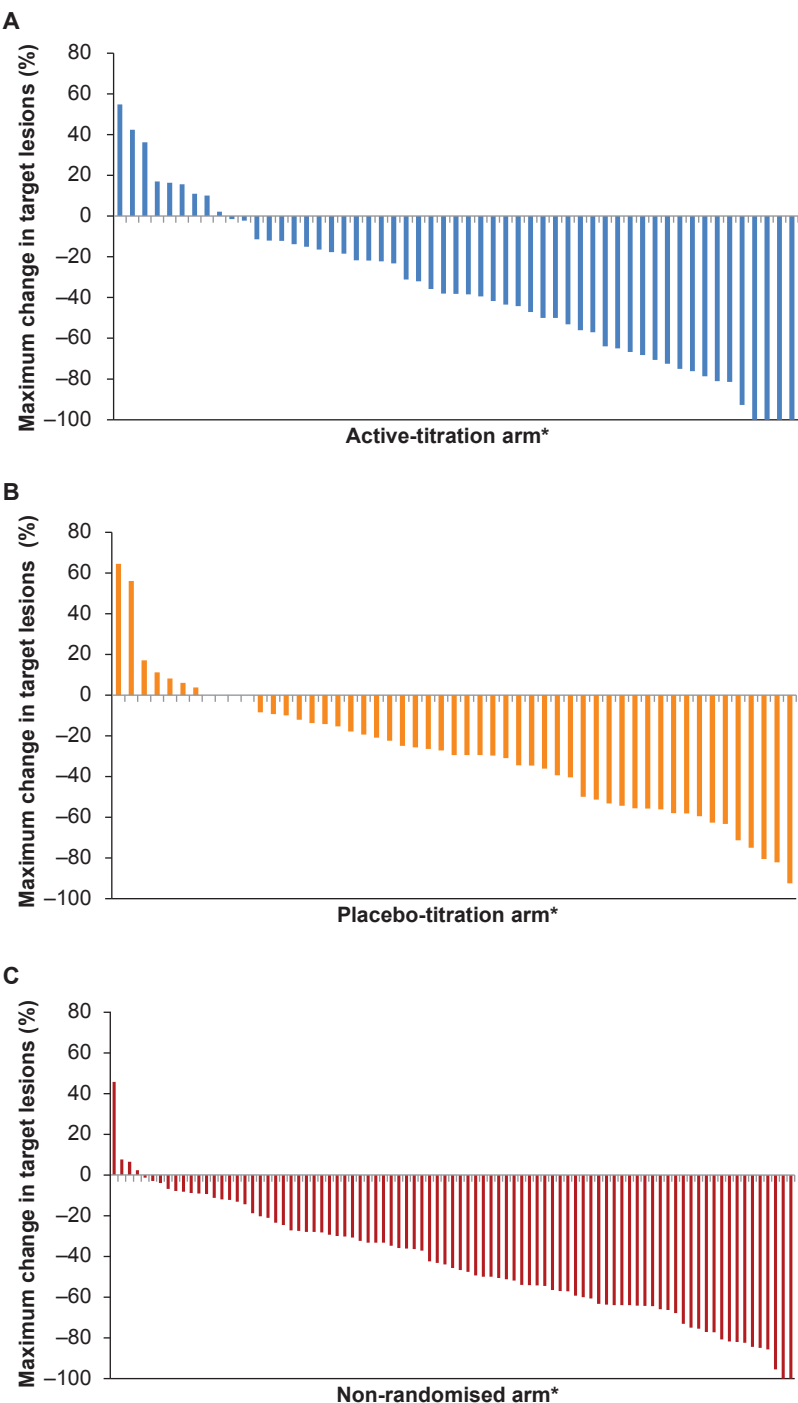


## Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Rini BI, Melichar B, Ueda T, et al. Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomised double-blind phase 2 trial. *Lancet Oncol* 2013; published online October 18. [http://dx.doi.org/10.1016/S1470-2045\(13\)70464-9](http://dx.doi.org/10.1016/S1470-2045(13)70464-9).

**Figure S1. Maximum tumour shrinkage (%) of target lesions in individual patients during the study in (A) active-titration, (B) placebo-titration, and (C) non-randomised arms.**



\*One patient in the active-titration arm, three patients in the placebo-titration arm, and two patients in the non-randomised arm were excluded because tumour shrinkage could not be determined. Data are based on a single scan.

**Table S1: Treatment-emergent, all-causality grade 3 or higher adverse events**

Adverse event, <sup>†</sup> n (%)	Total* (N=213)			Axitinib titration (n=56)			Placebo titration (n=56)			Non-randomised (n=91)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Hypertension	63 (30)	0	0	10 (18)	0	0	5 (9)	0	0	45 (49)	0	0
Diarrhoea	16 (8)	1 (<1)	0	6 (11)	1 (2)	0	2 (4)	0	0	8 (9)	0	0
Fatigue	13 (6)	1 (<1)	0	3 (5)	0	0	2 (4)	0	0	6 (7)	1 (1)	0
Weight decreased	13 (6)	0	0	4 (7)	0	0	3 (5)	0	0	6 (7)	0	0
Back pain	8 (4)	0	0	3 (5)	0	0	1 (2)	0	0	4 (4)	0	0
Disease progression	0	1 (<1)	7 (3)	0	0	1 (2)	0	1 (2)	0	0	0	6 (7)
Hand-foot syndrome	8 (4)	0	0	2 (4)	0	0	1 (2)	0	0	5 (5)	0	0
Decreased appetite	7 (3)	0	0	3 (5)	0	0	0	0	0	4 (4)	0	0
Dehydration	7 (3)	0	0	3 (5)	0	0	0	0	0	3 (3)	0	0
Hyponatraemia	5 (2)	2 (1)	0	3 (5)	0	0	0	0	0	1 (1)	2 (2)	0
Dyspnoea	5 (2)	1 (<1)	0	1 (2)	1 (2)	0	2 (4)	0	0	1 (1)	0	0
ALT increased	5 (2)	0	0	1 (2)	0	0	2 (4)	0	0	2 (2)	0	0
Arthralgia	5 (2)	0	0	1 (2)	0	0	2 (4)	0	0	2 (2)	0	0
Asthenia	5 (2)	0	0	0	0	0	2 (4)	0	0	3 (3)	0	0
Dizziness	5 (2)	0	0	1 (2)	0	0	2 (4)	0	0	2 (2)	0	0
Nausea	5 (2)	0	0	3 (5)	0	0	0	0	0	1 (1)	0	0
Blood sodium decreased	4 (2)	0	0	0	0	0	3 (5)	0	0	1 (1)	0	0
General physical health deterioration	3 (1)	0	1 (<1)	0	0	1 (2)	1 (2)	0	0	1 (1)	0	0
Hypokalaemia	3 (1)	1 (<1)	0	1 (2)	0	0	1 (2)	0	0	1 (1)	1 (1)	0
Mucosal inflammation	4 (2)	0	0	2 (4)	0	0	0	0	0	2 (2)	0	0
Syncope	4 (2)	0	0	2 (4)	0	0	1 (2)	0	0	1 (1)	0	0
Vomiting	4 (2)	0	0	3 (5)	0	0	0	0	0	1 (1)	0	0

ALT=alanine aminotransferase.

\*Includes 10 treated patients who withdrew during lead-in period. <sup>†</sup>Reported in  $\geq 2\%$  of patients in the total treated population.

## Investigators

The following investigators participated in the study: The University of Texas MD Anderson Cancer Center, Houston, TX, USA (E Jonasch), Cleveland Clinic Foundation, Cleveland, OH, USA (BI Rini), Saint-Petersburg State Healthcare Institution 'City Clinical Oncology Dispensary', Saint-Petersburg, Russia (P Karlov), Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic (B Melichar), State Healthcare Institution "Leningrad Regional Oncology Dispensary", Saint-Petersburg, Russia (LD Roman), Chiba Cancer Center, Chiba, Japan (T Ueda), Hannover Medical School, Hannover, Germany (V Grünwald), H Lee Moffitt Cancer Center, Tampa, FL, USA (MN Fishman), Federal State Institution "Russian Research Center of Roentgenology and Radiology", Moscow, Russia (SA Ivanov), Institution of Russian Academy of Medical Sciences, 'Russian Oncological Research Center n.a. N.N. Blokhin RAMS', Moscow, Russia (LV Demidov), Texas Oncology-Sammons Cancer Center, Dallas, TX, USA (TE Hutson), Samara Regional Clinical Oncology Dispensary, Samara, Russia (MV Kopp), Kinki University Hospital, Osaka, Japan (H Uemura), Keio University Hospital, Tokyo, Japan (M Oya), Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA (MA Carducci), Massachusetts General Hospital Cancer Center, Boston, MA, USA (MD Michaelson), Klinika komplexni onkologicke pece Masarykuv onkologicky ustav, Brno, Czech Republic (J Tomasek), Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN, USA (TF Logan), Bay Area Cancer Research Group, LLC, Pleasant Hill, CA, USA (JK Johl), Medical Radiology Research Center of the Minzdravsotsrazvitiya of Russia, Obninsk, Kaluga region, Russia (OB Karyakin), Hokkaido University Hospital, Hokkaido, Japan (N Shinohara), Akita University Hospital, Akita, Japan (K Numakura), Nebraska Methodist Hospital, Omaha, NE, USA (RJ Hauke), Hospital General Universitario Gregorio Marañón, Madrid, Spain (JA Arranz), Nemocnice na Bulovce Urologické oddeleni, Praha, Czech Republic (M Pesl), Ohio State University Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH, USA (TE Olencki), Washington University School of Medicine, St. Louis, MO, USA (J Picus), Oregon Health and Science University, Portland, OR, USA (CW Ryan), Kobe University Hospital, Hyogo, Japan (H Miyake), Comprehensive Blood and Cancer Center, Bakersfield, CA, USA (R Patel), Eberhardt-Karls-Universitaet Tuebingen, Tuebingen, Germany (A Stenzl), Cancer and Hematology Centers of Western Michigan, Grand Rapids, MI, USA (TJ O'Rourke), University of Cincinnati Cancer Center, Cincinnati, OH, USA (O Rixe), Tokushima University Hospital, Tokushima, Japan (H Kanayama), Kyushu University Hospital, Fukuoka, Japan (K Tatsugami), Hamamatsu University School of Medicine, University Hospital, Shizuoka, Japan

(T Takayama), Nagoya University Hospital, Aichi, Japan (Y Yoshino), Nagasaki University Hospital, Nagasaki, Japan (M Nishikido), University of Nebraska Medical Center, Omaha, NE USA (J Wang), Hospital Universitario La Paz Servicio De Oncologia, Madrid, Spain (EE Arranz), Krajska zdravotni, a.s. - Masarykova nemocnice v Usti nad Labem, Usti nad Labem, Czech Republic (J Schraml), Virginia Mason Medical Center, Seattle, WA, USA (TW Malpass), Nevada Cancer Institute, Las Vegas, NV (OB Goodman), Klinikum der J. W. Goethe-Universitaet, Medizinische Klinik II, Frankfurt, Germany (L Bergmann), Klinikum Weiden Klinik fuer Urologie, Weiden, Germany (T Klotz), Yamagata University Hospital, Yamagata, Japan (Y Tomita), Sapporo Medical University Hospital, Sapporo, Japan (H Kitamura), Japanese Foundation For Cancer Research Cancer Institute Hospital, Tokyo, Japan (S Takahashi), and National Cancer Center, Tokyo, Japan (H Fujimoto).