Supplementary table 1. Blood measurements

Measurements	Value (range)			
	Baseline	t=2	t=4	t=8
Hemoglobin (mmol/L)	7,5 (5,2-10,3)	7,2 (5,3-9,2)	6,8 (4,8-9,2)	6,5 (5,2-9,2)
WBC (x 10^9/L)	6,7 (2,9-11,1)	4,7 (2,2-7,5)	5,4 (1,8-12,3)	5,2 (1,4-13,4)
Neutrophils (x 10^9/L)	4,4 (1,7-9,6)	3 (1,3-6,2)	3,6 (1,1-8,5)	3,7 (0,9-12,1)
Eosinophils (x 10^9/L)	0,1 (0-0,5)	0,2 (0,05-0,4)	0,16 (0,03-0,62)	0,2 (0-0,64)
Basophils (x 10^9/L)	0,05 (0-0,1)	0,05 (0-0,1)	0,06 (0-0,18)	0,05 (0-0,1)
Lymphocytes (x 10^9/L)	1,5 (0,5-4,2)	1,1 (0,4-3,1)	1 (0,3-2,23)	0,8 (0,09-2,1)
Monocytes (x 10^9/L)	0,61 (0,2-1,15)	0,4 (0,1-0,8)	0,5 (0,2-1,47)	0,5 (0,02-1,15)
Platelets (x 10^9/L)	286 (121-585)	197 (47-528)	273 (85-691)	256 (76-684)
Corrected Calcium (mmol/L)	2,5 (2,2-3)	2,4 (2,1-2,7)	2,5 (2,2-3,3)	2,4 (2,1-3,0)
LDH (U/L)	250 (80-2133)	240 (80-1734)	341 (107-2614)	263 (113-454)

Supplementary table 2. Treatment-related toxicity per cohort[1]

Event	All cohorts	Cohort 0	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 2E
					Number of patients				
Neuropathy									
Any Grade	**4 (10%)**	**2**	**1**			**1**			
Grade 1	3 (8%)	1	1			1			
Grade 2	1 (3%)	1							
Grade ≥3	0								
Cough									
Any Grade	**14 (36%)**		**3**	**4**	**1**		**3**	**2**	**1**
Grade 1	11 (28%)		2	3	1		2	2	1
Grade 2	3 (8%)		1	1			1		
Grade ≥3	0								
Dyspnea									
Any Grade	**10 (26%)**	**1**	**3**	**2**			**1**	**2**	**1**
Grade 1	5 (13%)	1	1	2					1
Grade 2	4 (10%)		1				1	2	
Grade ≥3	1 (3%)		1						
Pneumonitis									
Any Grade	**7 (18%)**		**3**	**2**	**1**		**1**		
Grade 1	1 (3%)			1					
Grade 2	3 (8%)		1	1	1				
Grade ≥3	3 (8%)		2				1		
Mucositis									
Any Grade	**14 (36%)**	**1**	**1**	**1**	**3**	**2**	**1**	**2**	**3**
Grade 1	10 (26%)	1		1		2	1	2	3
Grade 2	4 (10%)		1		3				
Grade ≥3	0								
Nausea									
Any Grade	**12 (31%)**	**1**	**1**			**3**	**2**	**2**	**3**
Grade 1	6 (15%)		1			2		1	2
Grade 2	6 (15%)	1				1	2	1	1
Grade ≥3	0								
Diarrhea									
Any Grade	**11 (28%)**	**2**	**2**		**1**	**1**	**1**	**1**	**3**
Grade 1	8 (20%)	1	2		1			1	3
Grade 2	1 (3%)	1							
Grade ≥3	2 (5%)					1	1		
Vomiting									
Any Grade	**9 (23%)**	**1**	**1**			**2**	**2**	**2**	**1**
Grade 1	4 (10%)		1			1	1	1	
Grade 2	5 (13%)	1				1	1	1	1
Grade ≥3	0								
Dysgeusia									
Any Grade	**6 (15%)**	**1**		**2**			**1**	**1**	**1**
Grade 1	4 (10%)	1		1			1		1
Grade 2	2 (5%)			1				1	
Grade ≥3	0								
Stomatitis									
Any Grade	**5 (13%)**		**1**	**2**	**1**	**1**			
Grade 1	3 (8%)			1	1	1			
Grade 2	1 (3%)		1						
Grade ≥3	1 (3%)			1					
Constipation									
Any Grade	**4 (10%)**							**1**	**3**
Grade 1	1 (3%)								1
Grade 2	3 (8%)							1	2
Grade ≥3	0								
(Hemorrhagic) cystitis									
Any Grade	**7 (18%)**			**1**		**1**	**2**	**2**	**1**
Grade 1	2 (5%)						1		1
Grade 2	4 (10%)			1		1	1	1	
Grade ≥3	1 (3%)							1	
Pollakiuria									
Any Grade	**4 (10%)**					**1**		**2**	**1**
Grade 1	3 (8%)							2	1
Grade 2	1 (3%)					1			
Grade ≥3	0								
Fatigue									
Any Grade	**18 (46%)**	**2**	**2**	**4**	**1**		**3**	**2**	**4**
Grade 1	5 (13%)		2	2			1		
Grade 2	8 (20%)	1		2	1		1	1	2
Grade ≥3	5 (13%)	1					1	1	2
Anorexia									
Any Grade	**16 (41%)**	**3**	**1**	**2**		**4**	**1**	**2**	**3**
Grade 1	8 (20%)	2	1	1		2	1		1
Grade 2	8 (20%)	1		1		2		2	2
Grade ≥3	0								
Fever/ chills/flu									
Any Grade	**5 (13%)**			**2**	**2**	**1**			
Grade 1	5 (13%)			2	2	1			
Grade 2	0								
Grade ≥3	0								
Malaise									
Any Grade	4 (10%)	1		1					2
Grade 1	2 (5%)	1							1
Grade 2	1 (3%)			1					
Grade ≥3	1 (3%)								1
Rash									
Any Grade	15 (38%)	1	1	2	4	2	2	1	2
Grade 1	9 (23%)			1	2	2	1	1	2
Grade 2	6 (15%)	1	1	1	2		1		
Grade ≥3	0								

Event	All cohorts	Cohort 0	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 2E
					Number of patients				
Dry skin									
Any Grade	8 (20%)			1	3	2	1		1
Grade 1	6 (15%)			1	1	2	1		1
Grade 2	2 (5%)				2				
Grade ≥3	0								
Pruritus									
Any Grade	4 (10%)				2	2			
Grade 1	4 (10%)				2	2			
Grade 2	0								
Grade ≥3	0								
Anemia									
Any Grade	14 (36%)	1	1	3	1	1	3	2	2
Grade 1	2 (5%)	1	1						
Grade 2	10 (26%)			2	1	1	2	2	2
Grade ≥3	2 (5%)			1			1		
Hypercholesterolemia									
Any Grade	12 (31%)	1	1	2	4	1		1	2
Grade 1	3 (8%)				1				2
Grade 2	7 (18%)	1		2	2	1		1	
Grade ≥3	2 (5%)		1		1				
Lymphocytopenia									
Any Grade	10 (26%)		1		1	2	3	3	
Grade 1	0								
Grade 2	2 (5%)						1	1	
Grade ≥3	8 (20%)		1		1	2	2	2	
Hyperglycemia									
Any Grade	10 (26%)	1	2	2		1	2	1	1
Grade 1	1 (3%)								1
Grade 2	6 (15%)		2	2		1		1	
Grade ≥3	3 (8%)	1					2		
Thrombocytopenia									
Any Grade	10 (26%)		1	1	3	2	2		1
Grade 1	7 (18%)		1	1	2	1	1		1
Grade 2	1 (3%)				1				
Grade ≥3	2 (5%)					1	1		
Hypertriglyceridemia									
Any Grade	8 (20%)	1	2	1	2		1		1
Grade 1	3 (8%)	1	1		1				
Grade 2	3 (8%)			1			1		1
Grade ≥3	2 (5%)		1		1				
Leukocytopenia									
Any Grade	8 (20%)			1	1	1	1	1	3
Grade 1	2 (5%)								2
Grade 2	2 (5%)			1					1
Grade ≥3	4 (10%)				1	1	1	1	
*Electrolyte disturbance**									
Any Grade	7 (18%)	2				1		1	3
Grade 1	5 (13%)	2							3
Grade 2	0								
Grade ≥3	2 (5%)					1		1	
*Liver values increased***									
Any Grade	6 (15%)		1		1	1	1	2	
Grade 1	2 (5%)							2	
Grade 2	3 (8%)		1			1	1		
Grade ≥3	1 (3%)				1				
Neutropenia									
Any Grade	5 (13%)				1	1	1	1	1
Grade 1	0								
Grade 2	3 (8%)						1	1	1
Grade ≥3	2 (5%)				1	1			
Edema (extremities/ face)									
Any Grade	4 (10%)	1			1	1		1	
Grade 1	3 (8%)	1			1			1	
Grade 2	0								
Grade ≥3	1 (3%)					1			

[1] Reported in 10% or more of the treated patients
* Hypophosphatemia, hyponatremia, hypo- and hyperkalemia, hypocalcemia
** Alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase and
alkaline phosphatase
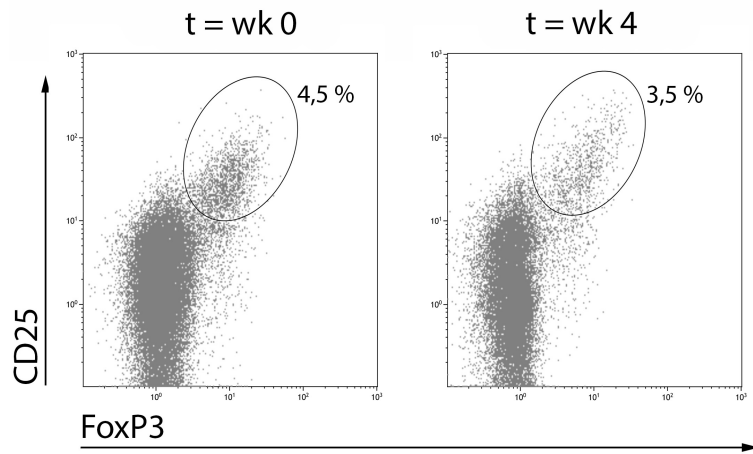
Supplementary fig. 1. Representative flow cytometry dot plots illustrating the changes in Tregs, defined as $CD3^+CD4^+CD25^{hi}FoxP3^+$
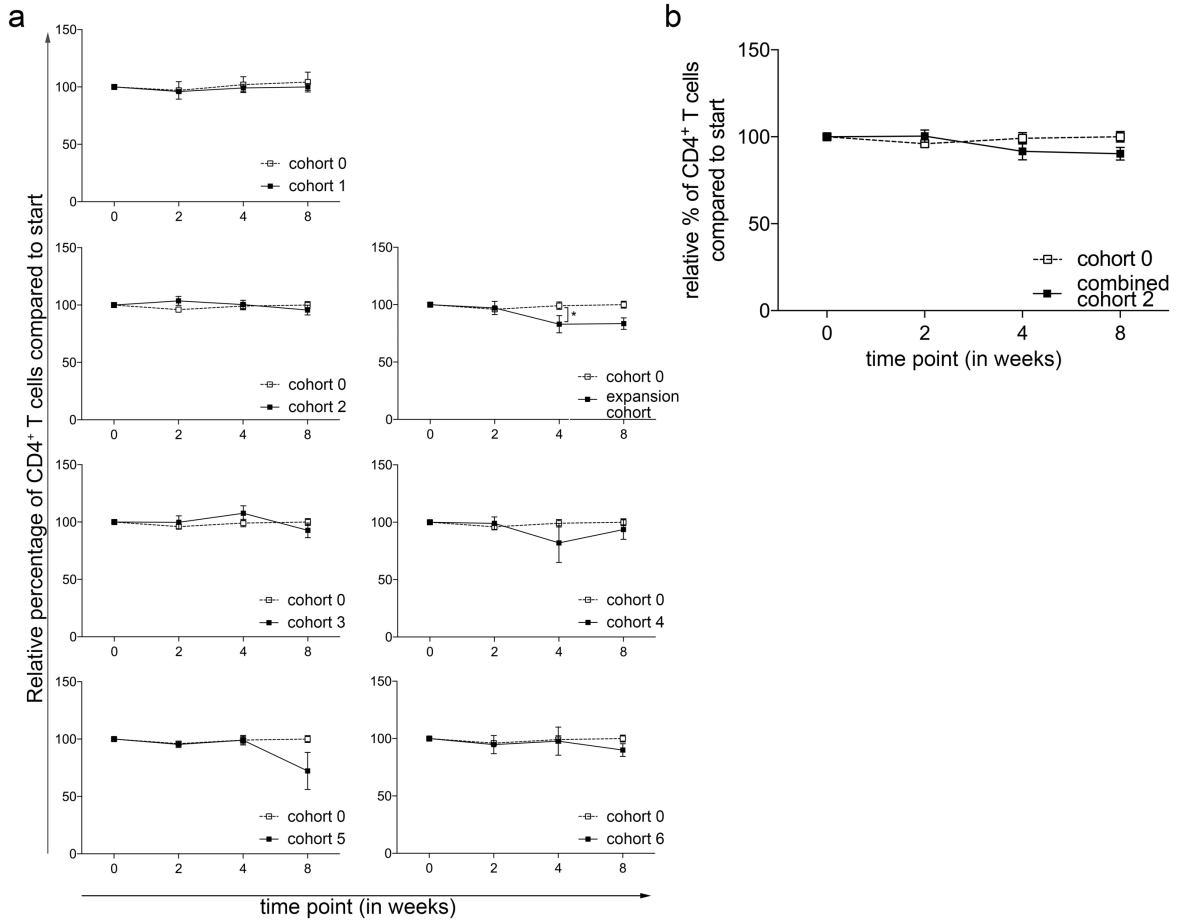
Supplementary fig. 2. Effect of different dosages and administration schedules of CTX when combined with a fixed dose of 10 mg everolimus on the frequency of CD4$^+$ T cells. a, Relative percentages of CD4$^+$ T cells within CD3$^+$ T cells were determined in freshly isolated PBMC from patients treated with different dosages and schedules of CTX, combined with a fixed dose of everolimus at baseline and subsequently 2, 4, and 8 weeks after start of treatment. b, Relative percentages of CD4$^+$ T cells within CD3$^+$ T cells are shown for cohort 2 combined with the expansion cohort. Patients were treated with 50 mg CTX once daily, combined with 10 mg everolimus once daily. Means ± SEM are shown; p-value indicated with asterisk; * p≤ 0.05.
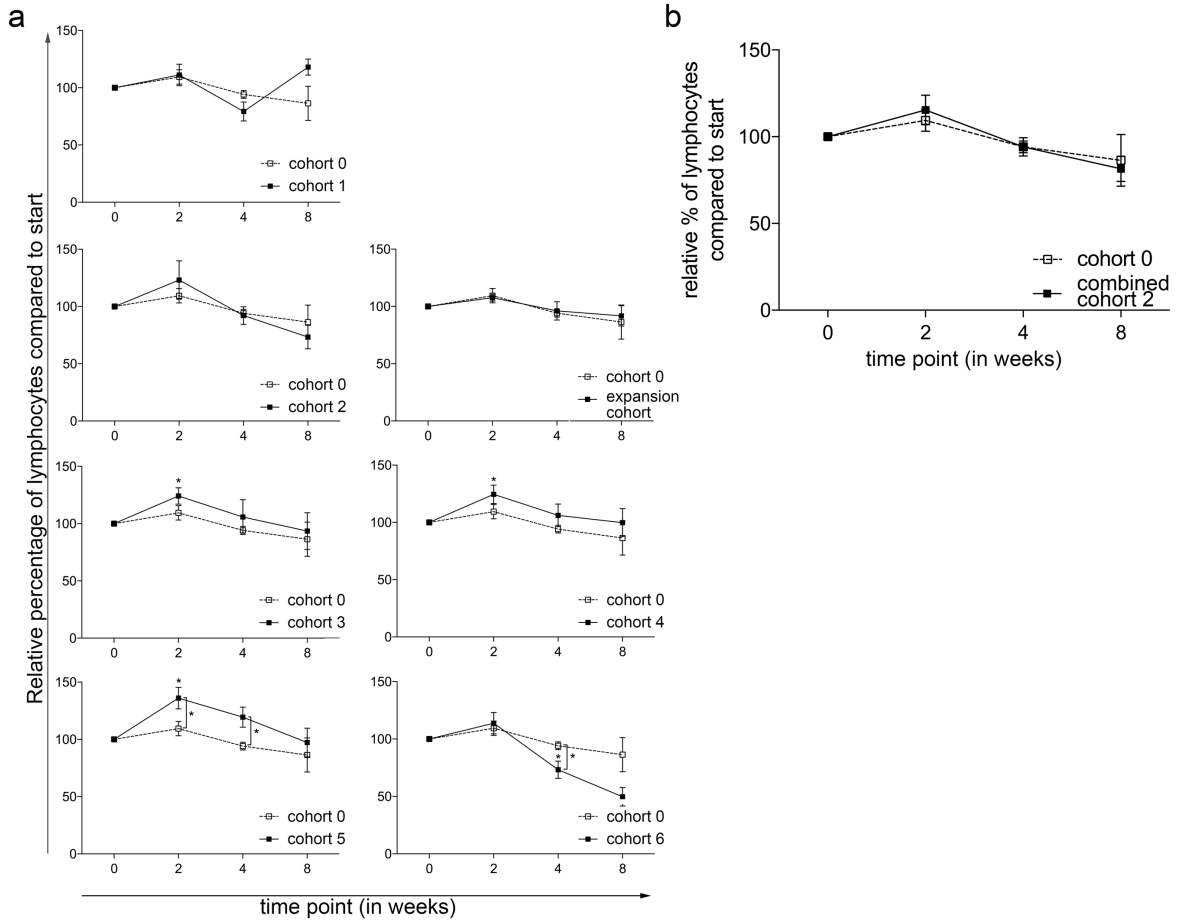
Supplementary fig. 3. Effect of different dosages and administration schedules of CTX when combined with a fixed dose of 10 mg everolimus on the frequency of lymphocytes. a, Relative percentages of lymphocytes were determined in freshly isolated PBMC from patients treated with different dosages and schedules of CTX, combined with a fixed dose of everolimus at baseline and subsequently 2, 4, and 8 weeks after start of treatment. b, Relative percentages of lymphocytes (within PBMC) are shown for cohort 2 combined with the expansion cohort. Patients were treated with 50 mg CTX once daily, combined with 10 mg everolimus once daily. Means ± SEM are shown; p-value indicated with asterisk; * p≤ 0.05.
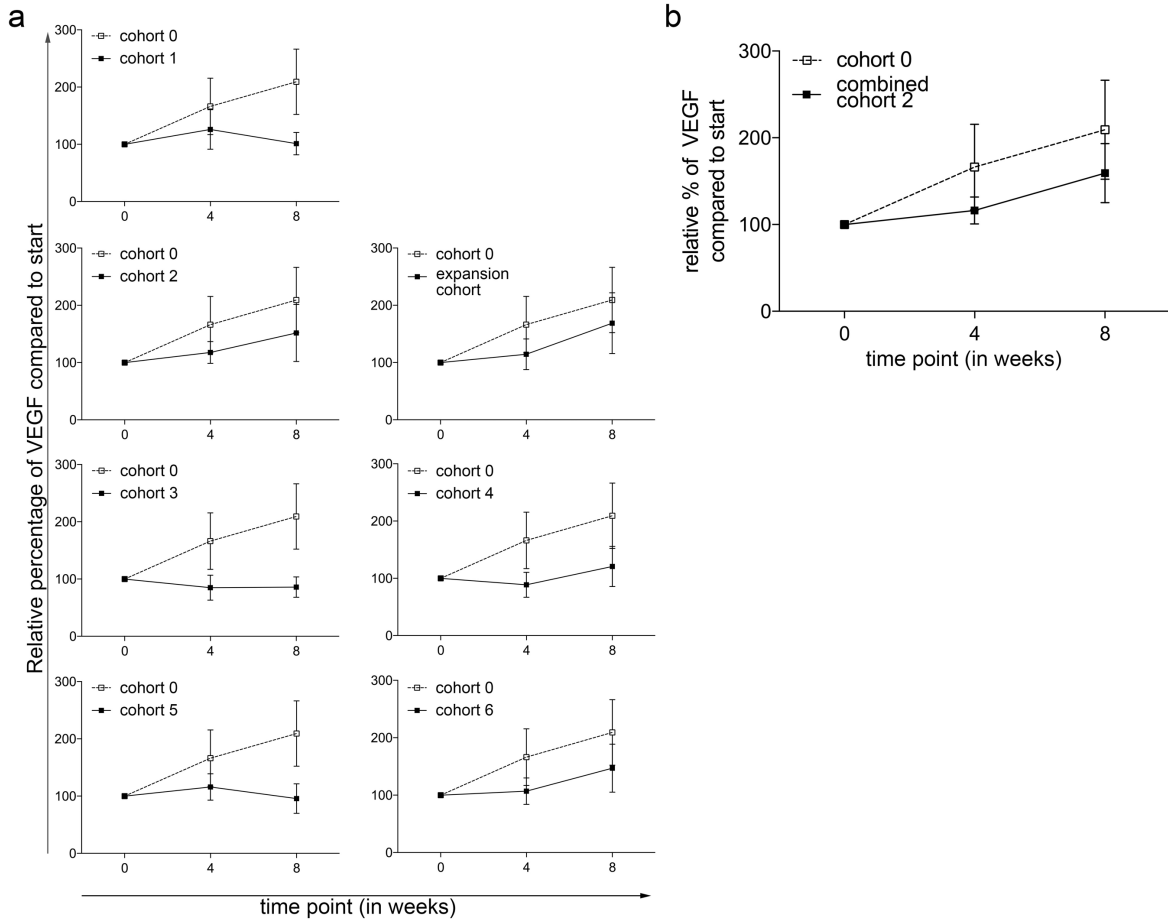
Supplementary fig. 4. Effect of different dosages and administration schedules of CTX when combined with a fixed dose of 10 mg everolimus on VEGF levels in plasma. a, VEGF levels were determined in heparin plasma at baseline and subsequently 4, and 8 weeks after start of treatment. Here, relative percentages are shown. Baseline VEGF levels (mean ± SD) per cohort: cohort 0 – 286 ± 193 pg/mL, cohort 1 – 255 ± 128 pg/mL, cohort 2 – 139 ± 104 pg/mL, cohort 3 – 122 ± 17 pg/mL, cohort 4 – 217 ± 65 pg/mL, cohort 5 – 362 ± 113 pg/mL, cohort 6 – 174 ± 27 pg/mL b, Relative percentages of VEGF plasma levels are shown for cohort 2 combined with the expansion cohort. Patients were treated with 50 mg CTX once daily, combined with 10 mg everolimus once daily. Mean VEGF level was 133 ± 25 pg/mL.
Means ± SEM are shown. No significant changes were observed.

Supplementary fig. 5. Kaplan-Meier curves for OS per cohort, compared to the total patient group.