

Nieuwe ontwikkelingen systemische therapie nierkanker

11 februari 2020

Paul Hamberg

Internist –oncoloog

Franciscus Gasthuis & Vlietland
Rotterdam/Schiedam

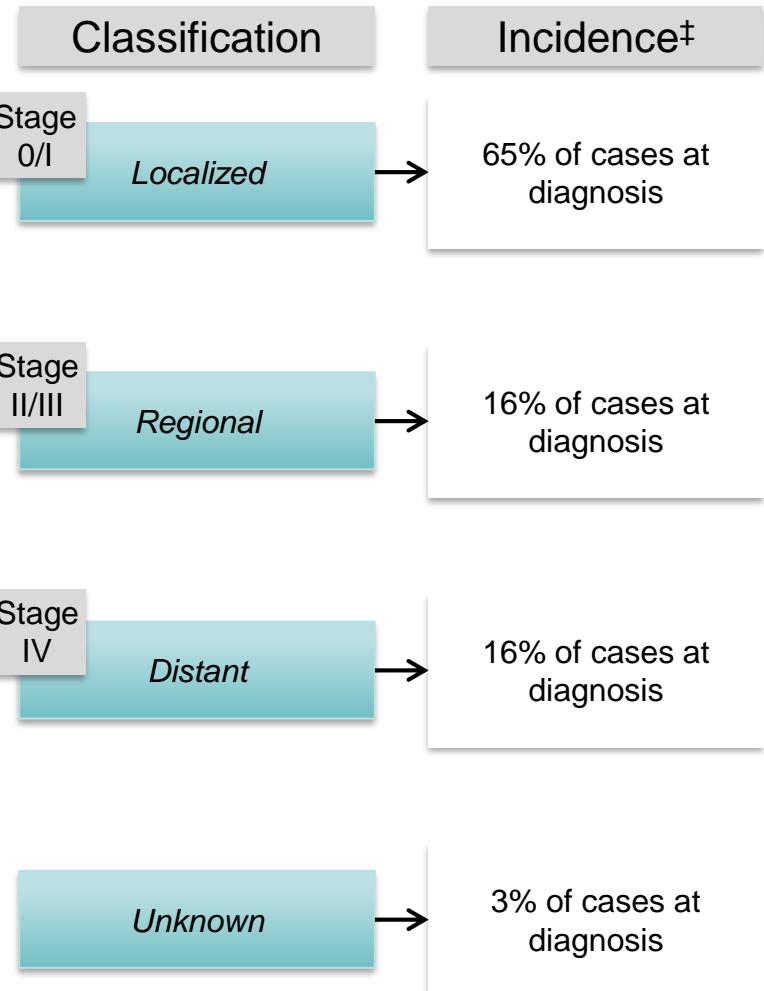


(potentiële) belangenverstrengeling	Geen / Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
<ul style="list-style-type: none"> • Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk ... 	<ul style="list-style-type: none"> • MSD, Astellas, Ipsen Janssen Roche Pfizer Bayer • Ipsen, astellas, janssen BMS Pfizer • nvt • Nvt

Niercelcarcinoom -epidemiologie NL

The Netherlands¹

New cases (estimated 2015)	2343
Deaths (estimated 2015)	932
Prevalence (estimated 2012)	12006



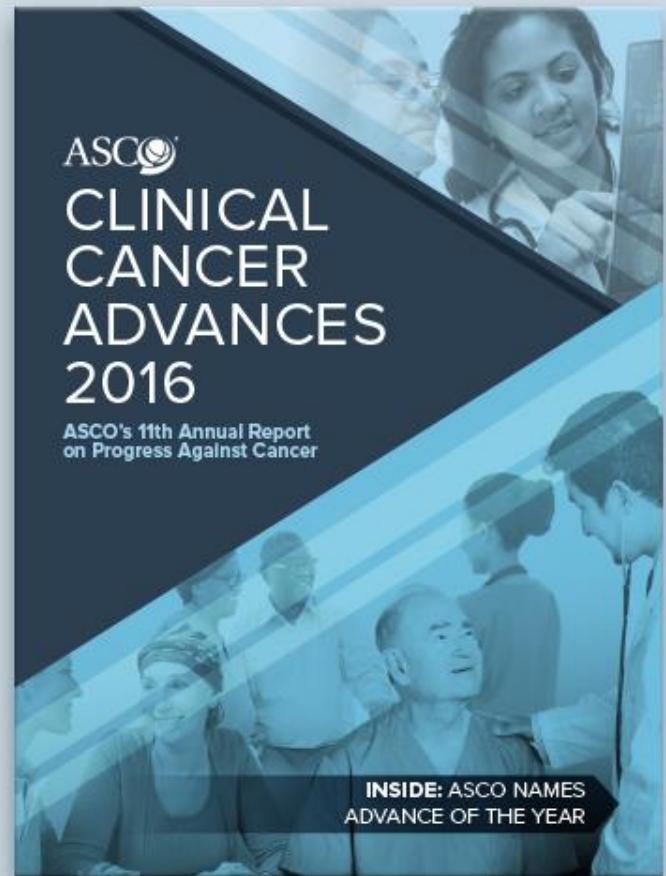
- Median age at diagnosis: 64 years*
- Median age at death: 71 years*



Click to watch

Cancer Immunotherapy: ASCO's Advance of the Year

Clinical Cancer Advances 2016 report



THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES.

M A Y , 1 8 9 3 .

THE TREATMENT OF MALIGNANT TUMORS BY REPEATED
INOCULATIONS OF ERYSIPelas: WITH A REPORT OF
TEN ORIGINAL CASES.¹

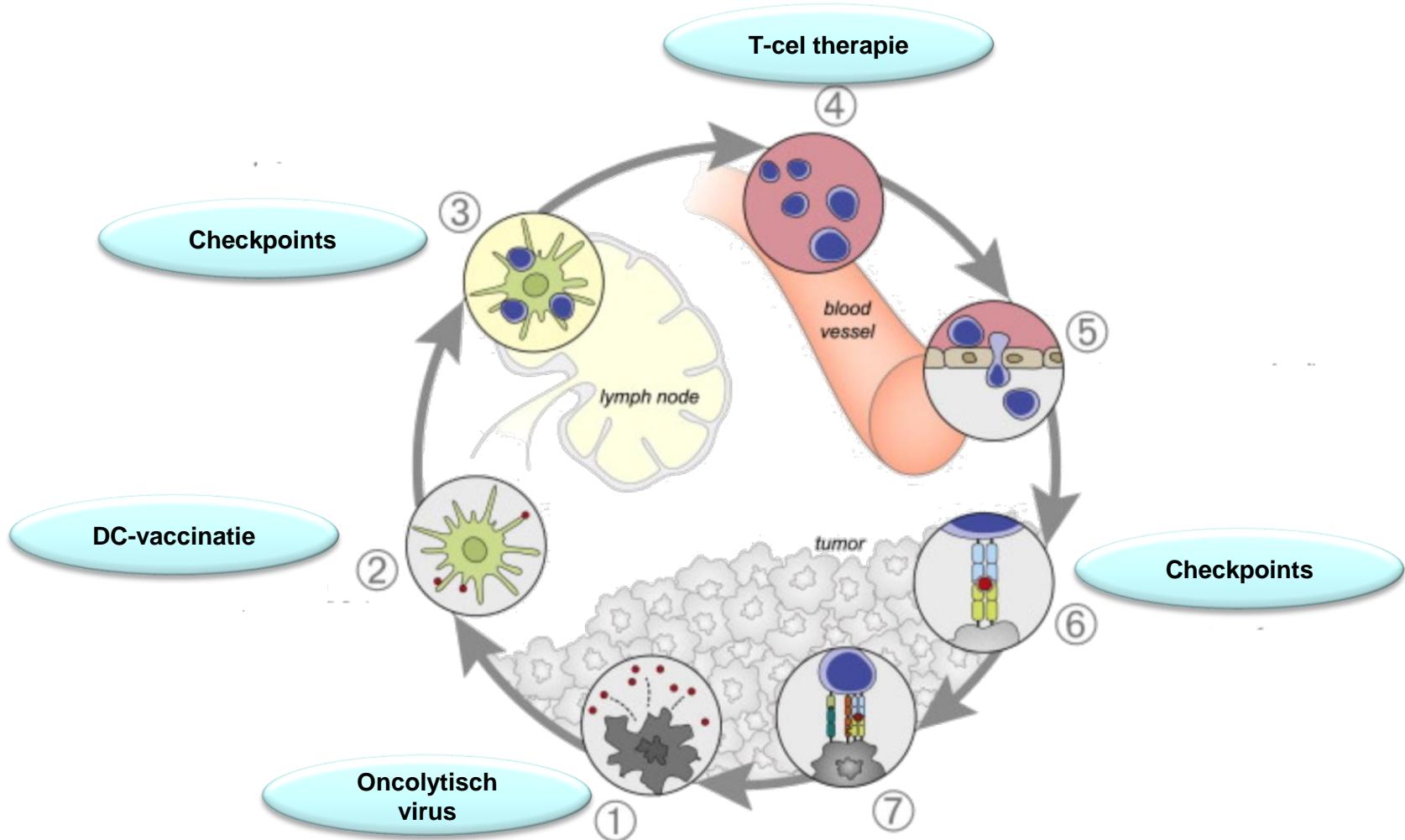
BY WILLIAM B. COLEY, M.D.,

ASSISTANT SURGEON TO THE HOSPITAL FOR RUPTURED AND CRIPPLED; INSTRUCTOR IN SURGERY
IN THE POST-GRADUATE MEDICAL SCHOOL, NEW YORK.

Immuno-modulerende middelen

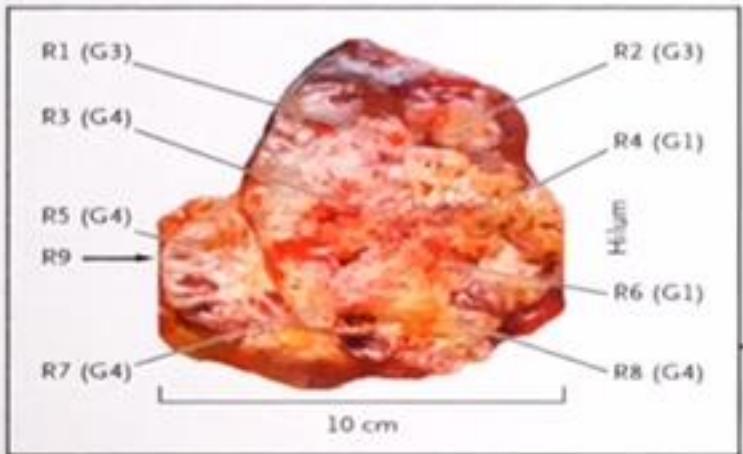


Cancer-immunity cycle

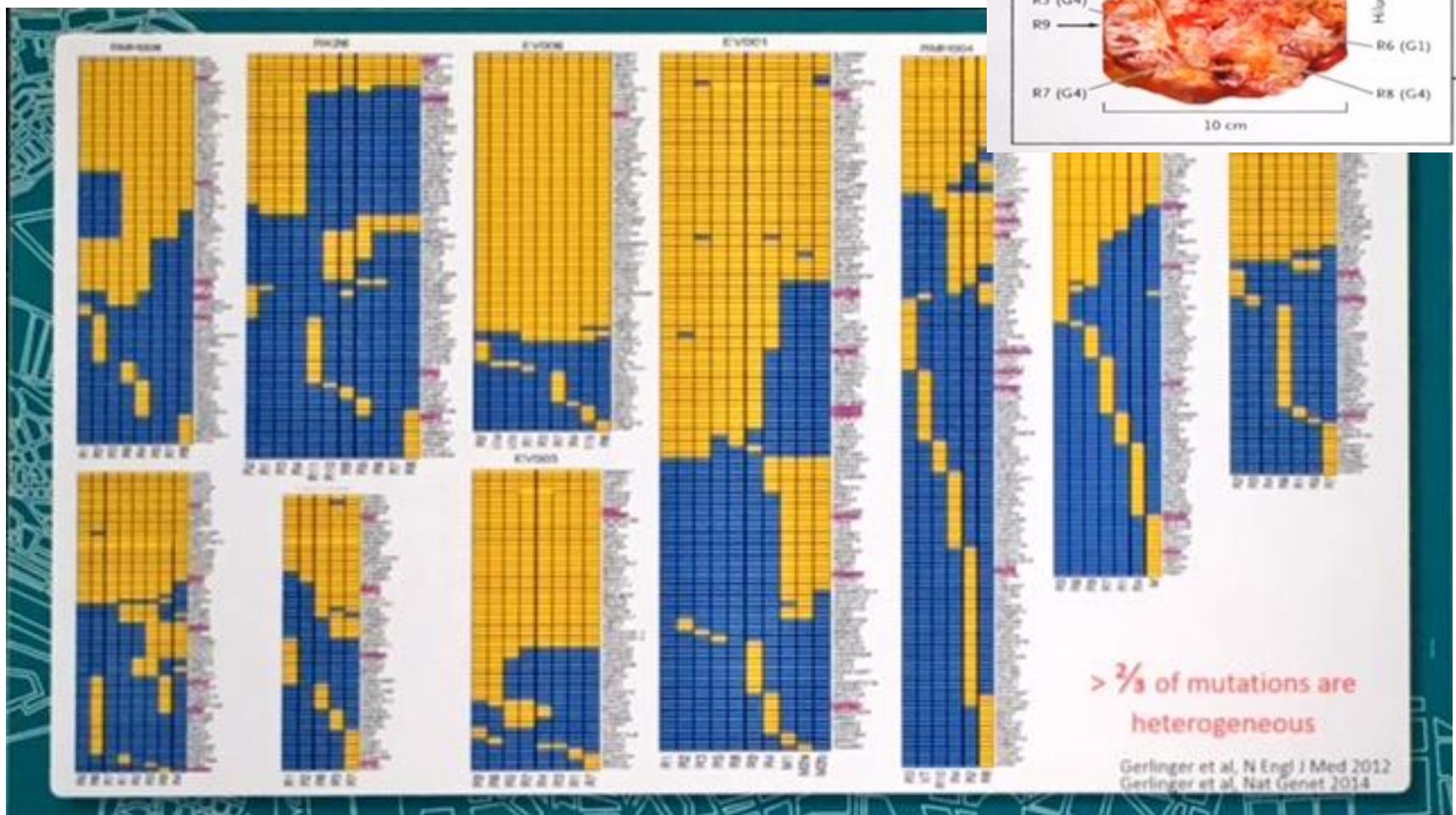


Intratumour Heterogeneity in Clear Cell Renal Cell Carcinomas (ccRCC)

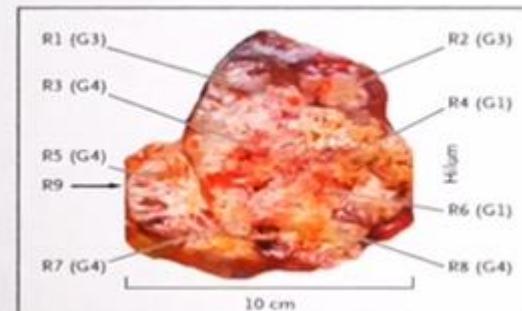
Biopsy Sites



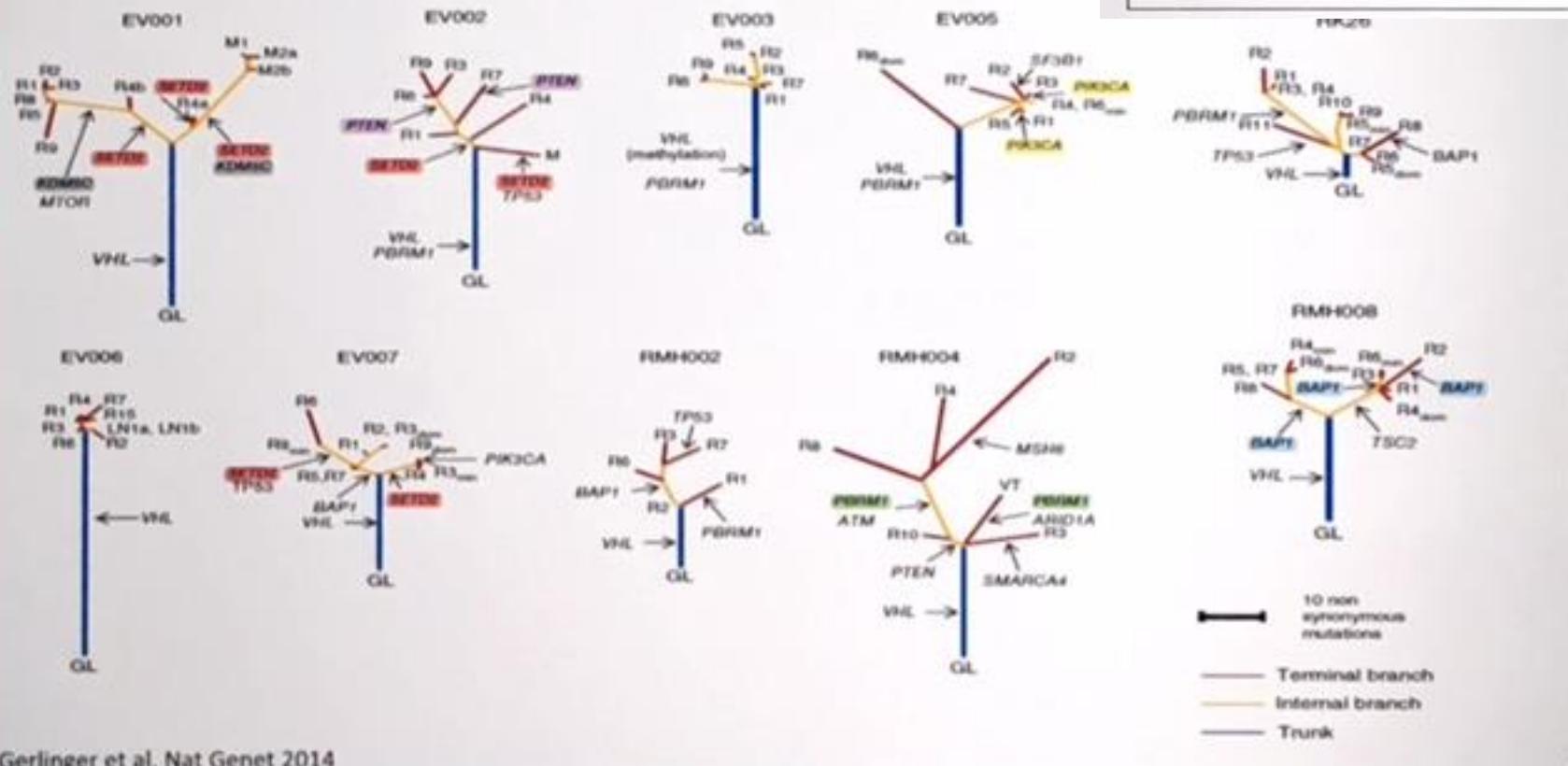
Gerlinger et al, NEJM 2012



Biopsy Sites



Branched Evolution and Spatial Separation ccRCC



Gerlinger et al, Nat Genet 2014

Diagnose van M1

Initieel M1 (synchroon)

- Indicatie cytoreductieve nefrectomie? Zo ja, timing na systemische therapie?
- Indicatie systemische therapie?

M1 metachroon

- Uitgestelde therapie?
- Metastasectomie?

Indien therapie: welke 1^e lijns behandeling?

Systemische therapie RCC

- Adjuvante therapie
 - Voor RCC nog geen adjuvante therapie met OS-benefit
 - Meerdere studies ongoing met Immunomodulerende middelen
- 1^e lijns therapie
- Combitherapie vs sequentie
- Combi immuno-immuno of combi immuno-TKI (of triplet)
- Patiënt-selectie

IMMEDIATE VERSUS DEFERRED CYTOREDUCTIVE NEPHRECTOMY IN PATIENTS WITH SYNCHRONOUS METASTATIC RENAL CELL CARCINOMA (MRCC) RECEIVING SUNITINIB.

The European Organization for Research and Treatment of Cancer (EORTC)
randomized trial 30073 SURTIME.

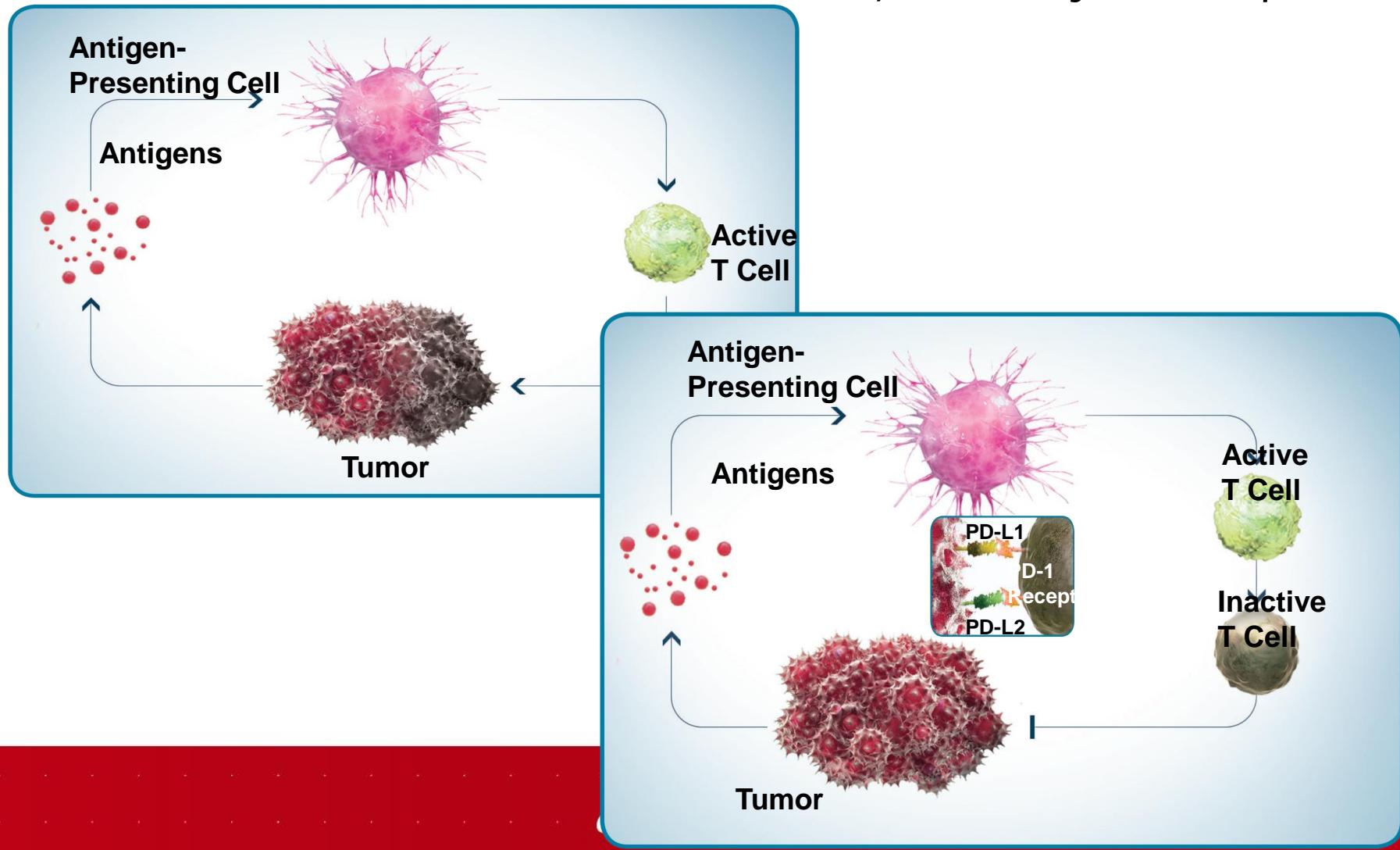
A. Bex*, P. Mulders, M. Jewett, J. Wagstaff, R. Van Velthoven, P. Laguna, L. Wood, H.H.E. van Melick, P. Soetekouw, J.B. Lattouf, T. Powles, I. De Jong, S. Rottey, B. Tombal, S. Marreaud, S. Collette, L. Collette, J. Haanen

*The Netherlands Cancer Institute, Amsterdam, The Netherlands, on behalf of the EORTC Genitourinary Cancer Group

Clinical trial identification NCT01099423

Immunotherapie bij RCC tm 2018

- Nivolumab: PD na eerdere VEGFR-TKI, dus 2^e lijns therapie



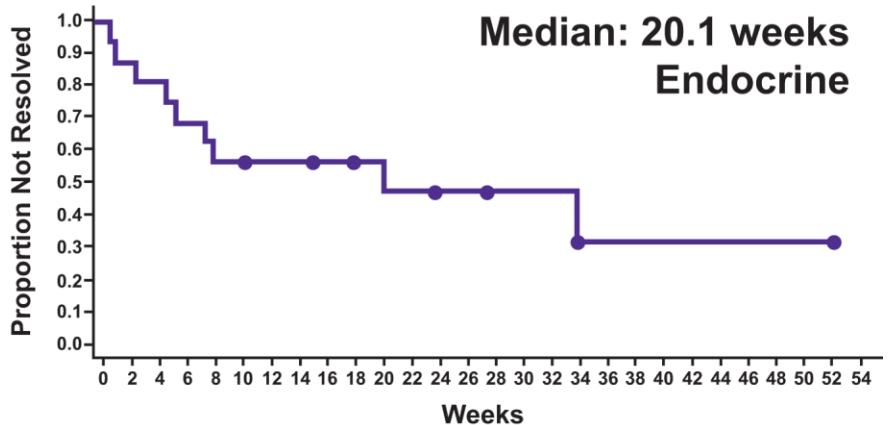
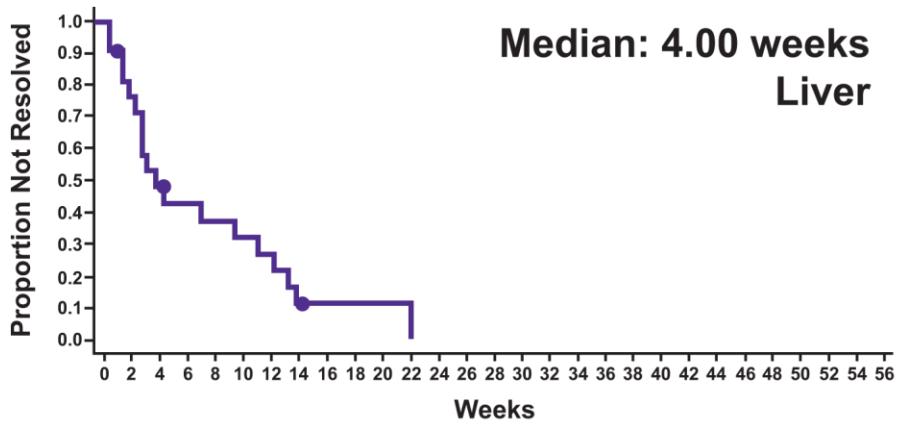
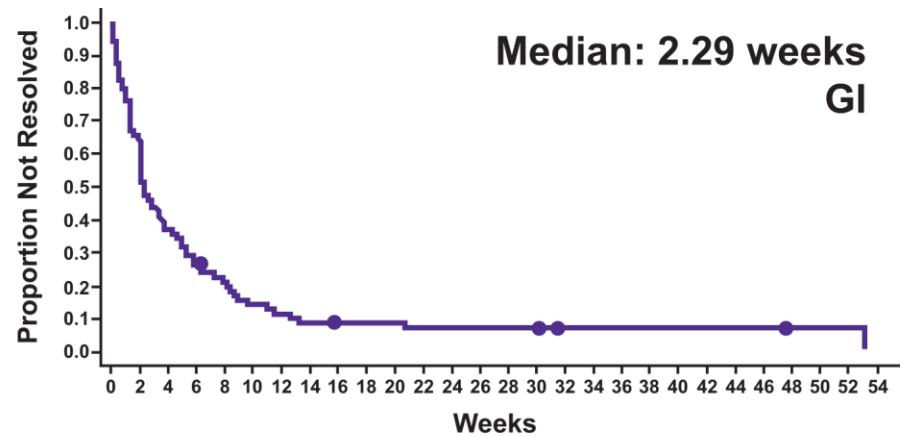
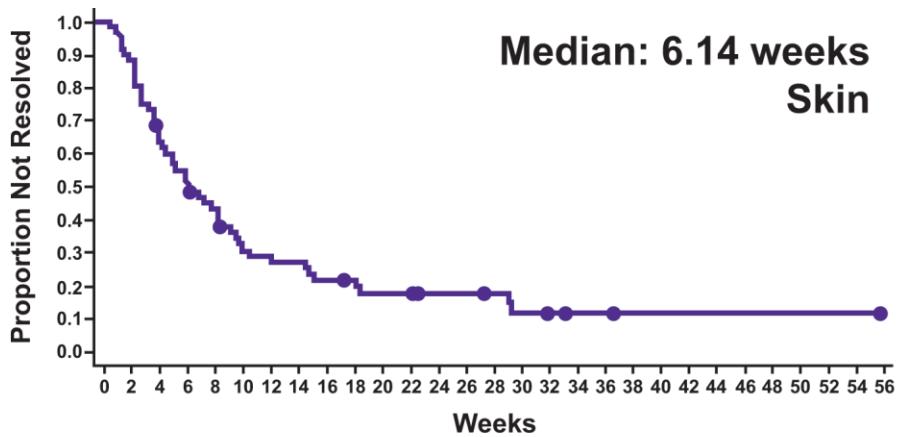
Treatment-Related AEs in ≥ 10% of Patients With mRCC

	Nivolumab N = 406			Everolimus N = 397		
	Any Grade	Grade 3	Grade 4*	Any Grade	Grade 3	Grade 4†
Treatment-related AEs, %	79	18	1	88	33	4
Fatigue	33	2	0	34	3	0
Nausea	14	<1	0	17	1	0
Pruritus	14	0	0	10	0	0
Diarrhea	12	1	0	21	1	0
Decreased appetite	12	<1	0	21	1	0
Rash	10	<1	0	20	1	0
Cough	9	0	0	19	0	0
Anemia	8	2	0	24	8	<1
Dyspnea	7	1	0	13	<1	0
Edema peripheral	4	0	0	14	<1	0
Pneumonitis	4	1	<1	15	3	0
Mucosal inflammation	3	0	0	19	3	0
Dysgeusia	3	0	0	13	0	0
Hyperglycemia	2	1	<1	12	3	<1
Stomatitis	2	0	0	29	4	0
Hypertriglyceridemia	1	0	0	16	4	1
Epistaxis	1	0	0	10	0	0

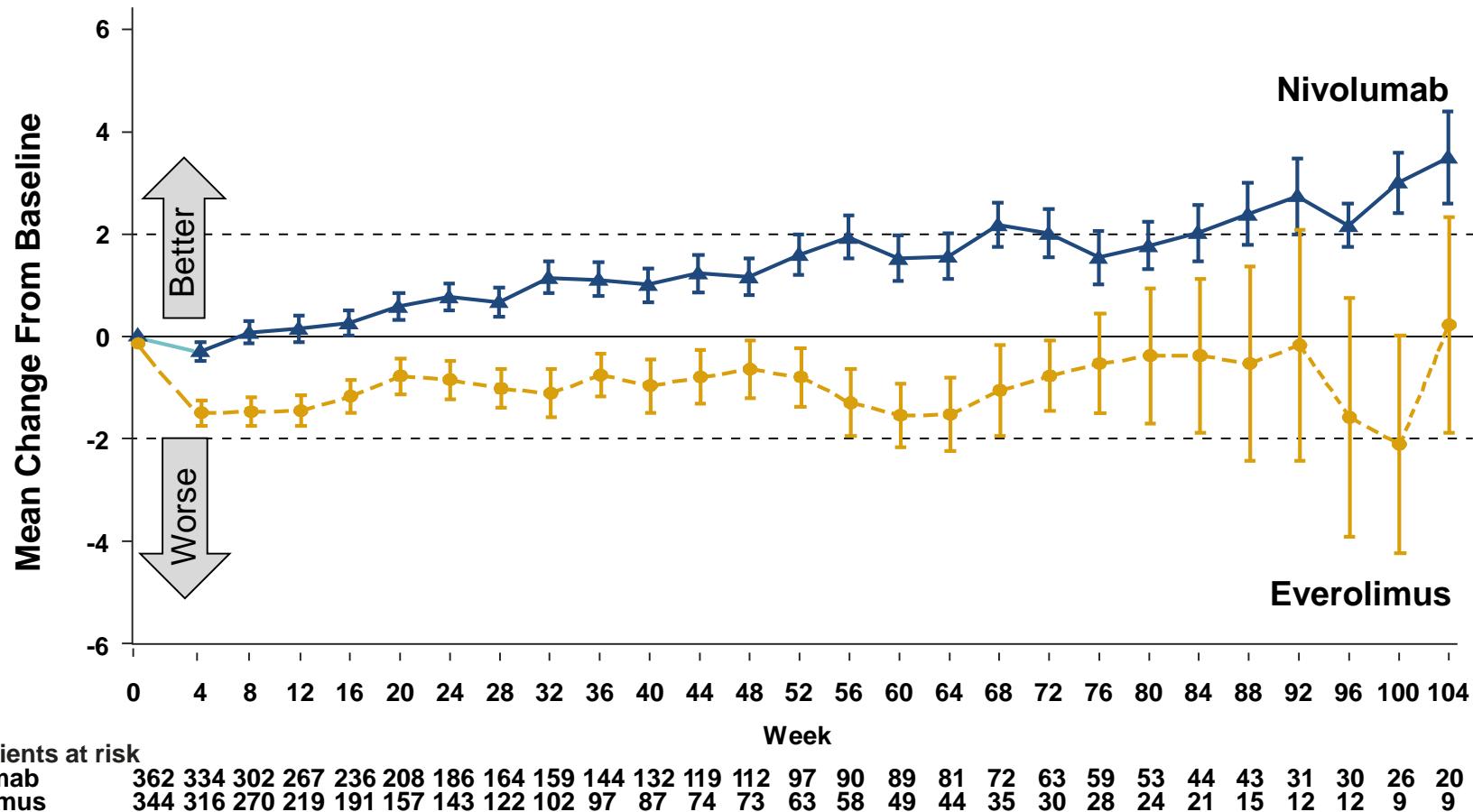
Onset of Immune-Mediated Adverse Reactions¹

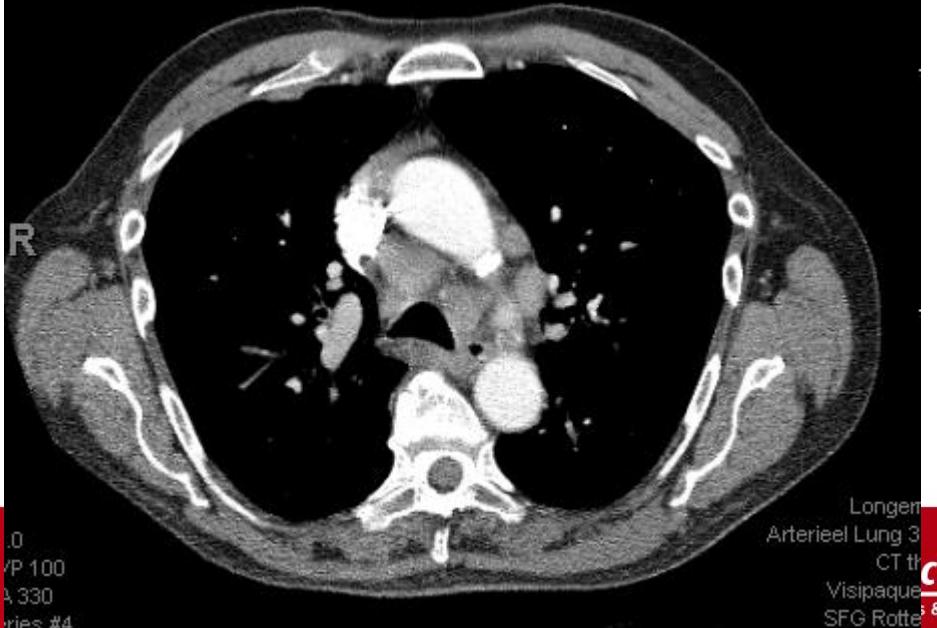
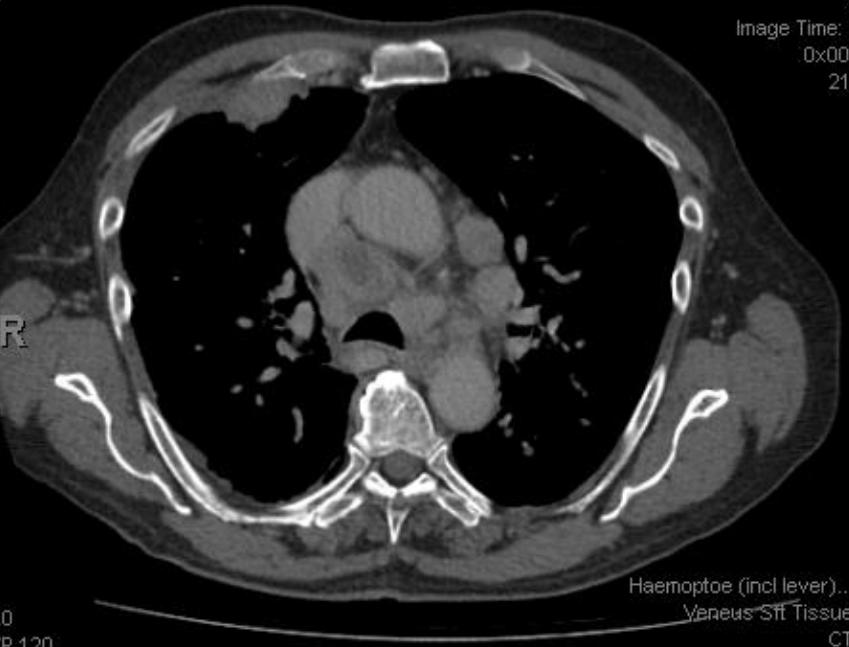
			OPDIVO (n=1728)
	All Grades n (%)	Grades 3–4 n (%)	Time or Median Time to Onset (range)
Pneumonitis	56 (3.2)	12 (0.7)	3.6 months (0.4 – 19.6 months)
Diarrhea or Colitis	235 (13.6)	27 (1.6)	1.8 months (0 – 20.9 months)
Hepatitis	121 (7.0)	31 (1.7)	1.9 months (0 – 18.7 months)
Endocrinopathy (Hypophysitis, Hypothyroidism, Hyperthyroidism Adrenal Insufficiency, Diabetes Mellitus or Diabetic Ketoacidosis)	149 (8.6)	2 (0.1)	2.8 months (0.4 – 14.0 months)
Nephritis and Renal Dysfunction	55 (3.2)	9 (0.5)	2.3 months (0 – 18.2 months)
Rash	484 (28.0)	17 (1.0)	1.4 months (0 – 17.2 months)

Meeste AEs verdwenen na 2-6 weken



Kwaliteit van leven nivolumab vs everolimus 2e lijn





Behandeling toxiciteit

- Ondersteunende zorg
- Uitsluiten infecties
- Steroïden
- Afhankelijk van type bijwerking toevoegen
 - MMF
 - Cyclofosfamide
 - Infliximab
 - TNF-alfa
 - etc

Systemische therapie 2020: patient selectie

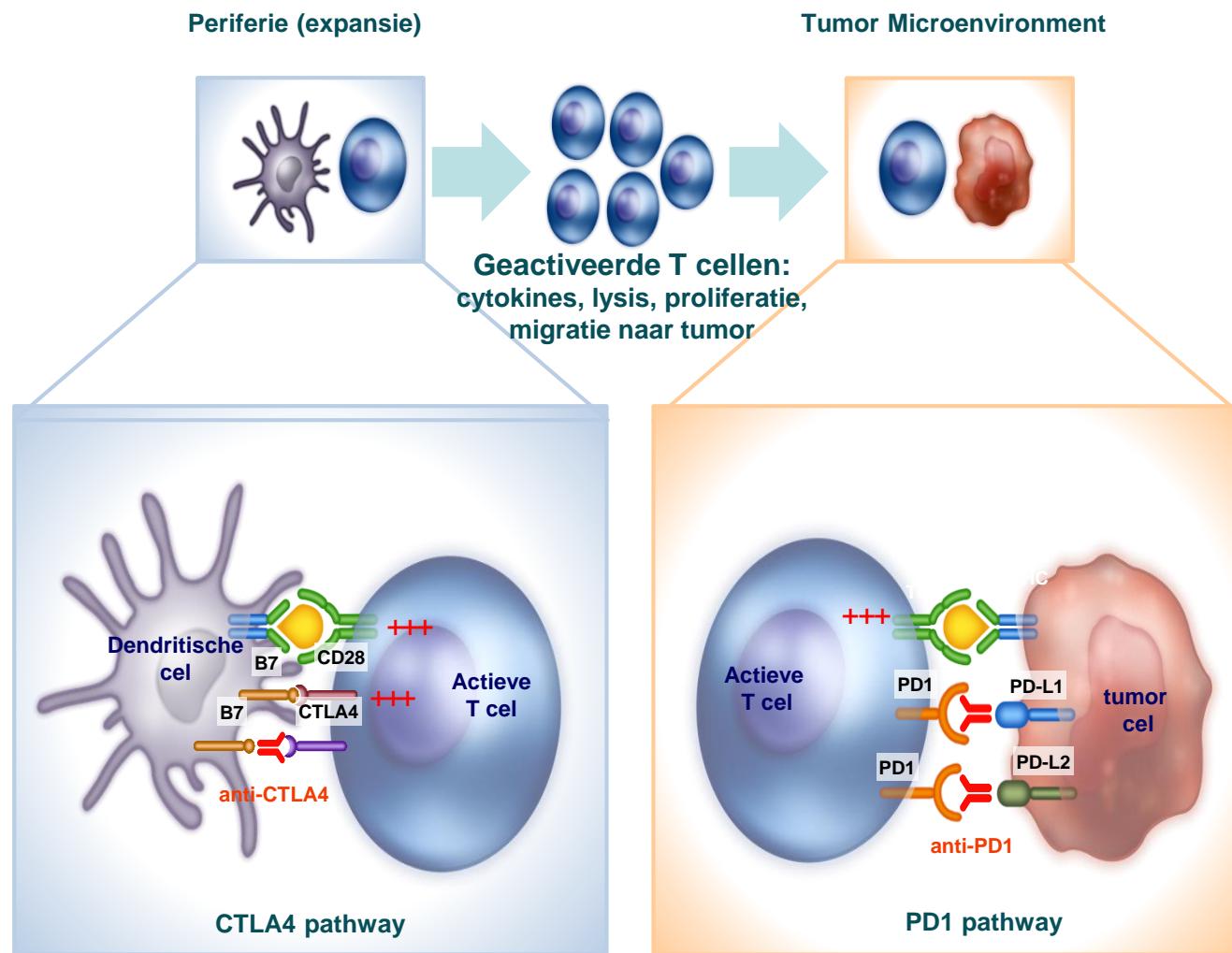
- Indicatie therapie of waakzaam wachten
- Indien therapie, dan keuze mede obv IMDC
 - Performance score (Karnofsky = < 70)
 - tijd van initiele diagnose tot start systemische therapie voor gemitastaseerde ziekte
 - Hb (< LLN)
 - Gecorrigeerd calcium (> ULN)
 - Absolute neutrofielen (> ULN)
 - Thrombocyten (> ULN)
- IMDC risico profiel categorie
 - 0: gunstig risico profiel volgens IMDC
 - 1-2 intermediate risicioprofiel volgens IMDC
 - 3 of meer : ongunstig risicoprofiel volgens IMDC

Opties indien therapie

1^e lijn

- gunstig risico profiel volgens IMDC
 - TKI (opties laat ik buitenbeschouwing)
 - (combi TKI-immuno?)
- Intermediate of gunstig risico profiel volgens IMDC
 - Combinatie immunotherapie (ipilimumab en nivolumab)
 - (combi TKI-immuno?)
 - Indien niet afdoende fit voor combi therapie: monotherapie TKI
- 2^e lijn
 - Na eerdere combi immunotherapie: sunitinib
 - Na TKI: monotherapie nivolumab

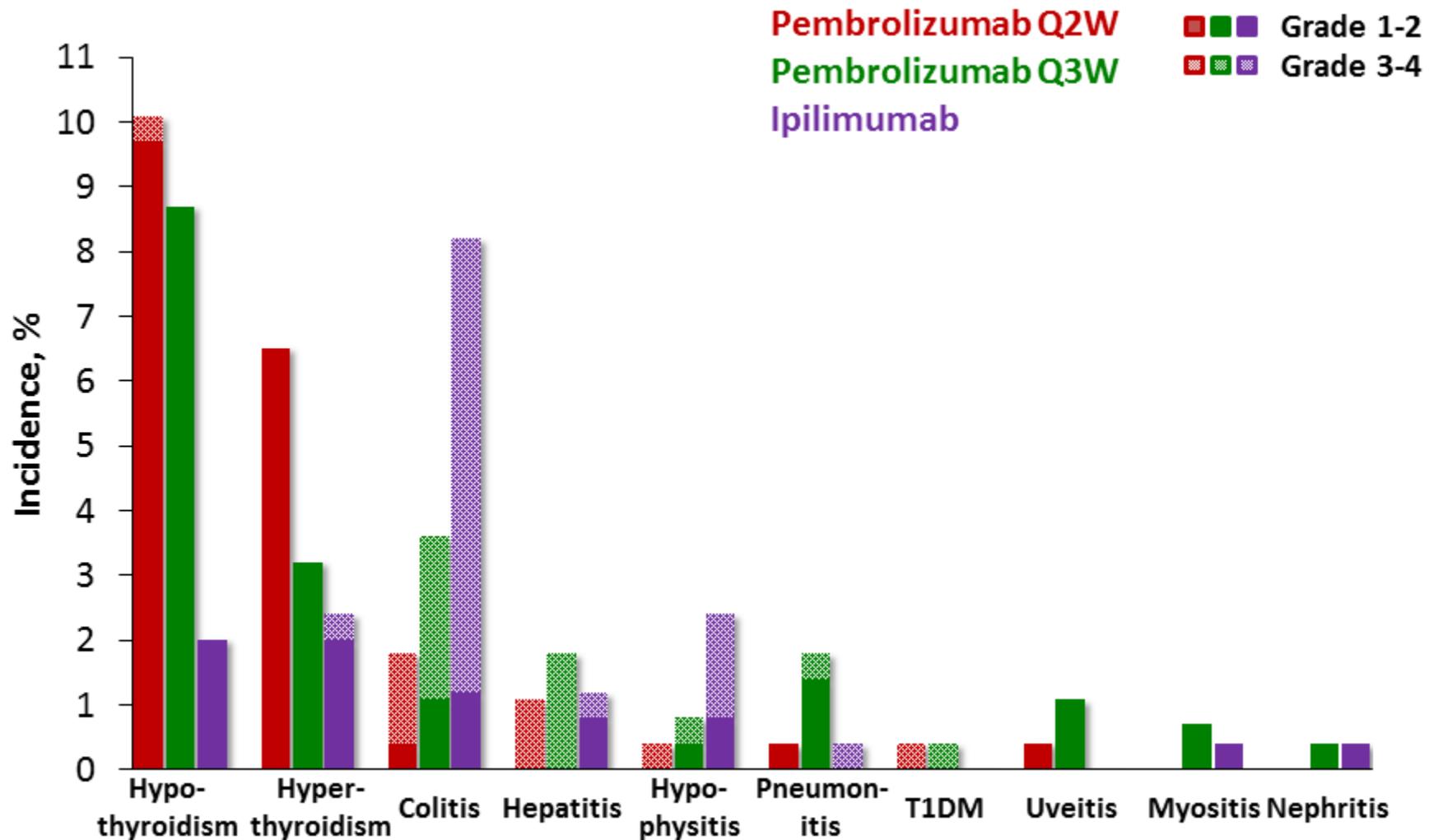
Twee paden: CTLA4 en PD1



Nivolumab + Ipilimumab vs Sunitinib for Treatment-Naïve Advanced or Metastatic Renal Cell Carcinoma (RCC): Results From CheckMate 214, Including Overall Survival by Subgroups

Robert J. Motzer,¹ Nizar M. Tannir,² David F. McDermott,³ Osvaldo Arén Frontera,⁴ Bohuslav Melichar,⁵ Elizabeth R. Plimack,⁶ Philippe Barthelemy,⁷ Saby George,⁸ Victoria Neiman,⁹ Camillo Porta,¹⁰ Toni K. Choueiri,¹¹ Thomas Powles,¹² Frede Donskov,¹³ Pamela Salman,¹⁴ Christian K. Kollmannsberger,¹⁵ Brian Rini,¹⁶ Sabeen Mekan,¹⁷ M. Brent McHenry,¹⁷ Megan Wind-Rotolo,¹⁷ Hans J. Hammers,¹⁸ Bernard Escudier¹⁹

Anti-CTLA4 vs anti-PD1

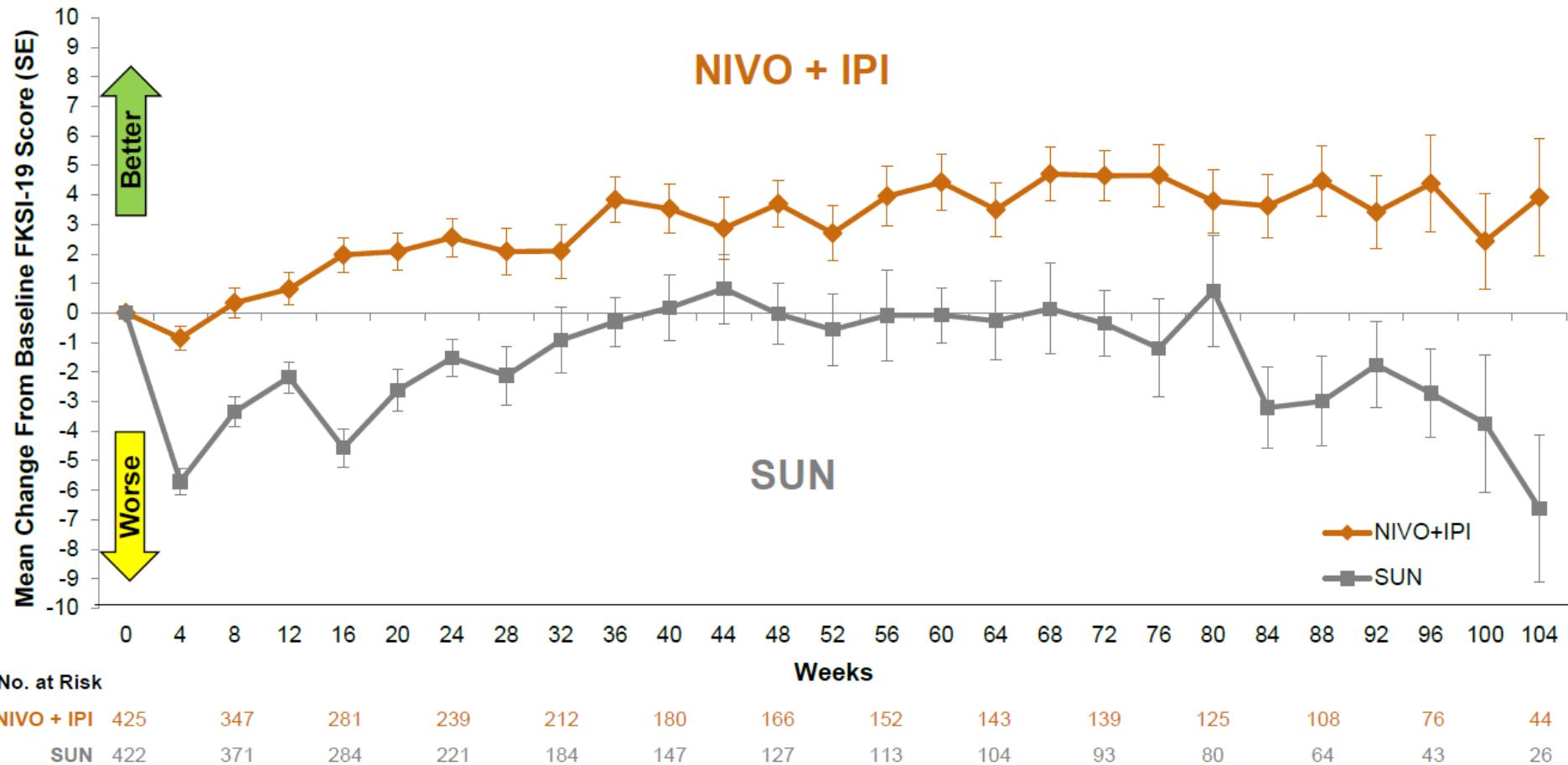


*Incidence not adjusted for duration of exposure.

Analysis cut-off date: September 3, 2014.

Ribas_AACR 2015_19Apr15

Patient-reported kidney cancer symptom index: IMDC intermediate/poor risk



Immuno gebaseerde opties bij RCC

- 3 opties immunotherapie RCC
 - Combi ipilimumab en nivolumab (1^e lijn)
 - Binnenkort TKI icm immunotherapie (1^e lijn)
 - Mono nivolumab (2^e lijn)
 - En hopelijk in de toekomst: adjuvant
- Voor & nadelen combi immuno-immuno vs TKI-immuno, incl anti PD1 vs anti PD-L1
- 2 studies gepubliceerd met TKI- immuno
 - Axitinib + pembrolizumab (Keynote 426)
 - Axitinib + avelumab (Javelin Renal 101)
- Geen onderling vergelijk beschikbaar met betrekking tot de 3 1^e lijns opties. Wel verschillen in PFS, OS, response rate en HR
- Geen biomarkers beschikbaar

Overwegingen bij 1^e lijntherapie

- Als fit en geen contra-indicatie EN indicatie systemische therapie EN intermediate/poor risk
- NB het hebben van weinig tumor volume is **niet** een reden reden om af te zien van waakzaam wachten om dan immunotherapie in te zetten (niet aangetoond bij RCC)
- Momenteel: ipilimumab icm nivolumab
- Spoedig (Q1/Q2 2020) meer keus, maar in afwachting van CieBOM en beoordeling door ZiN
- Echter KOSTEN zijn bij elke combi-immunotherapie gebaseerde behandeling te beschouwen als graad 3-4 toxiciteit!!

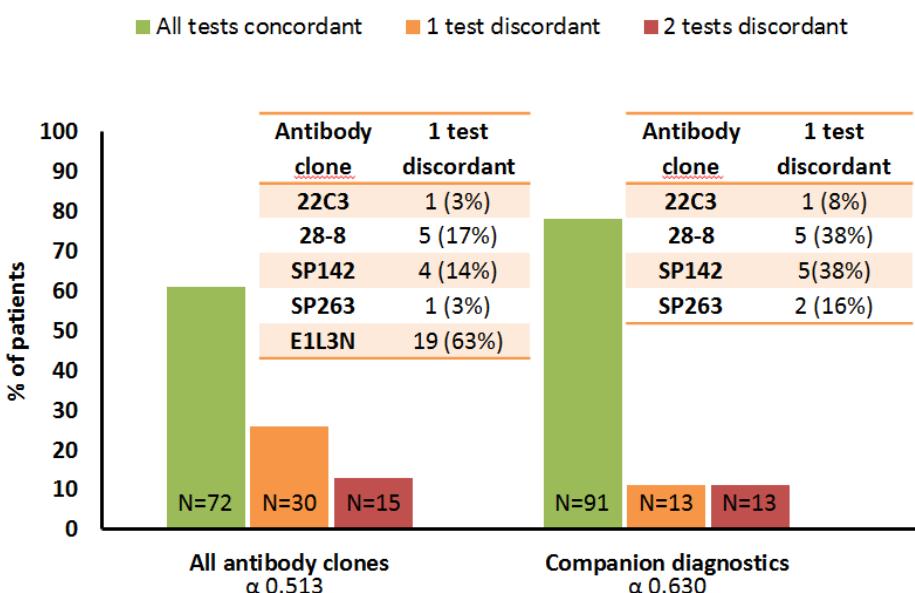
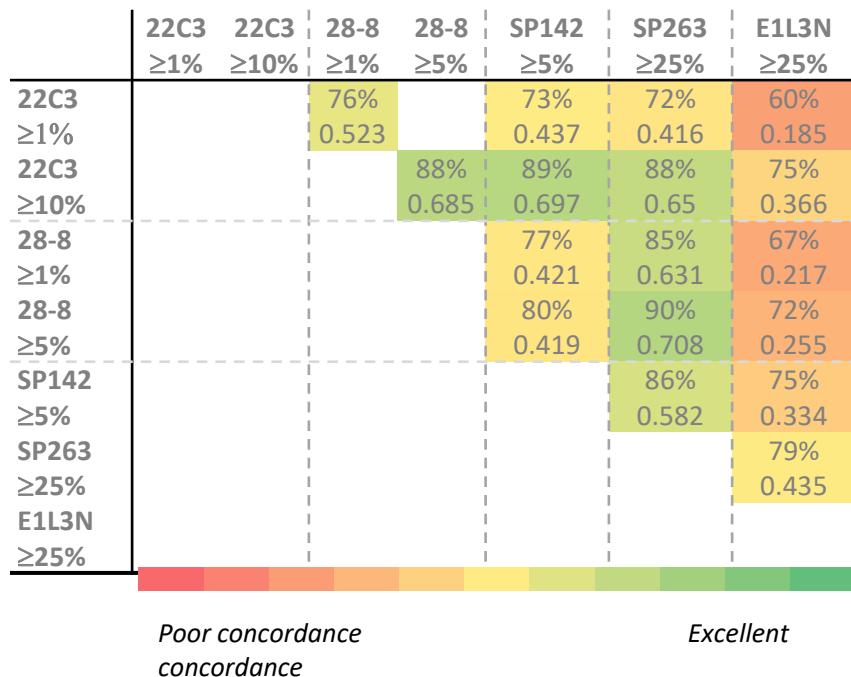
Immunotherapie bij gmet blaascarc

- Overzichtelijker dan RCC als het gaat om immunotherapie bij gmet ziekte

Positie immunotherapie

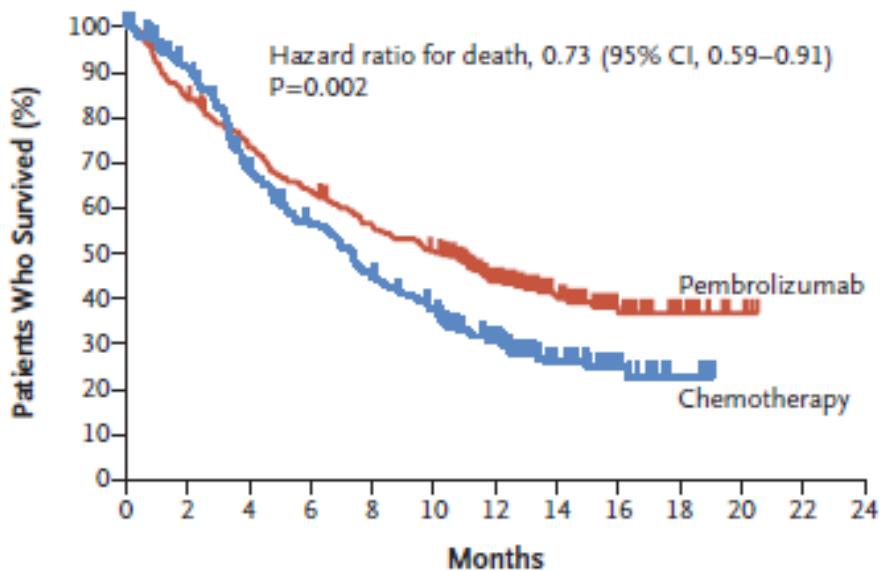
- 2^e lijn na eerdere platinum-bevattende chemotherapie OF
- 1^e lijn indien cisplatin unfit EN PD-L1 positief

Concordance in PD-L1 expression status



Met dank aan Rijnders Erasmus MC

A Overall Survival



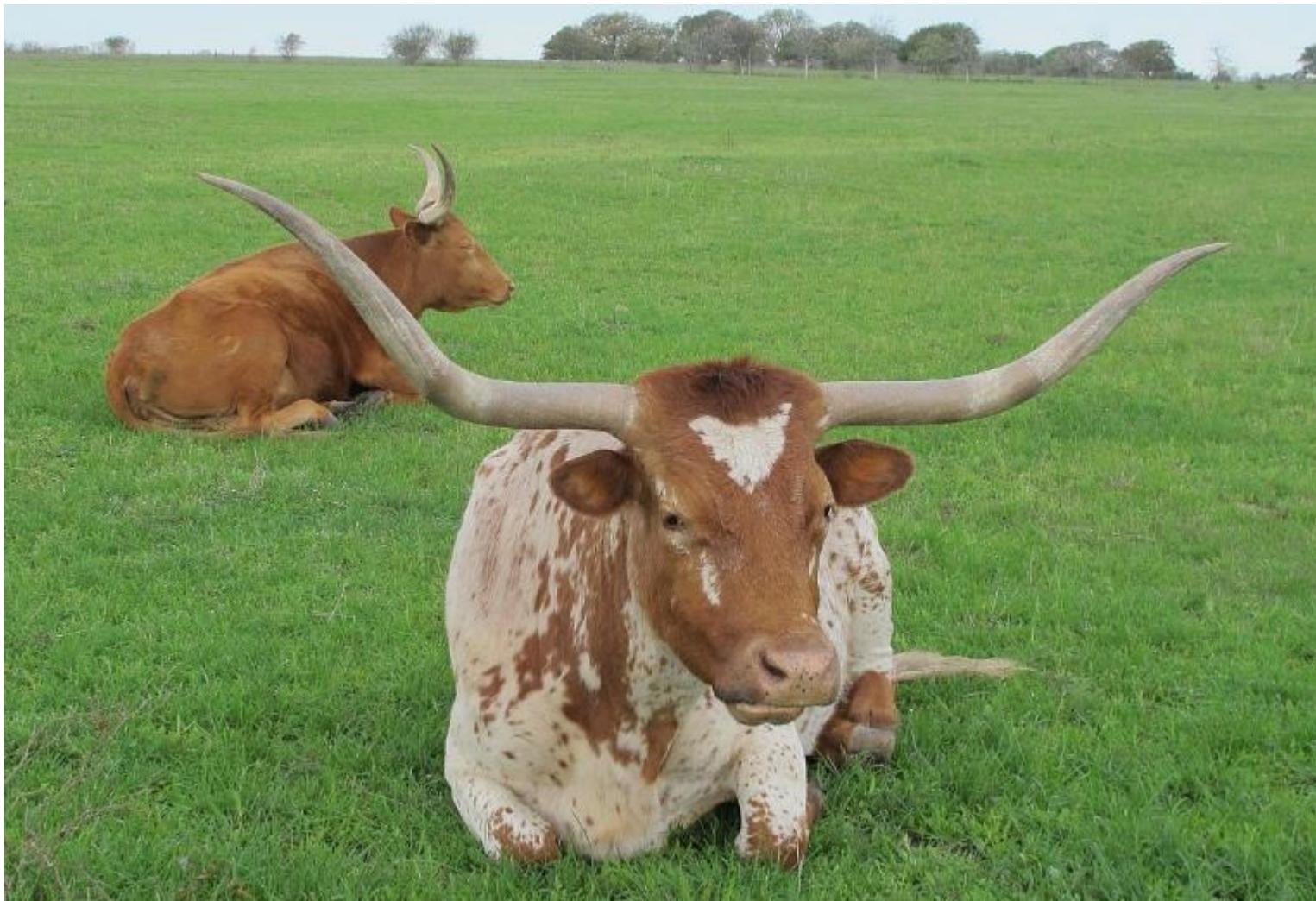
No. at Risk

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Pembrolizumab	270	226	194	169	147	131	87	54	27	13	4	0	0												
Chemotherapy	272	232	171	138	109	89	55	27	14	3	0	0	0												

Bellmunt et al NEJM 2017

Event	Pembrolizumab Group (N=266)		Chemotherapy Group (N=255)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	<i>number of patients (percent)</i>			
Treatment-related event†				
Any event	162 (60.9)	40 (15.0)	230 (90.2)	126 (49.4)
Event leading to discontinuation of treatment	15 (5.6)	12 (4.5)	28 (11.0)	16 (6.3)
Event leading to death	4 (1.5)	4 (1.5)	4 (1.6)	4 (1.6)
Event occurring in ≥10% of patients in either group‡				
Pruritus	52 (19.5)	0	7 (2.7)	1 (0.4)
Fatigue	37 (13.9)	3 (1.1)	71 (27.8)	11 (4.3)
Nausea	29 (10.9)	1 (0.4)	62 (24.3)	4 (1.6)
Diarrhea	24 (9.0)	3 (1.1)	33 (12.9)	2 (0.8)
Decreased appetite	23 (8.6)	0	41 (16.1)	3 (1.2)
Asthenia	15 (5.6)	1 (0.4)	36 (14.1)	7 (2.7)
Anemia	9 (3.4)	2 (0.8)	63 (24.7)	20 (7.8)
Constipation	6 (2.3)	0	52 (20.4)	8 (3.1)
Peripheral sensory neuropathy	2 (0.8)	0	28 (11.0)	5 (2.0)
Neutrophil count decreased	1 (0.4)	1 (0.4)	36 (14.1)	31 (12.2)
Peripheral neuropathy	1 (0.4)	0	27 (10.6)	2 (0.8)
Neutropenia	0	0	39 (15.3)	34 (13.3)
Alopecia	0	0	96 (37.6)	2 (0.8)

Event	Pembrolizumab Group (N=266)		Chemotherapy Group (N = 255)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
<i>number of patients (percent)</i>				
Event of interest§				
Any event	45 (16.9)	12 (4.5)	19 (7.5)	4 (1.6)
Hypothyroidism	17 (6.4)	0	3 (1.2)	0
Hyperthyroidism	10 (3.8)	0	1 (0.4)	0
Pneumonitis	11 (4.1)	6 (2.3)	1 (0.4)	0
Colitis	6 (2.3)	3 (1.1)	1 (0.4)	0
Infusion reaction	2 (0.8)	0	10 (3.9)	0
Nephritis	2 (0.8)	2 (0.8)	0	0
Severe skin reaction	2 (0.8)	1 (0.4)	3 (1.2)	3 (1.2)
Thyroiditis	2 (0.8)	0	0	0
Adrenal insufficiency	1 (0.4)	1 (0.4)	0	0
Myositis	0	0	1 (0.4)	1 (0.4)











Met dank voor de aandacht!
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Franciscus Gasthuis & Vlietland
Rotterdam/Schiedam