

Supplemental files

Supplemental table S1: specific toxicities (grade ≥3) of checkpoint inhibitors per age-group

	All patients		Patients aged 65-74		Patients aged 75 or older		p-value
	N	(%)*	N	(%)	N	(%)	
Anti-PD-1 treatment (N=920)							
All toxicity (grade ≥3)*	140	(15.2)	67	(13.9)	73	(16.6)	0.255
Specific toxicity (grade ≥3)*							
Bone marrow suppression	2	(0.2)	0	(0.0)	2	(0.5)	0.138
Neuropathy	3	(0.3)	1	(0.2)	2	(0.5)	0.510
Colitis	26	(2.8)	11	(2.3)	15	(3.4)	0.302
Kidney function deterioration	10	(1.1)	6	(1.2)	4	(0.9)	0.623
Nephritis	15	(1.6)	7	(1.5)	8	(1.8)	0.661
Dyspnea	7	(0.8)	4	(0.8)	3	(0.7)	0.796
Pneumonitis	16	(1.7)	5	(1.0)	11	(2.5)	0.089
Adrenal gland insufficiency	3	(0.3)	3	(0.6)	0	(0.0)	0.097
Hypopituitary insufficiency	3	(0.3)	2	(0.4)	1	(0.2)	0.617
Hypo (or hyper) thyroidism	3	(0.3)	2	(0.4)	1	(0.2)	0.617
Fatigue	5	(0.5)	3	(0.6)	2	(0.5)	0.729
Rash	10	(1.1)	6	(1.2)	4	(0.9)	0.623
Pruritis	4	(0.4)	2	(0.4)	2	(0.5)	0.927
Vitiligo	4	(0.4)	2	(0.4)	2	(0.5)	0.927
Hepatitis	20	(2.2)	9	(1.9)	11	(2.5)	0.510
Other	53	(5.8)	30	(6.2)	23	(5.2)	0.516
Ipilimumab							
All toxicity (grade ≥3)*	115	(31.6)	75	(31.9)	40	(31.0)	0.859
Specific toxicity (grade ≥3)*							
Bone marrow suppression	2	(0.5)	1	(0.5)	1	(0.4)	0.666
Colitis	50	(13.7)	31	(13.2)	19	(14.7)	0.684

Skin toxicity	7	(1.9)	1	(0.4)	6	(4.7)	0.005
Adrenal gland insufficiency	12	(3.3)	8	(3.4)	4	(3.1)	0.877
Hypopituitary insufficiency	23	(6.3)	18	(7.7)	5	(3.9)	0.156
Hypo (or hyper) thyroidism	11	(3.0)	9	(3.8)	2	(1.6)	0.224
Hepatitis	13	(3.6)	10	(4.3)	3	(2.3)	0.343
Other	33	(9.1)	19	(8.1)	14	(10.9)	0.379
Ipilimumab + nivolumab							
All toxicity (grade ≥3)*	86	(42.8)	59	(41.0)	27	(47.4)	0.409
Specific toxicity (grade ≥3)*							
Bone marrow suppression	2	(1.0)	1	(0.7)	1	(1.8)	0.495
Neuropathy	2	(1.0)	2	(1.4)	0	(0.0)	0.371
Colitis	26	(12.9)	18	(12.5)	8	(14.0)	0.770
Nephritis	8	(4.0)	3	(2.1)	5	(8.8)	0.029
Pneumonitis	8	(4.0)	3	(2.1)	5	(8.8)	0.029
Adrenal gland insufficiency	6	(3.0)	3	(2.1)	3	(5.3)	0.232
Hypopituitary insufficiency	5	(2.5)	4	(2.8)	1	(1.8)	0.675
Hypo (or hyper) thyroidism	2	(1.0)	1	(0.7)	1	(1.8)	0.495
Rash	5	(2.5)	4	(2.8)	1	(1.8)	0.675
Pruritis	2	(1.0)	2	(1.4)	0	(0.0)	0.371
Hepatitis	21	(10.4)	16	(11.1)	5	(8.8)	0.625
Other	21	(10.4)	16	(11.1)	5	(8.8)	0.625

**presented percentages include only patients who received the therapy that is mentioned*

Supplemental table S2: Reasons for discontinuation of treatment (first line)

	All patients		65-74		75+		<i>p-value</i>
	n	(%)	n	(%)	n	(%)	
Reasons for stopping anti-PD							0.026
Planned	105	(15.4)	61	(18.2)	44	(12.7)	
Progression	270	(39.6)	149	(44.5)	121	(35.0)	
Toxicity	102	(15.0)	41	(12.2)	61	(17.6)	
Choice of patient	18	(2.6)	7	(2.1)	11	(3.2)	
Bad condition of patient	32	(4.7)	13	(3.9)	19	(5.5)	
Death	13	(1.9)	5	(1.5)	8	(2.3)	
Other	30	(4.4)	12	(3.6)	18	(5.2)	
Unknown	111	(16.3)	47	(14.0)	64	(18.5)	
Reasons for stopping ipilimumab							<0.001
Planned	123	(59.4)	78	(56.9)	45	(64.3)	
Progression	39	(18.8)	35	(25.5)	4	(5.7)	
Toxicity	29	(14.0)	20	(14.6)	9	(12.9)	
Bad condition of patient	9	(4.3)	2	(1.5)	7	(10.0)	
Death	4	(1.9)	1	(0.7)	3	(4.3)	
Other	2	(1.0)	1	(0.7)	1	(1.4)	
Unknown	1	(0.5)	0	(0.0)	1	(1.4)	
Reasons for stopping ipilimumab/nivolumab							0.182
Planned	15	(7.5)	12	(8.3)	3	(5.3)	
Progression	47	(23.4)	40	(27.8)	7	(12.3)	
Toxicity	75	(37.3)	51	(35.4)	24	(42.1)	
Patients' choice	3	(8.0)	2	(1.4)	1	(1.8)	
Bad condition of patient	16	(8.0)	9	(6.3)	7	(12.3)	
Death	16	(8.0)	9	(6.3)	7	(12.3)	
Other	4	(2.0)	2	(1.4)	2	(3.5)	
Unknown	25	(12.4)	19	(13.2)	6	(10.5)	

Supplemental table S3: Hospital admissions

	All patients		65-74		75+		
	N	(%)	N	(%)	N	(%)	<i>p-value</i>
Admitted (any time)	1233	(55.6)	668	(58.6)	565	(52.4)	<i>0.003</i>
Mean nr admissions (SE)	3.6	(0.22)	3.7	(0.23)	3.3	(0.22)	<i>0.263</i>
Reasons for admission*							
toxicity of treatment	1880	(24.2)	1077	(25.7)	803	(22.4)	<i><0.001</i>
toxicity other treatment	138	(1.8)	111	(2.6)	27	(0.8)	
surgical complications	114	(1.5)	64	(1.5)	50	(1.4)	
palliative care	2312	(29.8)	1243	(29.7)	1069	(29.8)	
other	3316	(42.7)	1685	(40.2)	1631	(45.5)	
unknown	10	(0.1)	6	(0.1)	4	(0.1)	

**patients could be admitted more than once. Presented percentages represent the percentage of all admissions explained by the specified reason*

Supplemental table S4: Characteristics of patients discontinuing treatment due to toxicity
Anti-PD1

	Discontinuation due to toxicity		Other reason for discontinuation		Unknown or no discontinuation		<i>p-value</i>
Age	N	%	N	%	N	%	0.006
65-74	40	(41.2)	242	(53.5)	53	(40.2)	
75+	57	(58.8)	210	(46.5)	79	(59.8)	
Number of comorbidities							
0	11	(11.3)	46	(10.2)	14	(10.6)	0.767
1-2	39	(40.2)	199	(44.0)	63	(47.7)	
3 or more	43	(44.3)	197	(43.6)	50	(37.9)	
Unknown	4	(4.1)	10	(2.2)	5	(3.8)	
WHO classification							
0	47	(48.5)	222	(49.1)	68	(51.5)	0.762
1	33	(34.0)	160	(35.4)	42	(31.8)	
2	10	(10.3)	38	(8.4)	8	(6.1)	
3 or 4	0	(0.0)	6	(1.3)	2	(1.5)	
Unknown	7	(7.2)	26	(5.8)	12	(9.1)	
Response within 6 months							
No	286	(63.3)	42	(43.3)	67	(50.8)	<0.001
Yes	166	(36.7)	55	(56.7)	65	(49.2)	

Supplemental table S5: predictors of overall survival

	Univariate			Multivariate		
	HR	(95% C.I.)	<i>p-value</i>	HR	(95% C.I.)	<i>p-value</i>
Age						
65-74	Ref		<i><0.001</i>	Ref		<i>0.002</i>
75+	1.22	(1.1-1.35)		1.18	(1.06-1.31)	
Sex						
Male	Ref		<i>0.510</i>	Ref		<i>0.718</i>
Female	0.97	(0.87-1.07)		0.98	(0.88-1.09)	
Number of comorbidities						
0	Ref		<i>0.001</i>	Ref		<i>0.315</i>
1-2	1.10	(0.94-1.29)		1.08	(0.92-1.27)	
3 or more	1.33	(1.13-1.56)		1.15	(0.98-1.35)	
Unknown	1.08	(0.73-1.61)		1.28	(0.86-1.91)	
WHO classification						
0	Ref		<i><0.001</i>	Ref		<i><0.001</i>
1	1.80	(1.58-2.04)		1.50	(1.32-1.71)	
2	2.99	(2.54-3.52)		2.23	(1.89-2.64)	
3 or 4	6.10	(4.90-7.59)		3.48	(2.77-4.37)	
Unknown	2.17	(1.85-2.56)		2.02	(1.70-2.39)	
Tumour characteristics						
Number of metastatic sites						
1-2	Ref		<i><0.001</i>	Ref		<i>0.088</i>
3-5	1.15	(0.89-1.47)		1.24	(0.97-1.60)	
6 or more	2.27	(1.90-2.72)		2.17	(1.80-2.62)	
Unknown	1.28	(1.03-1.60)		1.29	(1.03-1.62)	
LDH						

Normal	Ref		<0.001	Ref		<0.001
Elevated	2.02	(1.81-2.24)		1.64	(1.47-1.83)	
Unknown	1.44	(1.19-1.74)		1.22	(1.00-1.49)	
Brain metastases						
No	Ref		<0.001	Ref		<0.001
Yes	1.79	(1.60-2.00)		1.56	(1.39-1.75)	
Unknown	1.72	(1.29-2.30)		1.63	(1.21-2.19)	
