Supplemental Methods

- Treatment-free survival (TFS) and time on protocol therapy were partitioned into survival states with and without toxicity, as illustrated below
- We examined treatment-related adverse events (TRAEs) reported between randomization and start of subsequent therapy (including TRAEs newly reported after cessation of protocol therapy) and counted the number of unique days with one or more TRAEs reported during the relevant period
    - If a TRAE started during protocol therapy and persisted after cessation, then the days were split and attributed to the relevant period
    - If a TRAE was unresolved at subsequent therapy initiation, then the days were truncated at that point
- Without double-counting TRAEs occurring on the same day, we summed the unique days during each period; these were represented as contiguous days, although they did not occur that way (1,2)
- Two additional endpoints were calculated for partitioning and illustration—time to cessation of both protocol therapy and its toxicity, and time to cessation of protocol therapy without toxicity—by adding and subtracting toxicity days from the time to protocol therapy cessation endpoint

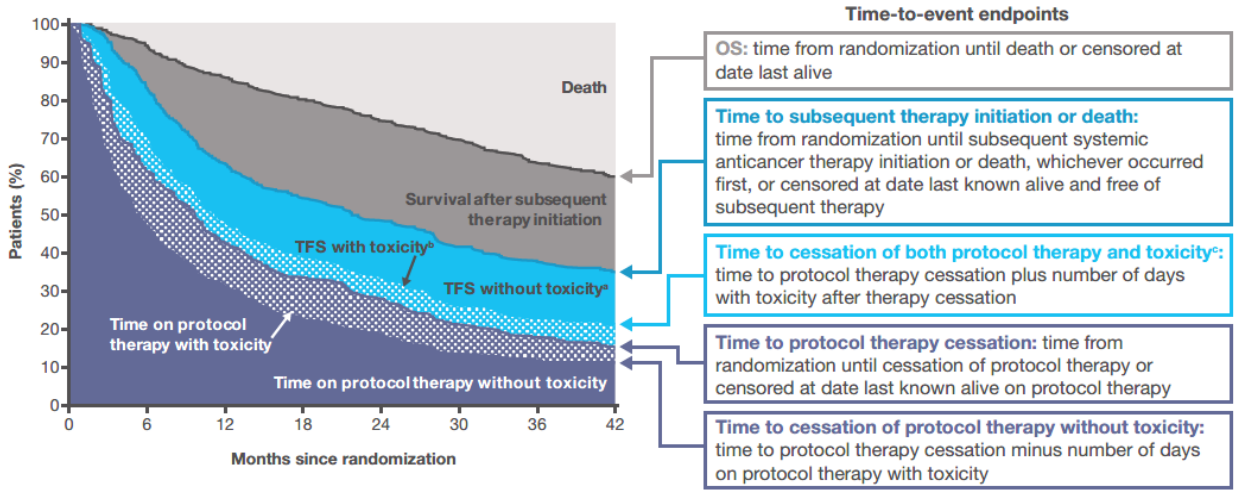


Figure S1.
Kaplan–Meier estimates of (**A**) overall survival, (**B**) time to subsequent systemic therapy initiation or death, and (**C**) time to protocol therapy cessation over the 42-month follow-up period for analysis, according to IMDC risk group. The 42-month Kaplan–Meier estimates (% event-free) and 42-month mean times are summarized below.

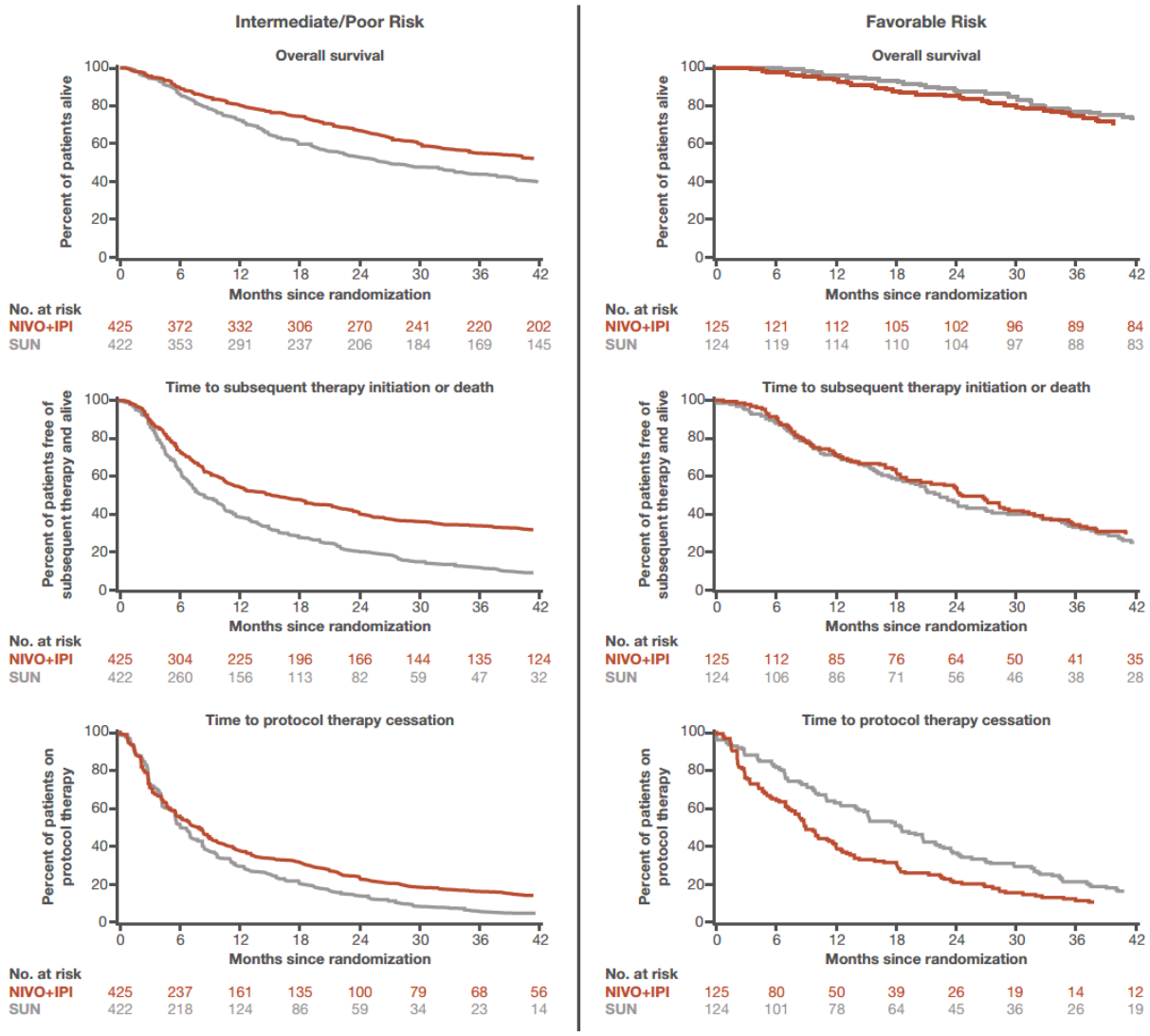


Figure S1 continued

	Intermediate/poor risk		Favorable risk		Intent-to-treat	
	NIVO+IPI	**SUN**	**NIVO+IPI**	**SUN**	**NIVO+IPI**	**SUN**
N patients randomized	***425***	***422***	***125***	***124***	***550***	***546***
Overall survival						
N events	207	255	43	37	250	292
KM percent event-free at 42 months	52%	39%	70.1%	73%	56%	47%
42-month mean time, months	30.1	25.9	36.2	37.5	31.5	28.6
Time to subsequent therapy initiation or death						
N events	289	377	90	99	379	476
KM percent event-free at 42 months	31%	9.0%	29%	24%	31%	12%
42-month mean time, months	21.0	13.9	25.0	23.9	21.9	16.2
Time to protocol therapy cessation						
N events	373	406	117	113	490	519
KM percent event-free at 42 months	14%	4.1%	9.6%	15%	13%	6.6%
42-month mean time, months	14.1	10.8	14.0	20.2	14.1	12.9

Abbreviations: International Metastatic Renal Cell Carcinoma Database Consortium; NIVO+IPI, nivolumab plus ipilimumab; SUN, sunitinib; KM, Kaplan–Meier estimate.
Overall survival was defined from randomization until death from any cause, or was censored on the date last known alive.
Time to subsequent therapy initiation or death was defined from randomization until initiation of subsequent systemic anticancer therapy or death, whichever occurred first, or censored at the date last known alive and free of subsequent therapy.
Time to protocol therapy cessation was defined from randomization until cessation of protocol therapy, or censored at the date last known alive on protocol therapy.

Table S1. Kaplan–Meier estimates of 12-, 24-, 36-, and 42-month percentages of patients surviving free from subsequent therapy initiation and free from protocol therapy cessation and surviving treatment-free, according to IMDC risk group. The percentages of patients surviving treatment-free were estimated by the differences in Kaplan–Meier estimates of the two defining endpoints (3).

Month	**Kaplan–Meier estimates at × months since randomization**	**Favorable risk**		**Intermediate/ poor risk**		**Intent-to-treat**	
		NIVO+IPI	**SUN**	**NIVO+IPI**	**SUN**	**NIVO+IPI**	**SUN**
		(%)	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
12	Surviving free from subsequent therapy initiation	71	71	54	39	58	46
	Free from protocol therapy cessation	40.0	63	38	29	38	37
	Surviving treatment-free	31	8.2	16	9.3	19.6	9.0
24	Surviving free from subsequent therapy initiation	53	46	41	20.3	44	26
	Free from protocol therapy cessation	21	36	23	14	23	19
	Surviving treatment-free	32	10.0	18	6.3	21	7.2
36	Surviving free from subsequent therapy initiation	34	33	34	12	34	17
	Free from protocol therapy cessation	11	21	16	5.6	15	9.1
	Surviving treatment-free	23	12	18	6.2	19	7.5
42	Surviving free from subsequent therapy initiation	29	24	31	9.0	31	12
	Free from protocol therapy cessation	9.6	15	14	4.1	13	6.6
	Surviving treatment-free	19.5	8.8	18	4.9	18	5.8

Figure S2.
TFS, survival after subsequent systemic therapy, and prior protocol therapy durations relative to time of protocol therapy cessation, according to IMDC risk. X-axis is truncated at 42 months before and 42 months after protocol therapy cessation.

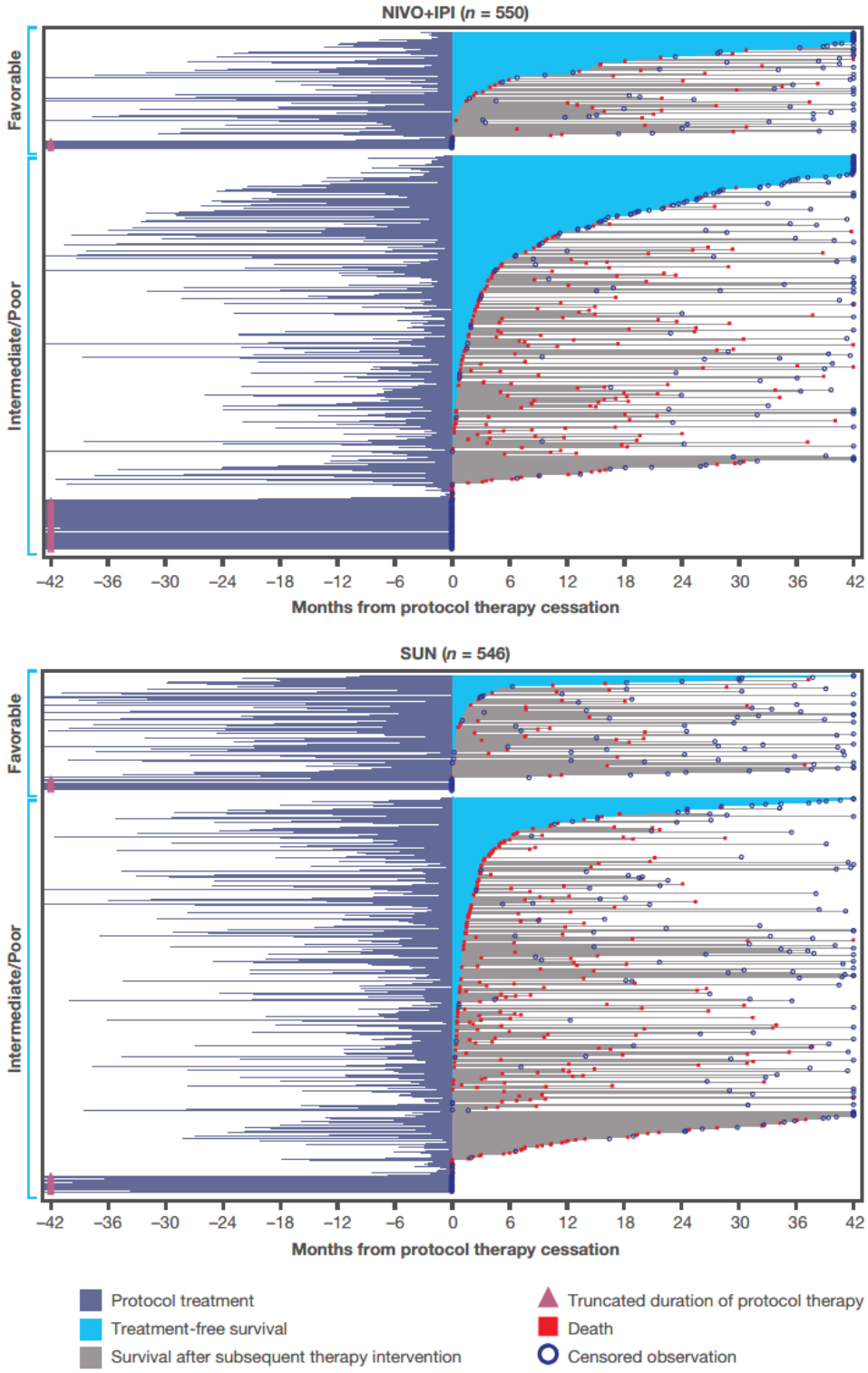
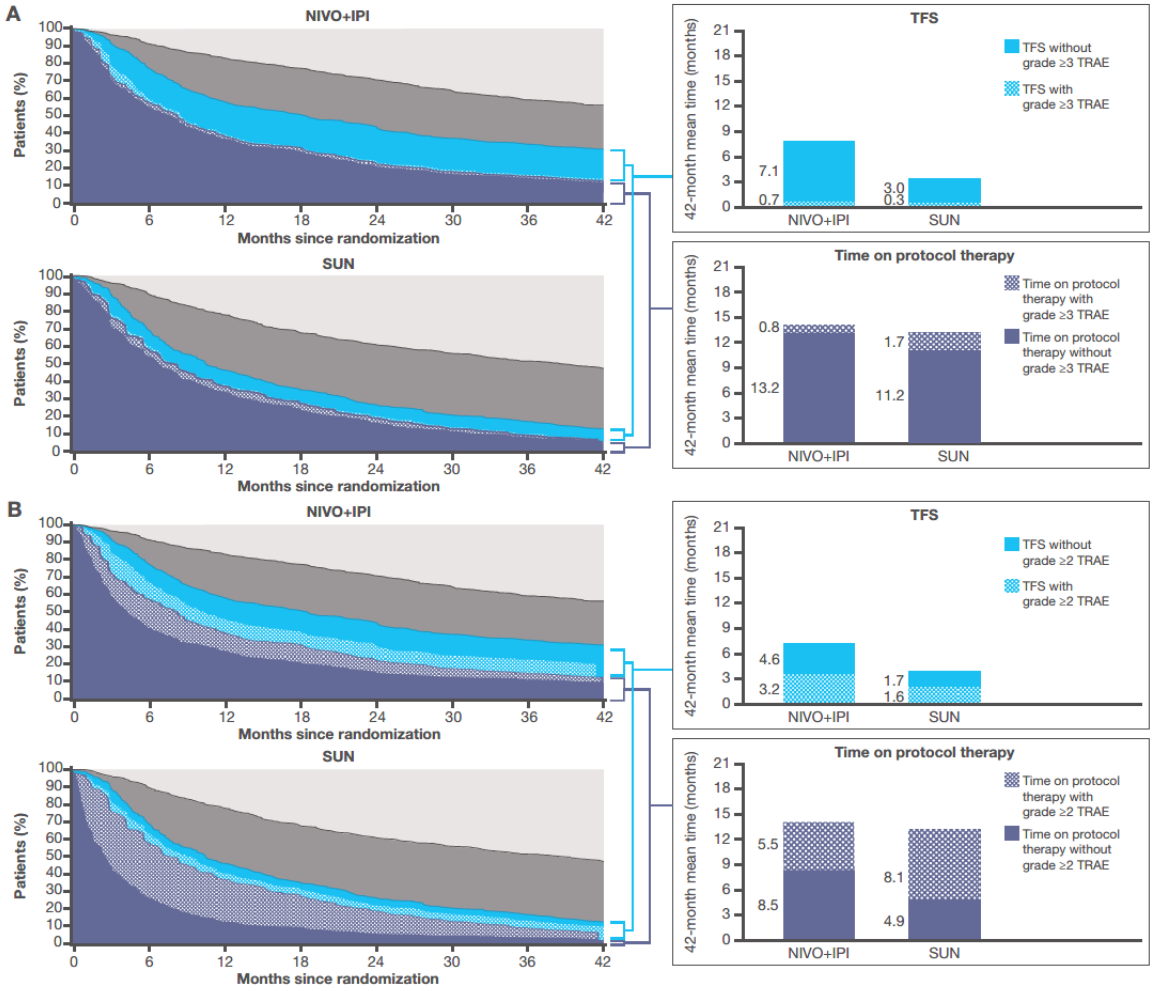


Figure S3.
Estimates of TFS, with and without toxicity, and other survival states over the 42-month period since randomization, according to treatment group in the overall intent-to-treat population of 1096 patients. Toxicity is defined alternatively by (**A**) grade ≥3 TRAEs and (**B**) grade ≥2 TRAEs. Abbreviation: RX, therapy.



Survival state	42-month mean time, months		Difference (95% CI)
	NIVO+IPI (*N* = 550)	SUN (*N* = 546)	NIVO+IPI versus SUN
Overall survival	31.5	28.6	
Survival after subsequent Rx initiation	9.5	12.4	−2.8 (−4.3 to −1.3)
TFS	7.8	3.3	4.6 (3.4–5.7)
Time on protocol Rx	14.1	12.9	1.2 (−0.4 to 2.7)
A. Grade ≥3 TRAE			
TFS without grade ≥3 TRAE	7.1	3.0	4.1 (3.0–5.2)
TFS with grade ≥3 TRAE	0.7	0.3	0.4 (0.1–0.8)
Protocol Rx with grade ≥3 TRAE	0.8	1.7	−0.9 (−1.4 to −0.3)
Protocol Rx without grade ≥3 TRAE	13.2	11.2	2.1 (0.6–3.5)
B. Grade ≥2 TRAE			
TFS without grade ≥2 TRAE	4.6	1.7	2.9 (1.9–3.8)
TFS with grade ≥2 TRAE	3.2	1.6	1.7 (0.9–2.4)
Protocol Rx with grade ≥2 TRAE	5.5	8.1	−2.5 (−3.8 to −1.3)
Protocol Rx without grade ≥2 TRAE	8.5	4.9	3.7 (2.6–4.7)

References

1. Goldhirsch A, Gelber RD, Simes RJ, Glasziou P, Coates AS. Costs and benefits of adjuvant therapy in breast cancer: a quality-adjusted survival analysis. J Clin Oncol 1989;7:36-44.
2. Gelber RD, Goldhirsch A, Cole BF. Evaluation of effectiveness: Q-TWiST. The International Breast Cancer Study Group. Cancer Treat Rev 1993;19(suppl A):73-84.
3. Huang B, Tian L, McCaw ZR, Luo X, Talukder E, Rothenberg M, et al. Analysis of response data for assessing treatment effects in comparative clinical studies. Ann Intern Med 2020;173:368-74.