariable Cox model for PFS (continuous variable) – Anti PD1 subset.

N=331	P-value of variable	HR (95% CI)	P-value of contrasts
BMI	0.462	1.01 (0.98 - 1.04)	-
Gender	0.820		
FEMALE		reference	
MALE		0.97 (0.73 - 1.28)	0.820
BRAF mutation	0.926		
Wild type		reference	
Mutated		0.98 (0.67 - 1.45)	0.926
Disease stage	0.618		
M1a+M1b		reference	
M1c+M1d		1.07 (0.81 - 1.41)	0.618
LDH value	<0.001*		
0		reference	
>=1		1.76 (1.30 - 2.39)	<0.001*
ECOG PS value	0.003*		
0		reference	
>=1		1.69 (1.19 - 2.38)	0.003*
Age	0.041*	0.99 (0.98 - 1.00)	-

Legend: HR: Hazard Ratio, CI: Confidence Interval

Note: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference.

Supplementary Table 11. Multivariable Cox model for PFS (continuous variable) – Target therapy subset.

N=216	P-value of variable	HR (95% CI)	P-value of contrasts
BMI	0.194	0.98 (0.94 - 1.01)	-
Gender	0.872		
FEMALE		reference	
MALE		0.98 (0.72 - 1.32)	0.872
Disease stage	0.398		
M1a+M1b		reference	
M1c1+M1d		1.16 (0.83 - 1.61)	0.398
LDH value	0.002*		
0		reference	
>=1		1.69 (1.21 - 2.35)	0.002*
ECOG PS value	<0.001*		
0		reference	
>=1		1.95 (1.32 - 2.89)	<0.001*
Age	0.748	1.00 (0.99 - 1.01)	-

Legend: HR: Hazard Ratio, CI: Confidence Interval

Note: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference.

Supplementary Table 12. Multivariable Cox model for PFS (categorical variable) – Target therapy subset.

N=216	P-value of variable	HR (95% CI)	P-value of contrasts
BMI	0.357		
Normal (BMI<25)		reference	
Overweight (BMI [25-30))		0.91 (0.64 - 1.28)	0.575
Obese (BMI>=30)		0.73 (0.48 - 1.12)	0.151
Gender	0.824		
FEMALE		reference	
MALE		0.97 (0.71 - 1.31)	0.824
Disease stage	0.477		
M1a+M1b		reference	
M1c+M1d		1.13 (0.81 - 1.59)	0.477
LDH value	0.003*		
0		reference	
>=1		1.67 (1.19 - 2.35)	0.003*
ECOG PS value	<0.001*		
0		reference	
>=1		1.96 (1.32 - 2.92)	<0.001*
Age	0.726	1.00 (0.99 - 1.01)	-

Legend: HR: Hazard Ratio, CI: Confidence Interval,

Note1: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference.

Supplementary Table 13. Multivariable Cox model for PFS (continuous variable) – *BRAF* mutated subset.

N=280	P-value of variable	HR (95% CI)	P-value of contrasts
BMI	0.067	0.97 (0.94 - 1.00)	-
Gender	0.774		
FEMALE		reference	
MALE		0.96 (0.74 - 1.25)	0.774
Disease stage	0.209		
M1a+M1b		reference	
M1c+M1d		1.20 (0.90 - 1.61)	0.209
LDH value	<0.001*		
0		reference	
>=1		1.89 (1.41 - 2.54)	<0.001*
ECOG PS value	<0.001*		
0		reference	
>=1		1.87 (1.32 - 2.65)	<0.001*
Age	0.464	1.00 (0.99 - 1.01)	-
Type of therapy*	0.714		
Immunotherapy		reference	
Target therapy		1.07 (0.75 - 1.52)	0.714

Legend: HR: Hazard Ratio, CI:Confidence Interval

Note: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different form the category chosen as reference.

Note: for type of therapy the PH assumption is not satisfied

Supplementary Table 14. Multivariable Cox model for PFS (categorical variable) – *BRAF* mutated subset.

N=278	P-value of variable	HR (95% CI)	P-value of contrasts
BMI	0.217		
Normal weight		reference	
Overweight		0.99 (0.73 - 1.35)	0.960
Obese		0.74 (0.50 - 1.08)	0.114
Gender	0.643		
FEMALE		reference	
MALE		0.94 (0.72 - 1.23)	0.643
Disease stage	0.224		
M1a+M1b		reference	
M1c+M1d		1.20 (0.89 - 1.62)	0.224
LDH value	<0.001*		
0		reference	
>=1		1.85 (1.37 - 2.49)	<0.001*
ECOG PS value	<0.001*		
0		reference	
>=1		1.89 (1.33 - 2.68)	<0.001*
Age	0.401	1.00 (0.98 - 1.01)	0.401
Type of therapy*	0.696		
Immunotherapy		reference	
Target therapy		1.07 (0.76 - 1.52)	0.696

Legend: HR: Hazard Ratio, CI:Confidence Interval

(*): the PH assumption for type of immunotherapy is not satisfied,

Note1: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference. **Note2:** Two underweight subjects were excluded from the analysis

Supplementary Table 15. Multivariate logistic regression model for DCR (continuous variable) – Immunotherapy subset.

N=402	P-value of variable	OR (95% CI)	P-value of contrasts
BMI	0.432	0.98 (0.93 - 1.03)	-
Type of immunotherapy	<0.001*		
AntiPD1		reference	
Ipilimumab		0.31 (0.16 - 0.60)	<0.001*
Braf Mutation	0.351		
Wild Type		reference	
Mutated		0.72 (0.35 - 1.45)	0.351
Gender	0.418		
FEMALE		reference	
MALE		1.23 (0.74 - 2.05)	0.418
Disease stage	0.020*		
M1a+M1b		reference	
M1c+M1d		0.54 (0.32 - 0.91)	0.020*
LDH value	0.078		
0		reference	
>=1		0.61 (0.36 - 1.06)	0.078
ECOG PS value	0.281		
0		reference	
>=1		0.69 (0.36 - 1.35)	0.281
Age in class	0.583		
<65		reference	
>=65		0.86 (0.50 - 1.48)	0.583

Legend: OR: Odds Ratio, CI: Confidence Interval

Note: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference.

Supplementary Table 16. Multivariate logistic regression model for DCR (categorical variable) – Immunotherapy subset.

N=395	P-value of variable	OR (95% CI)	P-value of contrasts
BMI	0.757		
Normal (BMI<25)		reference	
Overweight (BMI [25-30))		0.81 (0.47 - 1.42)	0.520
Obese (BMI>=30)		0.84 (0.42 - 1.68)	0.235
Type of immunotherapy	<0.001*		
AntiPD1		reference	
Ipilimumab		0.32 (0.16 - 0.62)	<0.001*
Braf Mutation	0.441		
Wild Type		reference	
Mutated		0.76 (0.38 - 1.53)	0.441
Gender	0.366		
FEMALE		Reference	
MALE		1.27 (0.76 - 2.129)	0.366
Disease stage	0.024*		
M1a+M1b		reference	
M1c+M1d		0.55 (0.33 - 0.92)	0.024*
LDH value	0.062		
0		reference	
>=1		0.59 (0.34 - 1.03)	0.062
ECOG PS value	0.290		
0		reference	
>=1		0.70 (0.35 - 1.36)	0.290
Age in class	0.806		
<65		reference	
>=65		0.93 (0.54 - 1.61)	0.806

Legend: OR: Odds Ratio, CI: Confidence Interval

Note1: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference. **Note2:** Seven underweight subjects were excluded from the analysis

Supplementary Table 17. Multivariate logistic regression model for DCR (continuous variable) – Target therapy subset.

N=214	P-value of variable	OR (95% CI)	P-value of contrasts
BMI	0.499	1.04 (0.93 - 1.17)	-
Gender	0.647		
FEMALE		reference	
MALE		1.27 (0.46 - 3.51)	0.647
Disease stage	0.240		
M1a+M1b		reference	
M1c+M1d		0.44 (0.11 - 1.74)	0.240
LDH value	0.061		
0		reference	
>=1		0.32 (0.10 - 1.05)	0.061
ECOG PS value	0.822		
0		reference	
>=1		1.16 (0.31 - 4.36)	0.822
Age	0.091	0.96 (0.92 - 1.01)	-

Legend: OR: Odds Ratio, CI: Confidence Interval

Note: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference.

Supplementary Table 18. Multivariate logistic regression model for DCR (categorical variable) – Target therapy subset.

N=212	P-value of variable	OR (95% CI)	P-value of contrasts
BMI	0.892		
Normal (BMI<25)		reference	
Overweight (BMI [25-30))		1.18 (0.38 - 3.68)	0.778
Obese (BMI>=30)		1.42 (0.33 - 6.16)	0.644
Gender	0.695		
FEMALE		reference	
MALE		1.24 (0.43 - 3.55)	0.695
Disease stage	0.287		
M1a+M1b		reference	
M1c+M1d		0.47 (0.12 - 1.89)	0.287
LDH value	0.063		
0		reference	
>=1		0.33 (0.10 - 1.06)	0.063
ECOG PS value	0.818		
0		reference	
>=1		1.17 (0.31 - 4.40)	0.818
Age	0.092	0.96 (0.92 - 1.01)	-

Legend: OR: Odds Ratio, CI: Confidence Interval

Note1: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference. **Note2:** Two underweight subjects were excluded from the analysis

Supplementary Table 19. Multivariate logistic regression model for DCR (continuous variable) – *BRAF* mutated subset.

N=277	P-value of variable	OR (95% CI)	P-value of contrasts
BMI	0.578	1.03 (0.94 - 1.12)	-
Type of first line therapy	<0.001*		
IMMUNO		reference	
TARGET		5.43 (2.22 - 13.3)	<0.001*
Gender	0.602		
FEMALE		reference	
MALE		1.23 (0.56 - 2.70)	0.602
Disease stage	0.108		
M1a+M1b		reference	
M1c+M1d		0.48 (0.19 - 1.18)	0.108
LDH value	0.025*		
0		reference	
>=1		0.35 (0.14 - 0.88)	0.025*
ECOG PS value	0.666		
0		reference	
>=1		1.25 (0.45 - 3.49)	0.666
Age	0.151	0.98 (0.95 - 1.01)	-

Legend: OR: Odds Ratio, CI: Confidence Interval

Note: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference.

Supplementary Table 20. Multivariate logistic regression model for DCR (categorical variable) – *BRAF* mutated subset.

N=275	P-value of variable	OR (95% CI)	P-value of contrasts
BMI	0.274		
Normal (BMI<25)		reference	
Overweight (BMI [25-30))		0.54 (0.22 - 1.35)	0.189
Obese (BMI>=30)		1.17 (0.35 - 3.86)	0.798
Type of first line therapy	<0.001*		
IMMUNO		reference	
TARGET		5.62 (2.29 - 13.78)	<0.001*
Gender	0.405		
FEMALE		Reference	
MALE		1.41 (0.63 - 3.15)	0.405
Disease stage	0.089		
M1a+M1b		reference	
M1c+M1d		0.45 (0.18 - 1.13)	0.089
LDH value	0.028*		
0		reference	
>=1		0.36 (0.14 - 0.90)	0.028*
ECOG PS value	0.686		
0		reference	
>=1		1.24 (0.44 - 3.49)	0.686
Age	0.153	0.98 (0.95 - 1.01)	-

Legend: OR: Odds Ratio; CI: Confidence Interval

Note1: for categorical variables, p-value of variables evaluates the overall impact of the variable on the outcome, while the p-value of each contrast evaluates if the considered category is statistically different from the category chosen as reference. **Note2:** Two underweight subjects were excluded from the analysis