Supplementary Material

Supplementary Table 1. Contributing centers.

Center	Location	No. patients enrolled	% Total cohort
Ospedali Riuniti di Ancona	Ancona	63	7.6
Azienda Ospedaliera Santi Antonio e Biagio e Cesare Arrigo	Alessandria	10	1.2
Azienda Ospedaliera Universitaria Policlinico di Bari	Bari	33	4
Policlinico Universitario Monserrato Casula	Cagliari	14	1.7
Policlinico Campus Biomedico	Roma	41	4.9
Azienda Ospedaliera Universitaria Careggi	Firenze	50	6
Ospedale SS Annunziata	Chieti	9	1.1
Centro di Riferimento Oncologico di Aviano	Aviano	34	4.1
Geneva University Hospital	Geneva	2	0.2
IRCCS Ospedale Policlinico San Martino	Genova	149	17.9
INT IRCCS SS Oncologia Medica Toraco-Polmonare	Milano	42	5
INT IRCCS SS Oncologia Medica GenitoUrinaria	Milano	20	2.4
INT IRCCS Fondazione Pascale	Napoli	30	3.6
INT IRCCS Istituto Regina Elena	Roma	10	1.2
Ospedale San Salvatore	L'Aquila	10	1.2
Ospedale S.M. Goretti	Latina	12	1.4
Ospedale Generale Provinciale	Macerata	7	0.8
Ospedale San Gerardo	Monza	30	3.6
AOU Luigi Vanvitelli	Napoli	3	0.4
Ospedale Michele e Pietro Ferrero ASL CN2	Verduno	2	0.2
Policlinico Fondazione IRCCS Ca' Granda	Milano	10	1.2
Ospedale Santa Maria delle Croci	Ravenna	8	1
AOU Sant'Andrea	Roma	26	3.1
Erasmus University Medical Center	Rotterdam	78	9.4
Policlinico Le Scotte UOC Immunoterapia Oncologica	Siena	22	2.6
Ospedale Santa Chiara	Trento	22	2.6
Policlinico Umberto I	Roma	15	1.8
Azienda Ospedaliera Universitaria di Verona	Verona	16	1.9
Ospedale di Circolo	Varese	66	7.9

Supplementary Table 2. Baseline clinical characteristics by treatment starting (canonical vs extended).

Characteristic	Upfront CD (%)	Upfront ED (%)
No. (n = 812)	550 (67.7)	262 (32.3)
Age, median (range), y	67 (26-93)	67 (28-94)
Gender		
Female	189 (34.4)	100 (38.2)
Male	361 (65.6)	162 (61.8)
ECOG-PS		
0-1	524 (95.3)	241 (92)
≥ 2	24 (4.4)	21 (8)
Unknown	2 (0.3)	0
Smoking status		
Current	98 (17.8)	40 (15.3)
Former	241 (43.8)	84 (32)
Never	211 (38.4)	138 (52.7)
Treatment setting		
First line	264 (48)	116 (44.3)
≥ 2nd line	198 (36)	85 (32.4)
Adjuvant	88 (16)	61 (23.3)
Number of metastatic sites[a]		
<2	129 (27.9)	42 (20.9)
≥ 2	287 (62.1)	132 (65.7)
Unknown	46 (10)	27 (13.4)
Surgery[b]		
Yes	357 (64.9)	198 (75.6)
No	193 (35.1)	64 (24.4)
Concomitant radiotherapy[c]		
Yes	107 (19.5)	49 (18.7)
No	440 (80)	213 (81.3)
Unknown	3 (0.5)	0
Type of ICI		
Pembrolizumab	211 (38.4)	61 (23.3)
Nivolumab	339 (61.6)	201 (76.7)
Tumor type		
NSCLC	172 (31.3)	32 (12.2)
Melanoma	270 (49.1)	41 (15.6)
Renal	100 (18.2)	186 (71.1)
Other	8 (1.4)	3 (1.1)
irAEs onset		
Yes	303 (55.1)	108 (41.2)
No	247 (44.9)	154 (58.8)
Treatment cycles, median (range), No.[d]	13 (1-121)	7 (1-44)

[a]Percentage calculated on the number of patients with metastatic cancer. [b]Surgery refers to resection of primitive tumor or metastatic site or both. [c]Radiotherapy concomitant to ICIs refers to primitive tumor or metastatic site or both. [d]Upfront CD treatment is Q3W (pembrolizumab) or Q2W (nivolumab), upfront ED treatment is Q6W (pembrolizumab) or Q4W (nivolumab).

CD, canonical interval dosing; ECOG-PS, Eastern Operative Oncology Group-Performance status; ED, extended interval dosing; ICI, immune checkpoint inhibitor; irAEs, immune related adverse events, NSCLC, non-small cell lung cancer.

Supplementary Table 3. Baseline clinical characteristics by irAEs onset.

Characteristics	irAEs (%)	No irAEs (%)
No. (n = 812)	411 (50.6)	401 (49.4)
Age, median (range), y	67 (33-90)	67 (26-94)
Gender		
Female	149 (36.3)	140 (34.9)
Male	262 (63.7)	261 (65.1)
ECOG-PS		
0-1	393 (95.6)	372 (93)
≥ 2	17 (4.1)	23 (6)
Smoking Status		
Current	82(20)	56 (14)
Former	152 (37)	173 (43.1)
Never	177 (43)	172 (42.9)
Treatment setting		
First line	208 (50.6)	172 (42.9)
≥ 2nd line	124 (30.2)	159 (39.7)
Adjuvant	79 (19.2)	70 (17.4)
Number of metastatic sites[a]		
< 2	86 (26)	85 (25.7)
≥ 2	209 (63)	210 (63.4)
Unknown	37 (11)	36 (10.9)
Surgery[b]		
Yes	288 (70.1)	267 (66.6)
No	123 (29.9)	134 (33.4)
Concomitant radiotherapy[c]		
Yes	79 (19.2)	77 (19)
No	329 (80)	324 (81)
Unknown	3 (0.8)	0
Type of ICI		
Pembrolizumab	128 (31.1)	144 (35.9)
CD	115 (28)	96 (23.9)
ED	13 (3.1)	48 (12)
Nivolumab	283 (68.9)	257 (64.1)
CD	188 (45.8)	151 (37.7)
ED	95 (23.1)	106 (26.4)

[a]Percentage calculated on the number of patients with metastatic cancer. [b]Surgery refers to resection of primitive tumor or metastatic site or both. [c]Radiotherapy concomitant to ICIs refers to primitive tumor or metastatic site or both.
CD, canonical interval dosing; ECOG-PS, Eastern Operative Oncology Group-Performance status; ED, extended interval dosing; ICI, immune checkpoint inhibitor; irAEs, immune related adverse events.

Supplementary Table 4. Toxicity of *upfront* canonical interval dosing ICI, by tumor type.

	All (%) n=550		NSCLC (%) n=172		Melanoma (%) n=270		Renal (%) n=100		Other (%) n=8	
	any	**G3-G4**	**any**	**G3-G4**	**any**	**G3-G4**	**any**	**G3-G4**	**any**	**G3-G4**
Patients with irAEs	225 (40.9)	17 (3.1)	67 (38.9)	3 (1.7)	121 (44.8)	10 (3.7)	33 (33)	2 (2)	4 (50)	2 (25)
Spectrum of irAEs										
Thyroiditis	69 (12.6)	1 (0.1)	18 (10.5)	0 (0)	39 (14.5)	0 (0)	9 (9)	1 (1)	3 (37.5)	0 (0)
Diarrhea/colitis	46 (8.4)	3 (0.5)	15 (8.7)	1 (0.6)	26 (9.7)	2 (0.7)	4 (4)	0 (0)	1 (12.5)	0 (0)
Endocrine	18 (3.3)	2 (0.3)	5 (2.9)	0 (0)	11 (4.1)	1 (0.4)	0 (0)	0 (0)	2 (25)	1 (12.5)
Hepatitis	26 (4.7)	5 (0.9)	8 (4.6)	2 (1.2)	17 (6.3)	3 (1.1)	1 (1)	0 (0)	0 (0)	0 (0)
Neural	8 (1.5)	0 (0)	6 (3.5)	0 (0)	2 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Arthralgia	45 (8.2)	1 (0.1)	15 (8.7)	0 (0)	25 (9.3)	1 (0.4)	5 (5)	0 (0)	0 (0)	0 (0)
Asthenia	57 (10.4)	0 (0)	17 (9.9)	0 (0)	32 (11.9)	0 (0)	7 (7)	0 (0)	1 (12.5)	0 (0)
Dermatitis	77 (14)	4 (0.7)	19 (11)	0 (0)	45 (16.7)	3 (1.1)	12 (12)	1 (1)	1 (12.5)	1 (12.5)
Pneumonitis	12 (2.2)	0 (0)	7 (4.1)	0 (0)	2 (0.7)	0 (0)	3 (3)	0 (0)	0 (0)	0 (0)
Other	23 (4.2)	1 (0.1)	6 (3.5)	0 (0)	11 (4.1)	0 (0)	3 (3)	0 (0)	3 (37.5)	1 (12.5)

ICI, Immune checkpoint inhibitor; irAEs, Immune-related adverse events; NSCLC, non-small cell lung cancer.

Supplementary Table 5. Toxicity of extended interval dosing ICI at time of first switching, by tumor type.

	All (%) n=550		NSCLC (%) n=172		Melanoma (%) n=270		Renal (%) n=100		Other (%) n=8	
	any	G3-G4	any	G3-G4	any	G3-G4	any	G3-G4	any	G3-G4
Patients with irAEs[a]	77 (15)	7 (1.4)	22 (14.9)	3 (2)	35 (13.4)	2 (0.8)	20 (20.7)	2 (2)	0 (0)	0 (0)
Spectrum of irAEs										
Thyroiditis	16 (3.1)	1 (0.2)	7 (4.7)	0 (0)	7 (2.7)	1 (0.4)	2 (2.1)	0 (0)	0 (0)	0 (0)
Diarrhea/colitis	17 (3.3)	3 (0.6)	7 (4.7)	2 (1.4)	7 (2.7)	0 (0)	3 (3.1)	1 (1)	0 (0)	0 (0)
Endocrine	2 (0.4)	0 (0)	1 (0.7)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatitis	6 (1.2)	0 (0)	1 (0.7)	0 (0)	3 (1.2)	0 (0)	2 (2.1)	0 (0)	0 (0)	0 (0)
Neural	2 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Arthralgia	12 (2.3)	1 (0.2)	2 (1.4)	0 (0)	8 (3.1)	1 (0.4)	2 (2.1)	0 (0)	0 (0)	0 (0)
Asthenia	26 (5.1)	1 (0.2)	7 (4.7)	0 (0)	11 (4.2)	0 (0)	8 (8.2)	1 (1)	0 (0)	0 (0)
Dermatitis	17 (3.3)	0 (0)	1 (0.7)	0 (0)	10 (3.8)	0 (0)	6 (6.2)	0 (0)	0 (0)	0 (0)
Pneumonitis	3 (0.6)	1 (0.2)	1 (0.7)	1 (0.6)	0 (0)	0 (0)	2 (2.1)	0 (0)	0 (0)	0 (0)
Other	5 (1)	0 (0)	0 (0)	0 (0)	4 (1.5)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)

[a]irAE data (at time of first switch) missing for 40 patients (24 NSCLC, 11 melanoma, 3 renal, 2 other).
ICI, Immune checkpoint inhibitor; irAEs, Immune-related adverse events; NSCLC, non-small cell lung cancer.

Supplementary Table 6. Long-term toxicity of extended interval dosing ICI (including all cycles after switching), by tumor type.

	All (%) n=550		NSCLC (%) n=172		Melanoma (%) n=270		Renal (%) n=100		Other (%) n=8	
	any	G3-G4	any	G3-G4	any	G3-G4	any	G3-G4	any	G3-G4
Patients with irAEs[a]	179 (37.1)	23 (4.8)	54 (41.5)	7 (5.4)	87 (34.7)	11 (4.4)	38 (39.6)	5 (5.2)	0 (0)	0 (0)
Spectrum of irAEs										
Thyroiditis	40 (8.3)	1 (0.2)	18 (13.8)	0 (0)	18 (7.2)	1 (0.4)	4 (4.2)	0 (0)	0 (0)	0 (0)
Diarrhea/colitis	46 (9.5)	6 (1.2)	15 (11.4)	3 (2.3)	21 (8.4)	2 (0.8)	10 (10.4)	1 (1)	0 (0)	0 (0)
Endocrine	12 (2.5)	2 (0.4)	2 (1.5)	0 (0)	10 (4)	2 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatitis	13 (2.7)	1 (0.2)	1 (0.8)	0 (0)	10 (4)	1 (0.4)	2 (2.1)	0 (0)	0 (0)	0 (0)
Neural	5 (1)	1 (0.2)	1 (0.8)	0 (0)	3 (1.2)	1 (0.4)	1 (1)	0 (0)	0 (0)	0 (0)
Arthralgia	46 (9.5)	2 (0.4)	9 (6.9)	0 (0)	25 (10)	2 (0.8)	12 (12.5)	0 (0)	0 (0)	0 (0)
Asthenia	53 (10.9)	1 (0.2)	16 (12.2)	0 (0)	24 (9.6)	0 (0)	13 (13.5)	1 (1)	0 (0)	0 (0)
Dermatitis	62 (12.8)	6 (1.2)	15 (11.5)	2 (1.5)	29 (11.6)	2 (0.8)	18 (18.7)	3 (3.2)	0 (0)	0 (0)
Pneumonitis	13 (2.7)	3 (0.6)	4 (3.1)	3 (2.3)	5 (2)	0 (0)	4 (4.2)	0 (0)	0 (0)	0 (0)
Other	22 (4.5)	1 (0.2)	5 (3.8)	0 (0)	11 (4.4)	1 (0.4)	6 (6.2)	0 (0)	0 (0)	0 (0)

[a]irAE data (at time of first switch and after) missing for 67 patients (42 NSCLC, 19 melanoma, 4 renal, 2 other).
ICI, Immune checkpoint inhibitor; irAEs, Immune-related adverse events; NSCLC, non-small cell lung cancer.

Supplementary Table 7. Toxicity of *upfront* extended interval dosing ICI, by tumor type.

	All (%) n=262		NSCLC (%) n=32		Melanoma (%) n=186		Renal (%) n=41		Other (%) n=3	
	any	**G3-G4**	**any**	**G3-G4**	**any**	**G3-G4**	**any**	**G3-G4**	**any**	**G3-G4**
Patients with irAEs	107 (40.8)	14 (5.3)	6 (18.7)	1 (3.1)	91 (48.9)	8 (4.3)	10 (24.4)	5 (12.2)	0 (0)	0 (0)
Spectrum of irAEs										
Thyroiditis	26 (9.9)	3 (1.1)	1 (3.1)	0 (0)	22 (11.8)	2 (1.1)	3 (7.3)	1 (2.4)	0 (0)	0 (0)
Diarrhea/colitis	32 (12.2)	2 (0.8)	2 (6.2)	0 (0)	26 (14)	1 (0.5)	4 (9.8)	1 (2.4)	0 (0)	0 (0)
Endocrine	4 (1.5)	0 (0)	0 (0)	0 (0)	4 (2.2)	2 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatitis	12 (4.6)	4 (1.5)	1 (3.1)	1 (3.1)	8 (4.3)	2 (1.1)	3 (7.3)	1 (2.4)	0 (0)	0 (0)
Neural	3 (1.1)	1 (0.4)	0 (0)	0 (0)	3 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Arthralgia	2 (0.8)	0 (0)	0 (0)	0 (0)	19 (10.2)	1 (0.5)	1 (2.4)	0 (0)	0 (0)	0 (0)
Asthenia	24 (9.2)	0 (0)	0 (0)	0 (0)	21 (11.3)	0 (0)	3 (7.3)	0 (0)	0 (0)	0 (0)
Dermatitis	32 (12.2)	0 (0)	1 (3.1)	0 (0)	30 (16.1)	0 (0)	1 (2.4)	0 (0)	0 (0)	0 (0)
Pneumonitis	16 (6.1)	3 (1.1)	2 (6.2)	0 (0)	11 (5.9)	1 (0.5)	3 (7.3)	2 (4.9)	0 (0)	0 (0)
Other	12 (4.6)	1 (0.4)	1 (3.1)	0 (0)	11 (5.9)	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)

ICI, Immune checkpoint inhibitor; irAEs, Immune-related adverse events; NSCLC, non-small cell lung cancer.