Nye behandlinger til udbredt nyrekræft

Frede Donskov

Overlæge, lektor, dr.med.

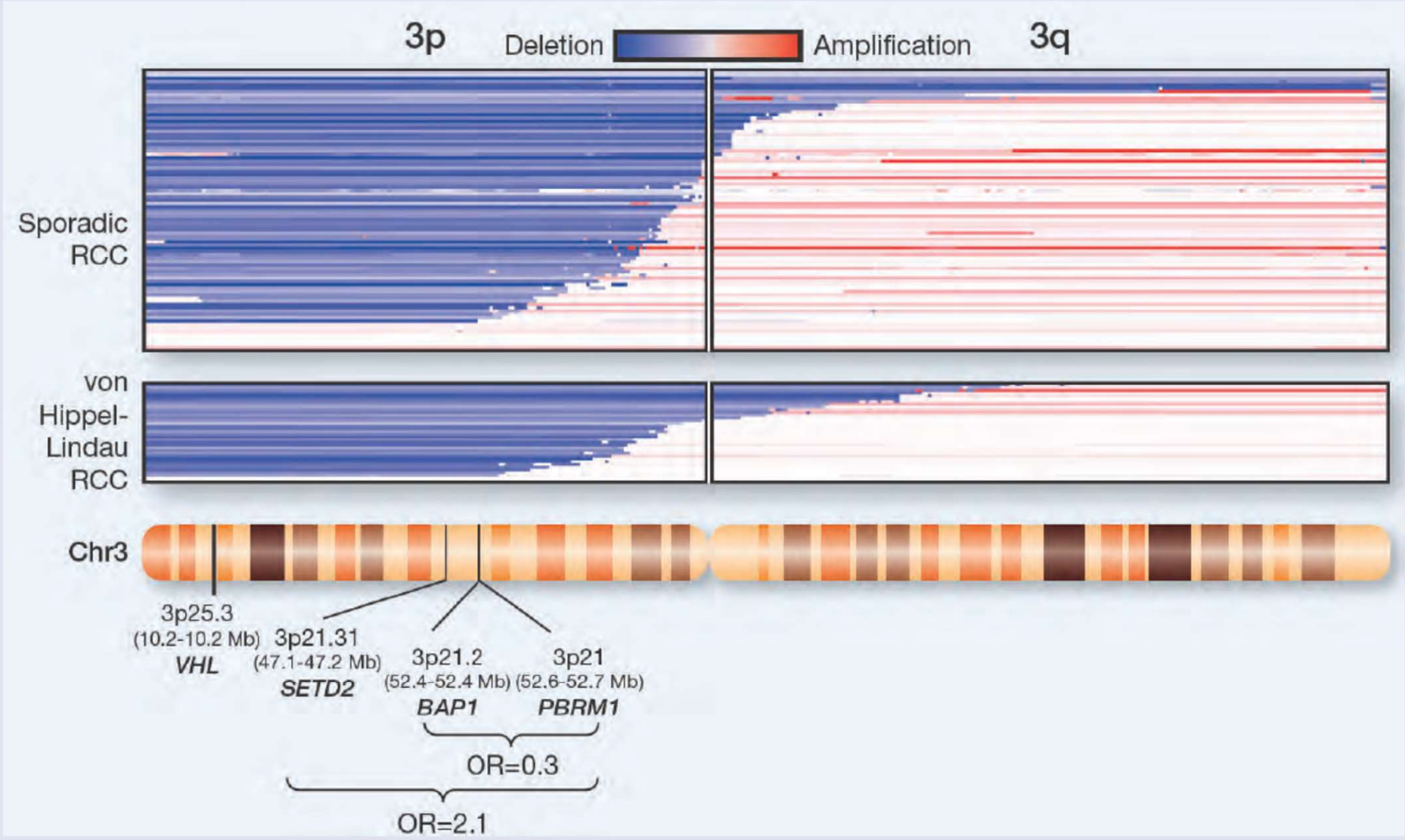
Onkologisk afdeling

Aarhus Universitetshospital

Nyrekræft: Stop rygning

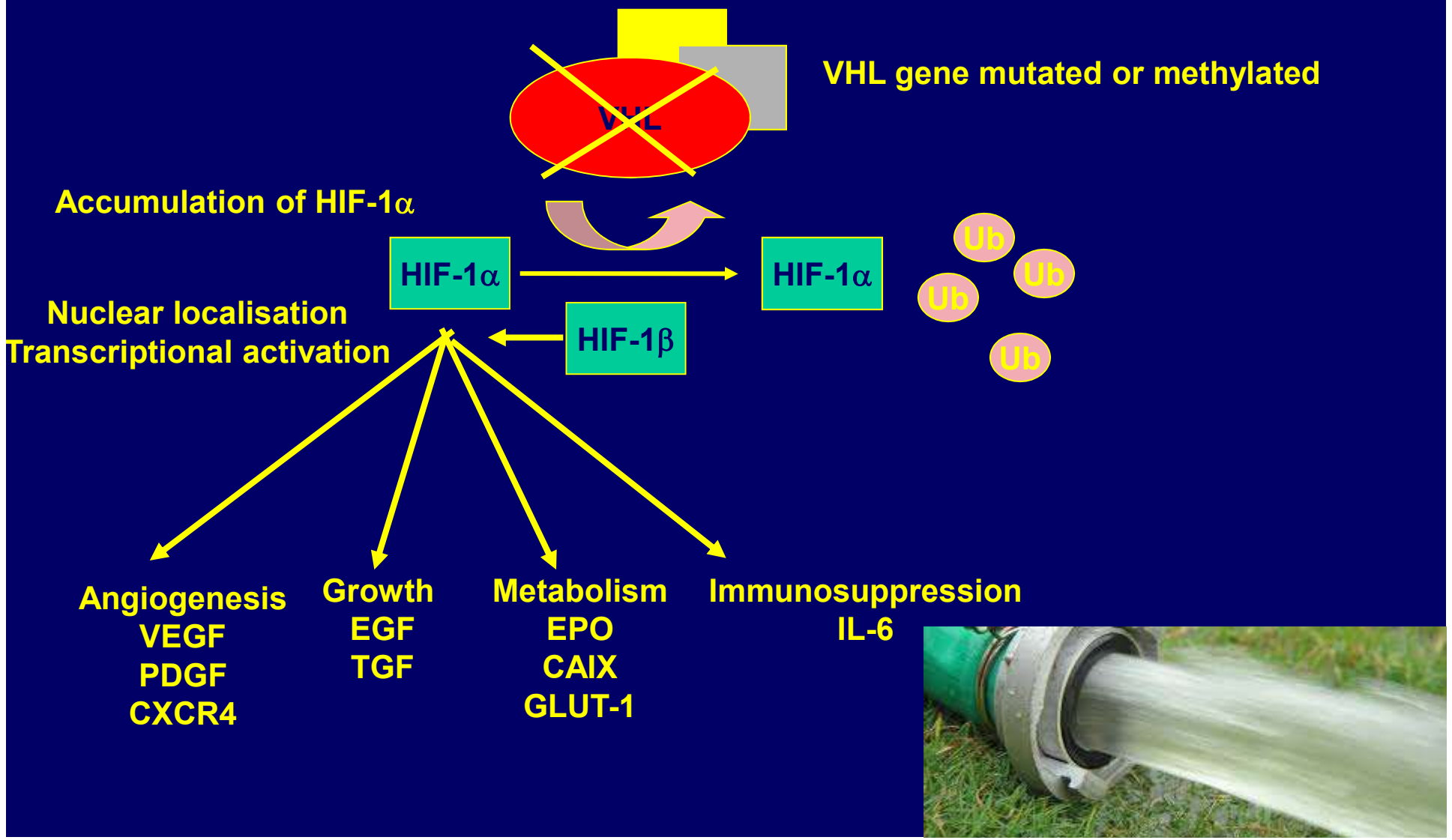
30% pga tobak

RCC er en erhvervet "genetisk" sygdom

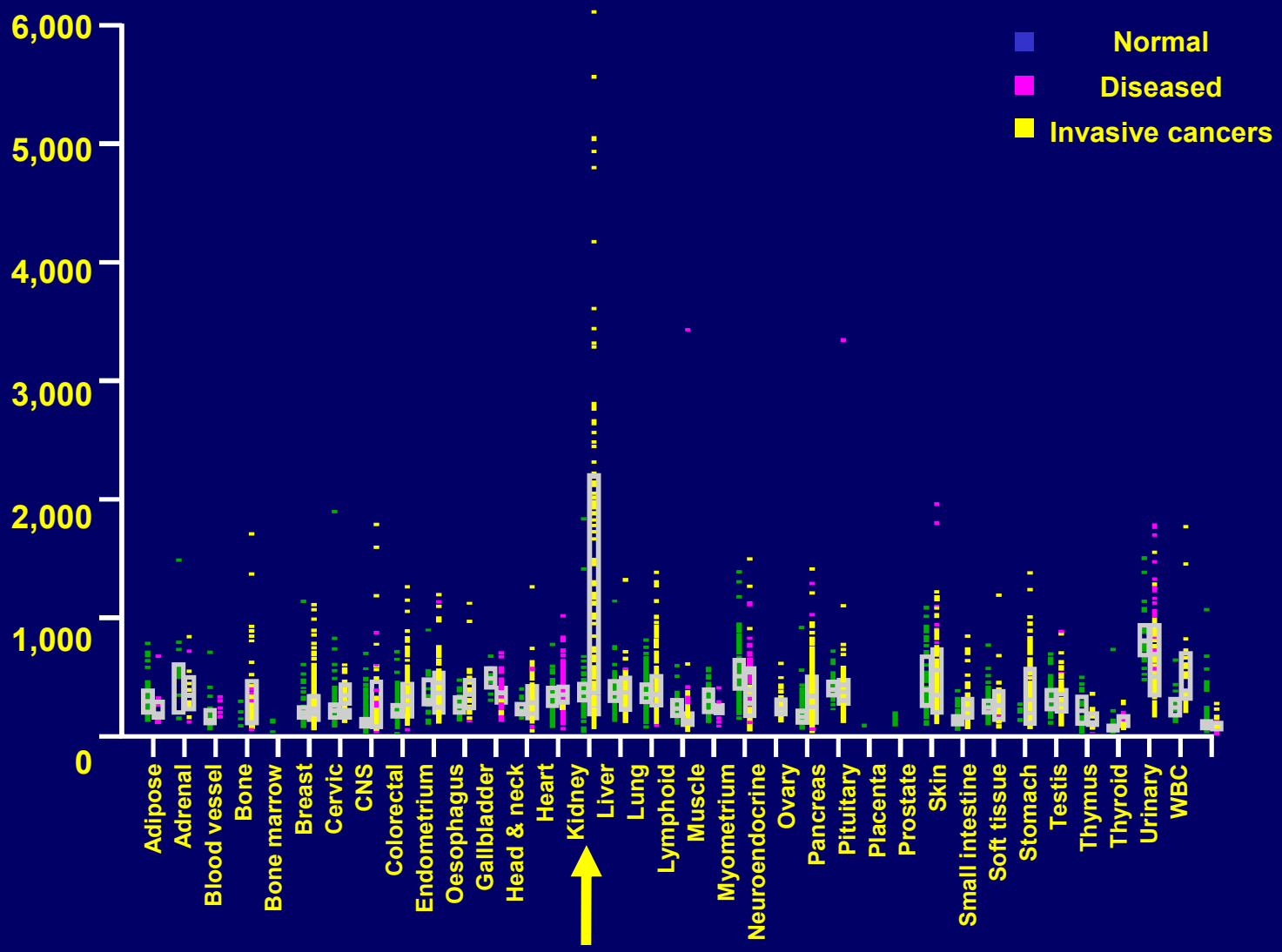


Pena-Llopis et al., *Cancer Research* 2013

VHL in clear cell RCC

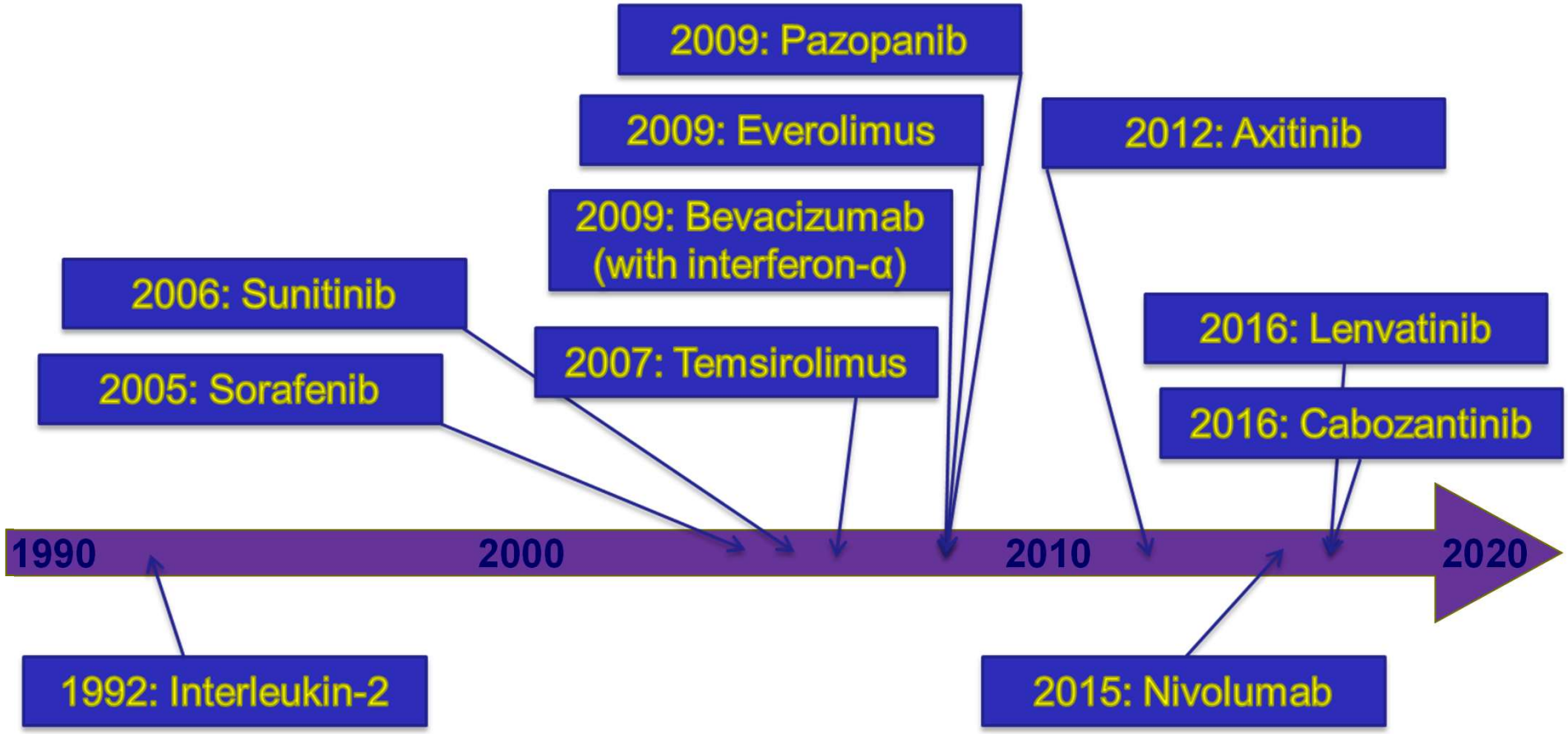


Expression af VEGF

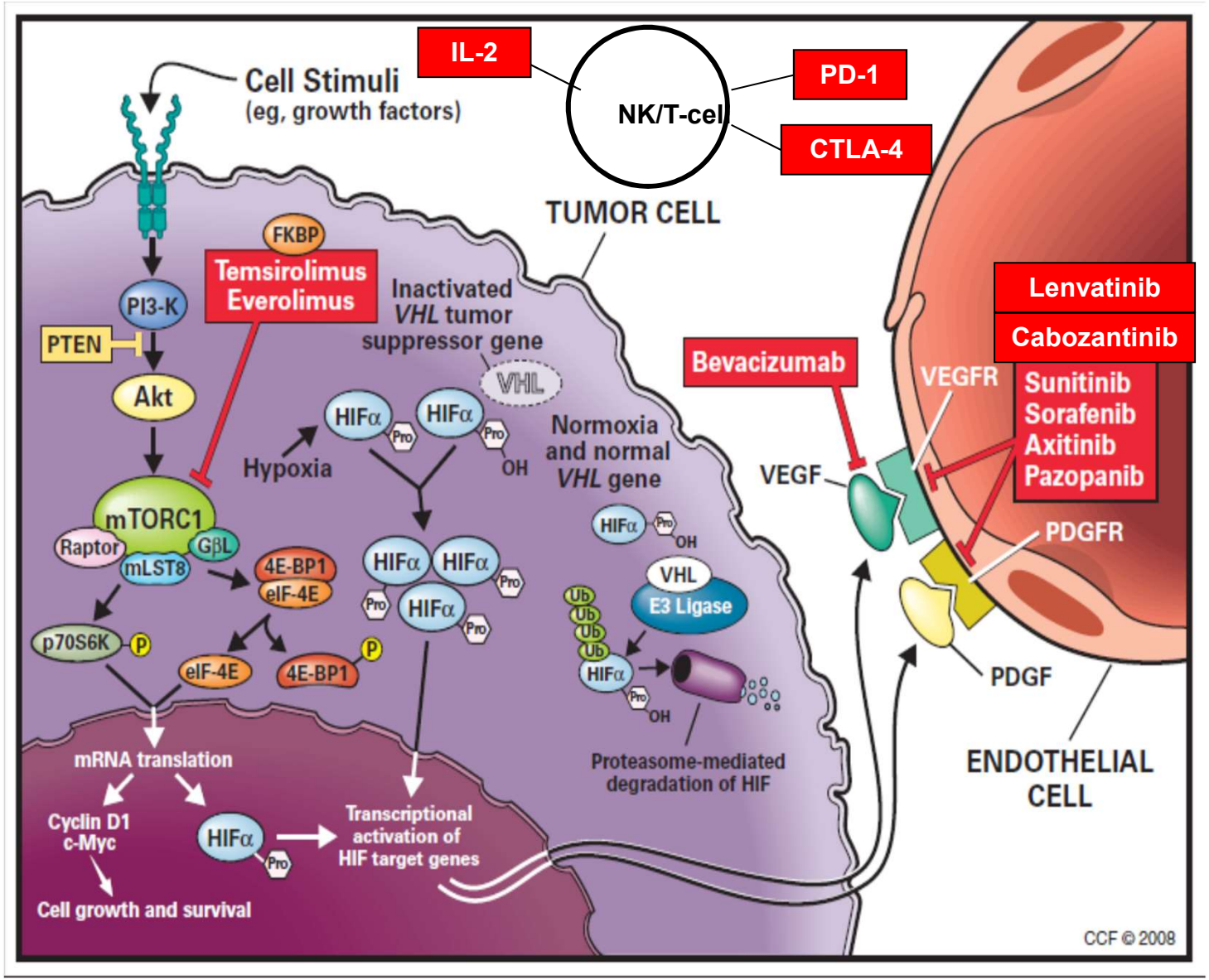


Behandlinge af mRCC: Store fremskridt på få år

12 FDA and EMA godkendelser



mRCC- store fremskridt på få år



Rini, Lancet 2009

Prognostisk stratificering ved mRCC: Betydning af enkle kliniske faktorer

Table 6. Results of Multivariate Analysis

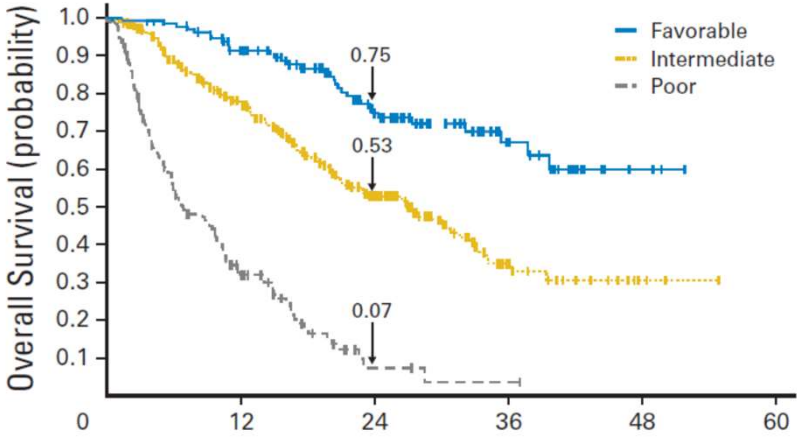
	Parameter Estimate	SE	χ^2	*P*	Risk Ratio	95% CI
Lactate dehydrogenase	0.9019	0.1230	53.74	.0001	2.46	1.94-3.14
Hemoglobin	0.5439	0.0897	36.75	.0001	1.72	1.45-2.05
Corrected calcium	0.5268	0.1147	21.11	.0001	1.69	1.35-2.12
Karnofsky performance status	0.4050	0.0967	17.56	.0001	1.50	1.24-1.81
Prior nephrectomy	0.2992	0.0908	10.87	.001	1.35	1.13-1.61

No. of Risk Factors	% of Patients	% of Patients Alive	Median Survival (months)	95% CI	1-Year Survival (%)	3-Year Survival (%)
0	25	18	19.9	17.1-27.9	71	31
1 or 2	53	7	10.3	8.9-11.4	42	7
3, 4, or 5	22	0.7	3.9	3.4-5.0	12	0

MSKCC (Motzer), JCO 1999; 17:2530-2540

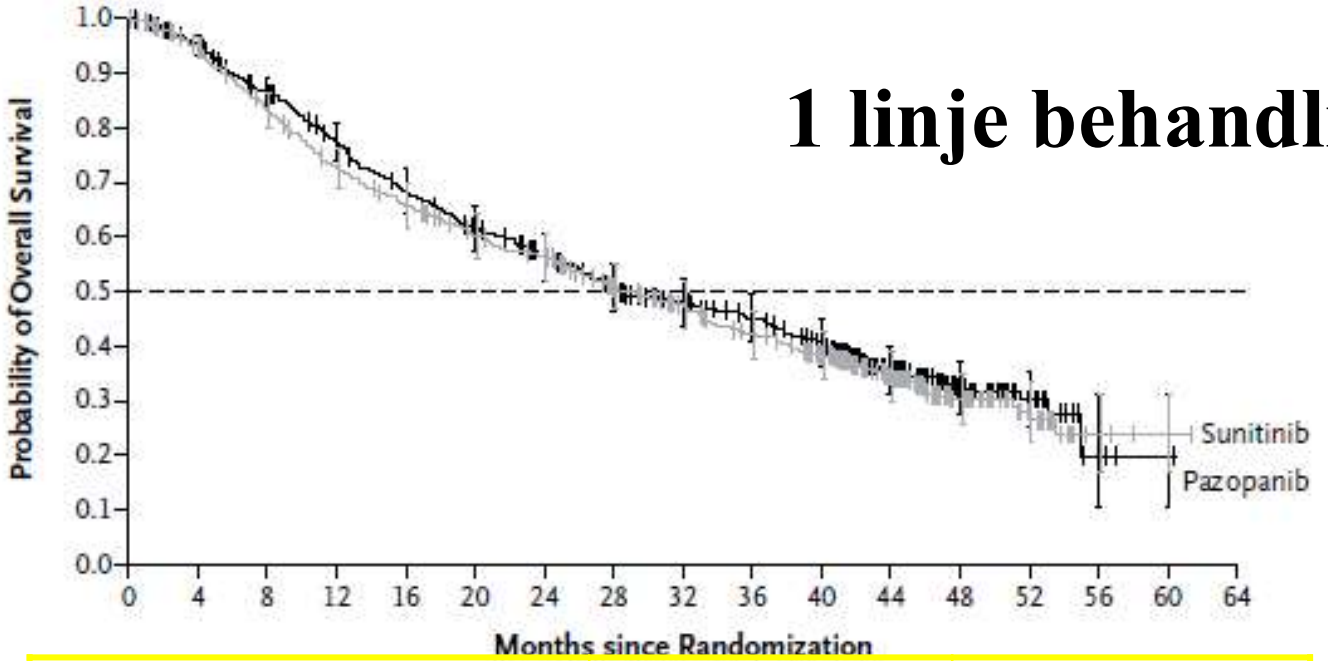
Table 3. Multivariable Analysis and Final Model

Parameter	Parameter Estimate ± SE	Hazard Ratio	95% CI	*P*
Clinical				
KPS < 80%	0.92 ± 0.14	2.51	1.92 to 3.29	< .0001
Time from diagnosis to treatment < 1 year	0.35 ± 0.13	1.42	1.09 to 1.84	.0098
Laboratory				
Hemoglobin < LLN	0.54 ± 0.14	1.72	1.31 to 2.26	.0001
Calcium > ULN	0.59 ± 0.17	1.81	1.29 to 2.53	.0006
Neutrophil count > ULN	0.88 ± 0.17	2.42	1.72 to 3.39	< .0001
Platelet count > ULN	0.40 ± 0.16	1.49	1.09 to 2.03	.0121



IMDC (Heng) JCO 2009; 27: 5794-99

1 linje behandling



	pazopanib	sunitinib
Med OS	28.3 mo	29.1 mo
MSKCC Fav	42.5 mo	43.6 mo
MSKCC Int	26.9 mo	26.1 mo
MSKCC poor	9.9 mo	7.7 mo
Second line	55%	54%
Tx-stop due to AE	24%	20%

ACTA ONCOLOGICA, 2018
https://doi.org/10.1080/0284186X.2018.1433324

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

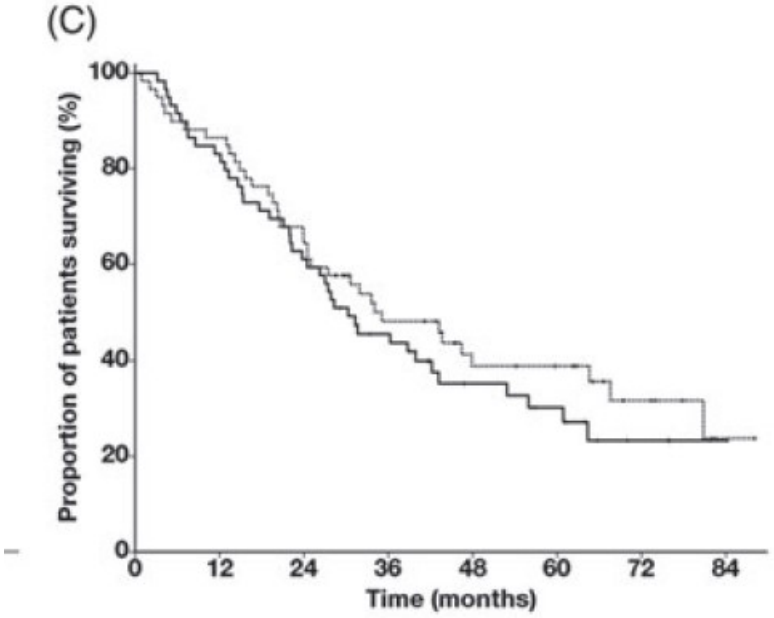
A randomized phase II trial of interleukin-2 and interferon-α plus bevacizumab versus interleukin-2 and interferon-α in metastatic renal-cell carcinoma (mRCC): results from the Danish Renal Cancer Group (DaRenCa) study-1

Frede Donskov[a], Niels Viggo Jensen[b], Torben Smidt-Hansen[a], Line Brøndum[a] and Poul Geertsen[c]

[a]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; [b]Department of Oncology, Odense University Hospital, Odense, Denmark; [c]Department of Oncology, Herlev Hospital, University of Copenhagen, Denmark

Table 1. Demographics and baseline characteristics.

	IL-2/IFN/BEV		IL-2/IFN	
	N = 59		*N* = 59	
Age, years (range)	58	(28–70)	55	(37–69)
Sex, *n* (%)				
Male	46	(78)	47	(80)
Karnofsky PS, *n* (%)				
100	31	(53)	37	(63)
90	19	(32)	16	(27)
80	6	(10)	4	(7)
70	3	(5)	2	(3)
IMDC risk, *n* (%)				
Favorable	14	(24)	12	(20)
Intermediate	32	(54)	36	(61)
Poor	13	(22)	11	(19)
MSKCC risk, *n* (%)				
Favorable	30	(51)	31	(52)
Intermediate	29	(49)	28	(48)
Metastasis-free interval, *n* (%)				
<1 year	43	(73)	45	(76)
Nephrectomy, *n* (%)				
Yes	50	(85)	51	(86)
Sites of disease, *n* (%)				
Primary *in situ*	10	(17)	8	(14)
Local recurrence	3	(5)	6	(10)
Lung metastases	47	(80)	49	(83)
Lung mets only	8	(14)	8	(14)
Lymph node mets	37	(63)	37	(63)
Bone metastases	16	(27)	9	(15)
Liver metastases	8	(14)	9	(15)



2 linje behandling

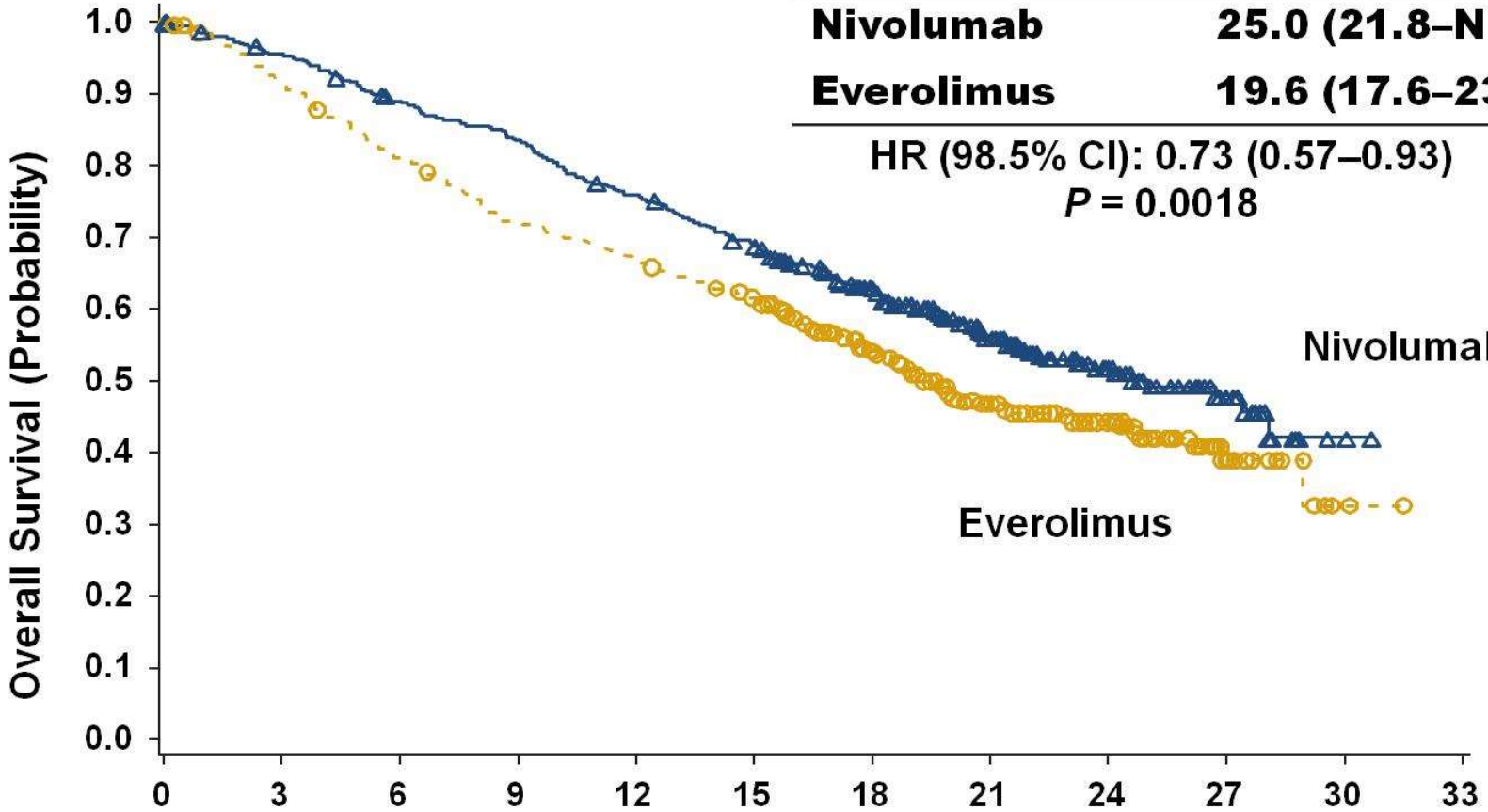
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 5, 2015 VOL. 373 NO. 19

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

Overall survival



No. of patients at risk

Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

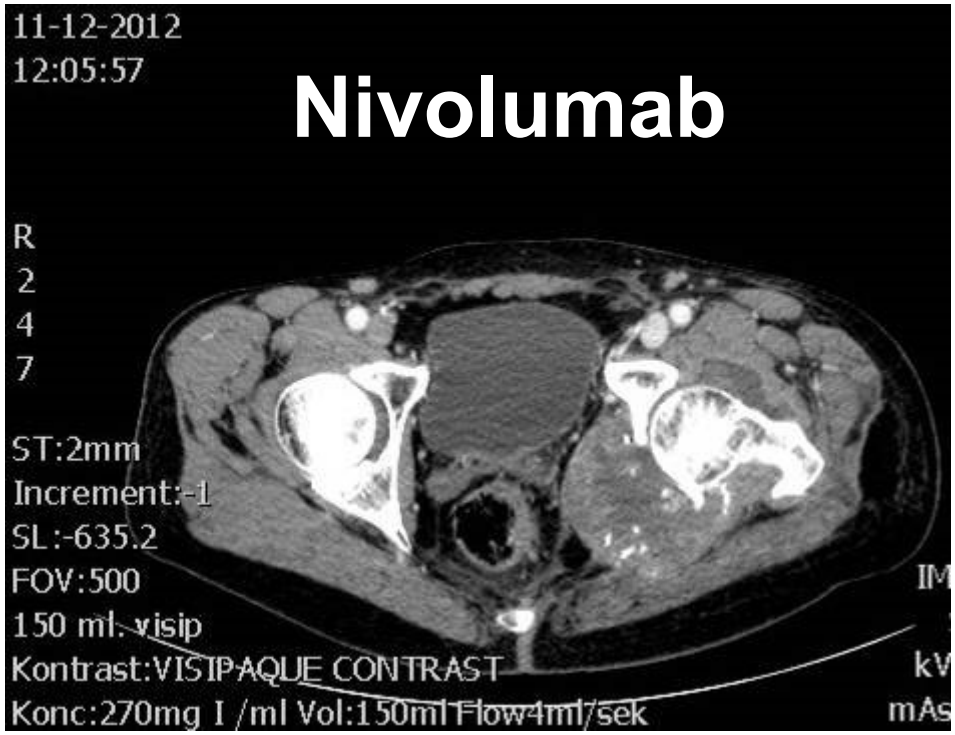
Minimum follow-up was 14 months.

NE, not estimable.

Antitumor activity

	Nivolumab N = 410	Everolimus N = 411
Objective response rate, %	25	5
Odds ratio (95% CI)	5.98 (3.68–9.72)	
P value	<0.0001	
Best overall response, %		
Complete response	1	1
Partial response	24	5
Stable disease	34	55
Progressive disease	35	28
Not evaluated	6	12
Median time to response, months (range)	3.5 (1.4–24.8)	3.7 (1.5–11.2)
Median duration of response, months (range)*	12.0 (0–27.6)	12.0 (0–22.2)
Ongoing response, n/N (%)	49/103 (48)	10/22 (45)

*For patients without progression or death, duration of response is defined as the time from the first response (CR/PR) date to the date of censoring.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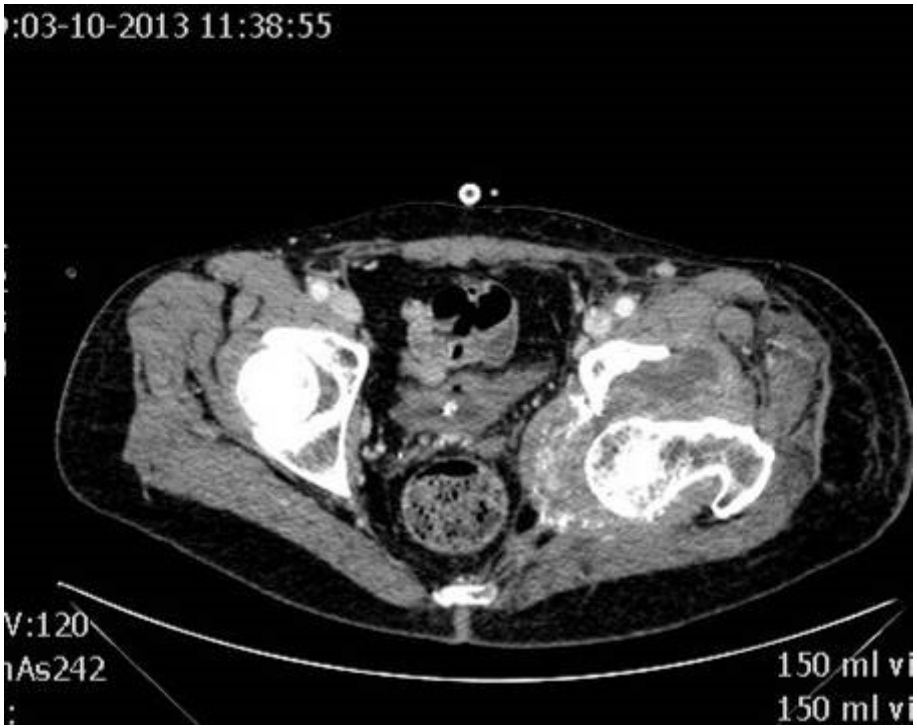
12:05:57
Nivolumab
R
2
4
7
ST:2mm
Increment:-1
SL:-635.2
FOV:500
150 ml. visip
Kontrast:VISIPAQUE CONTRAST
Konc:270mg I /ml Vol:150ml Flow4ml/sek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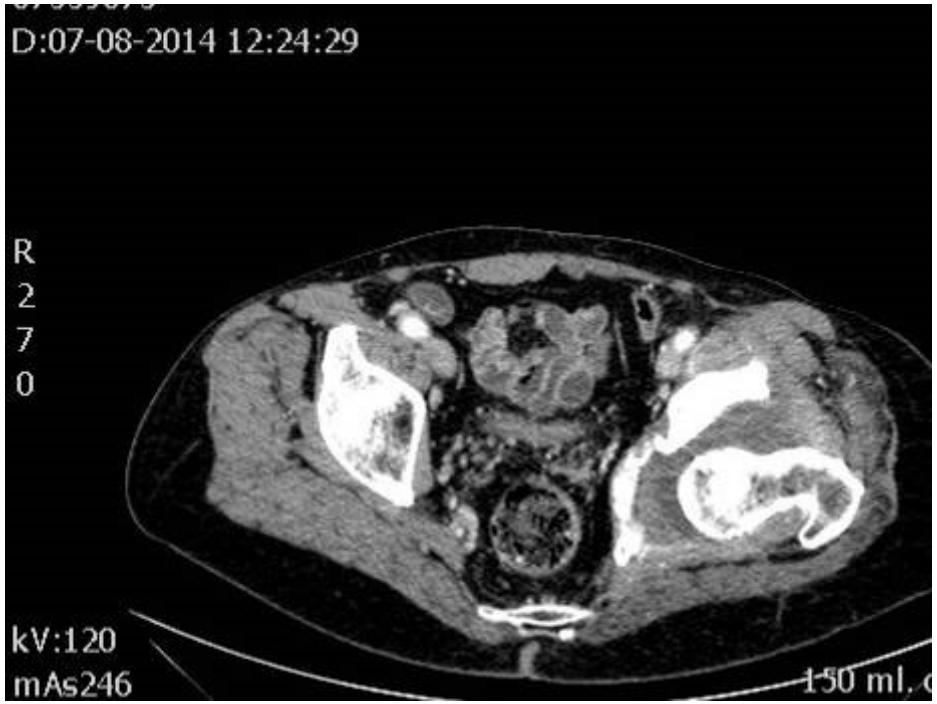
V:120
As242
150 ml vi
150 ml vi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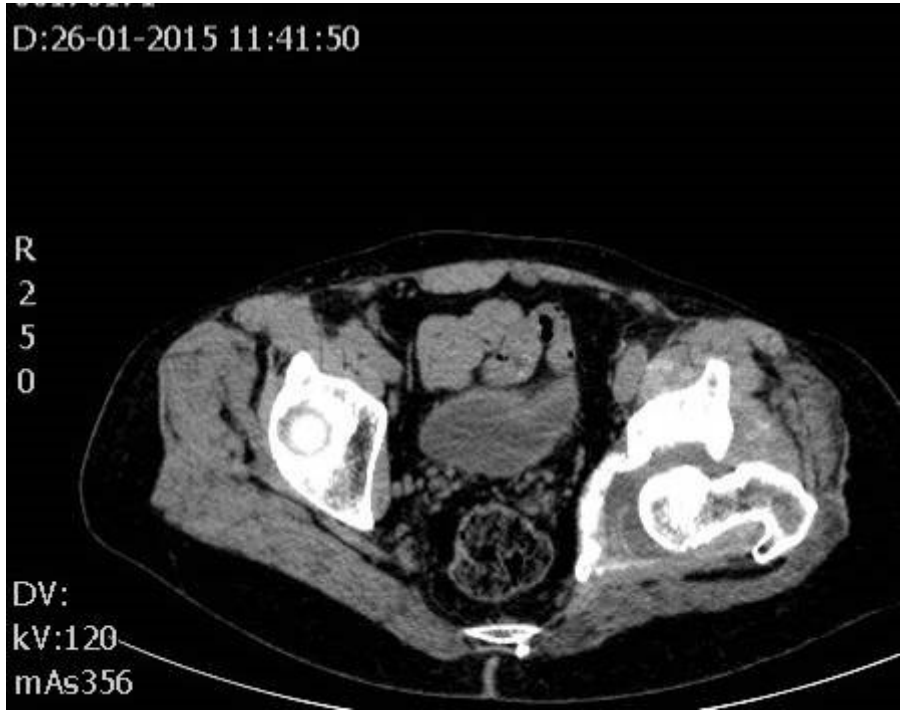
R
2
7
0
kV:120
mAs246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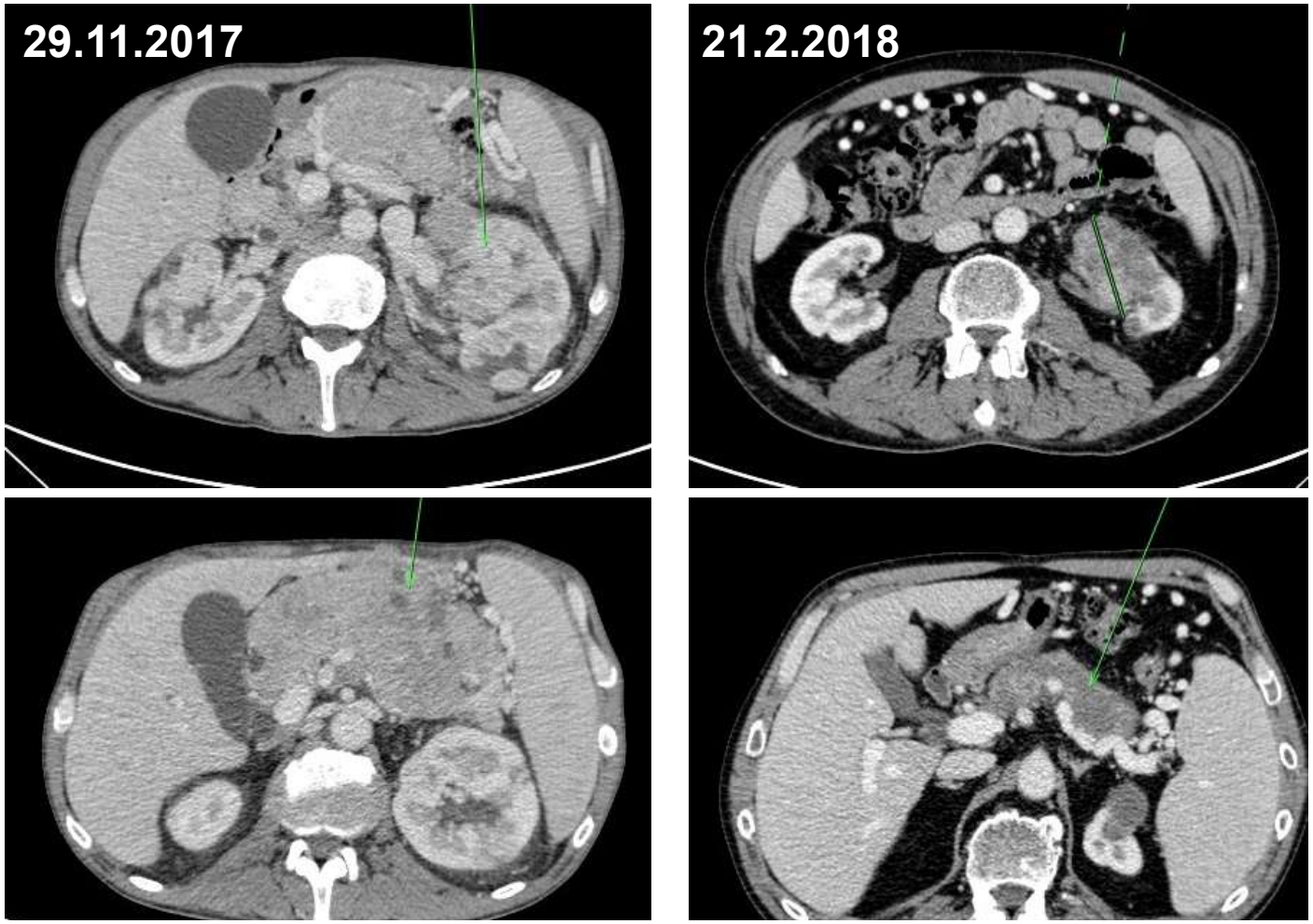
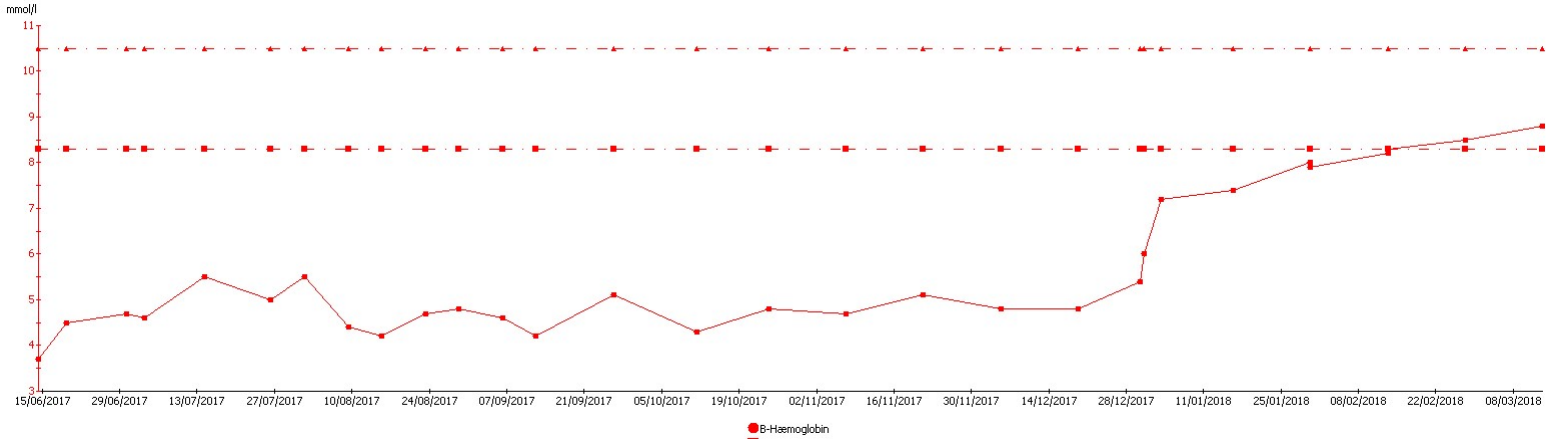
R
2
5
0
DV:
kV:120
mAs356


29.11.2017
21.2.2018


mmol/l
11
10
9
8
7
6
5
4
3
15/06/2017
29/06/2017
13/07/2017
27/07/2017
10/08/2017
24/08/2017
07/09/2017
21/09/2017
05/10/2017
19/10/2017
02/11/2017
16/11/2017
30/11/2017
14/12/2017
28/12/2017
11/01/2018
25/01/2018
08/02/2018
22/02/2018
08/03/2018
B-Haemoglobin

Safety Summary

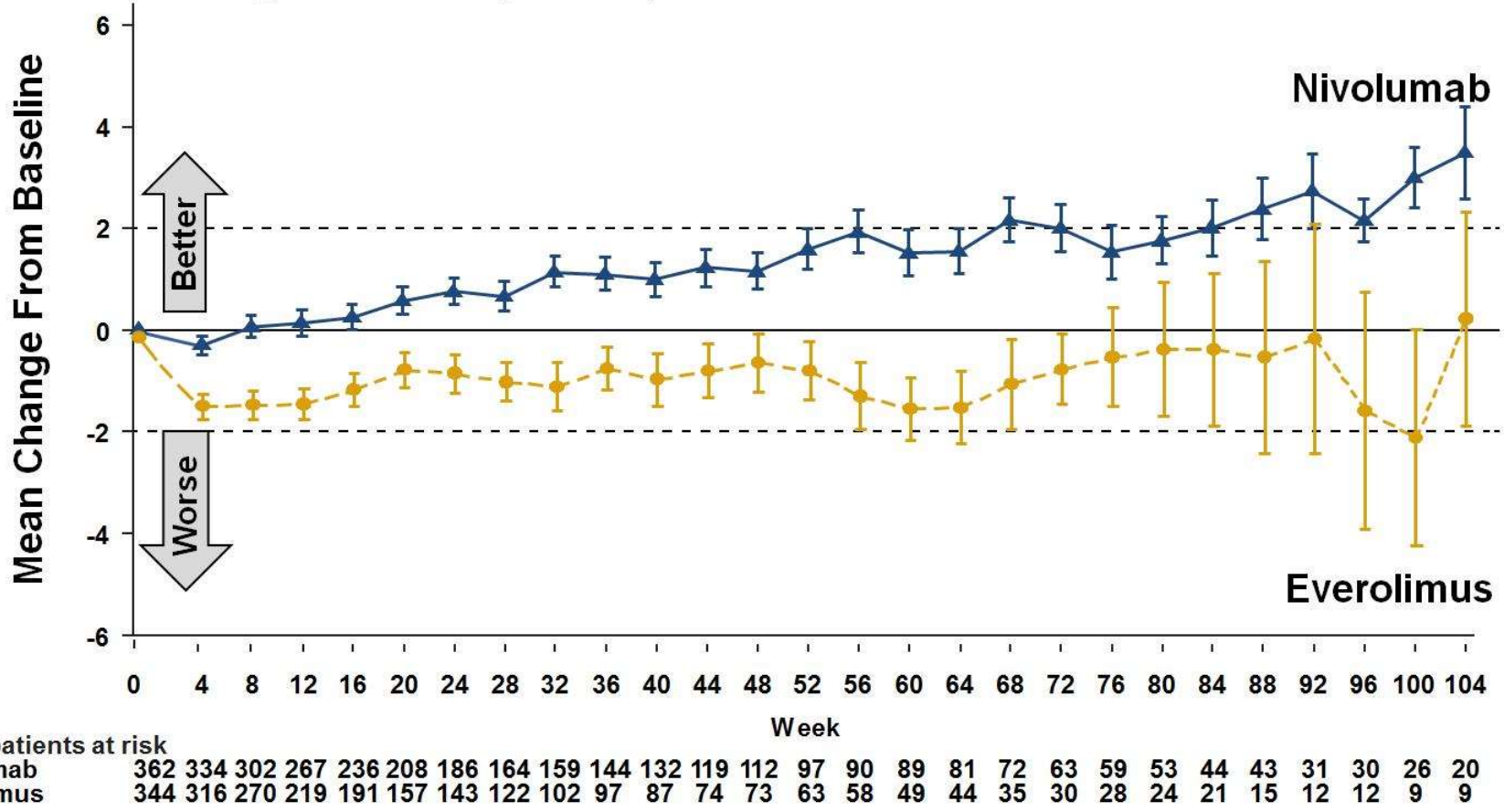
	Nivolumab N = 406		Everolimus N = 397	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related AEs, %	79	19	88	37
Treatment-related AEs leading to discontinuation, %	8	5	13	7
Treatment-related deaths, n	0		2[a]	

- 44% of patients in the nivolumab arm and 46% of patients in the everolimus arm were treated beyond progression

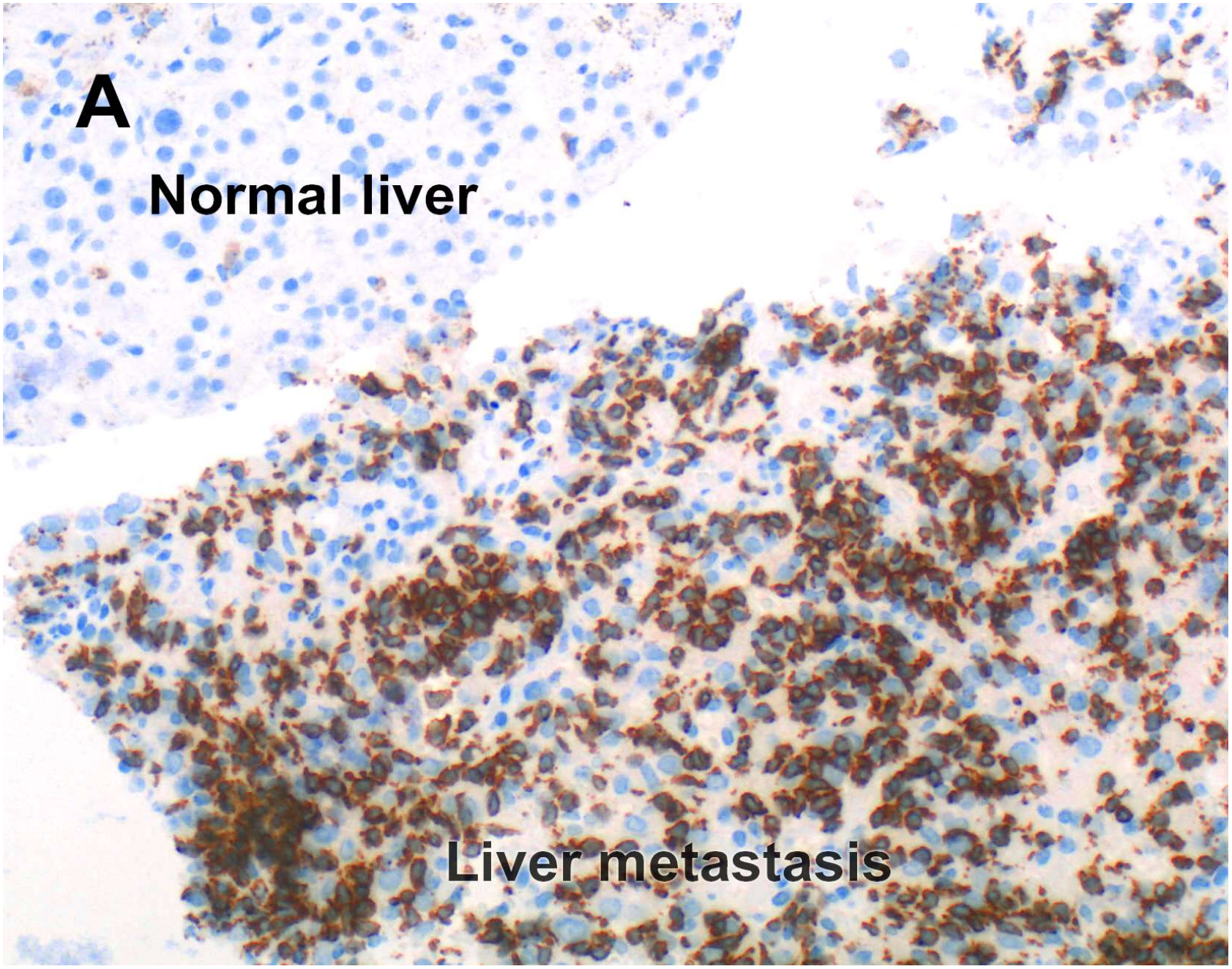
[a] Septic shock (1), bowel ischemia (1).

Change from baseline in quality of life scores on FKSI-DRS

- Mean change from baseline in the nivolumab group increased over time and differed significantly from the everolimus group at each assessment through week 76 ($P<0.05$)



Questionnaire completion rate: ≥80% during the first year of follow-up.



Donskov F, Cancer Immunol Immunotherapy 2004

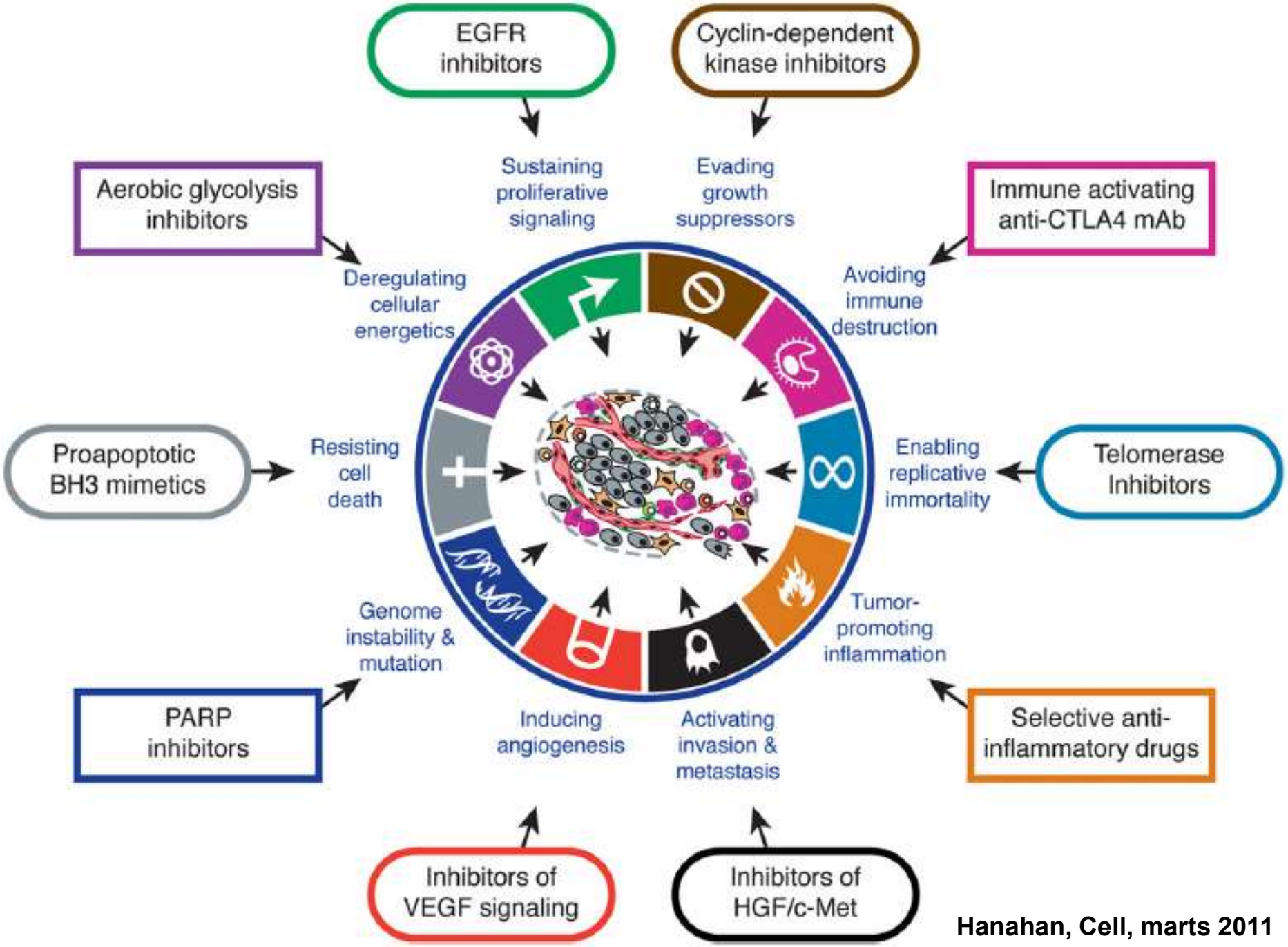
2 linje behandling

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

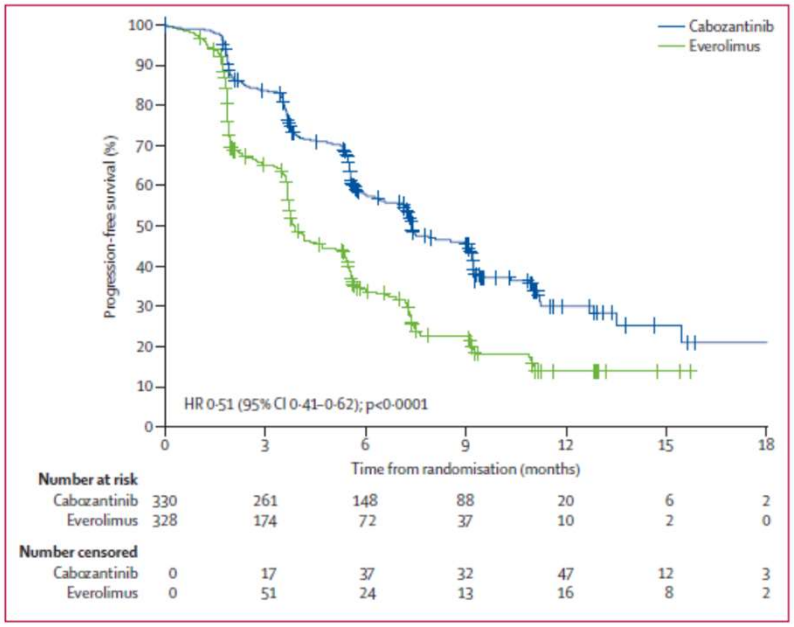
T.K. Choueiri, B. Escudier, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donskov, H. Hammers, T.E. Hutson, J.-L. Lee, K. Peltola, B.J. Roth, G.A. Bjarnason, L. Géczi, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Borgman-Hagey, C. Hessel, C. Scheffold, G.M. Schwab, N.M. Tannir, and R.J. Motzer, for the METEOR Investigators*



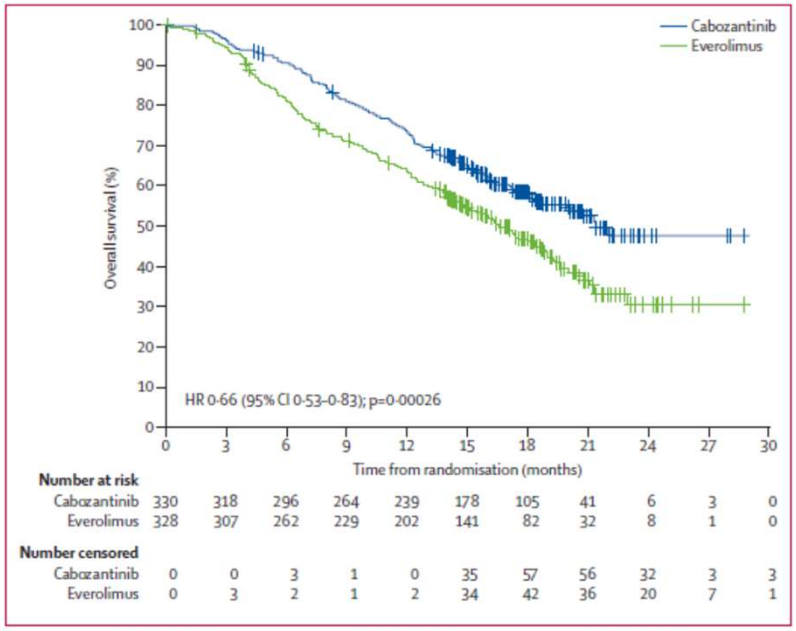
Hanahan, Cell, marts 2011

Cabozantinib først lægemiddel ved mRCC med signifikant forbedret RR, PFS og OS ift komparator

Med PFS 7.4 vs 3.9 mo



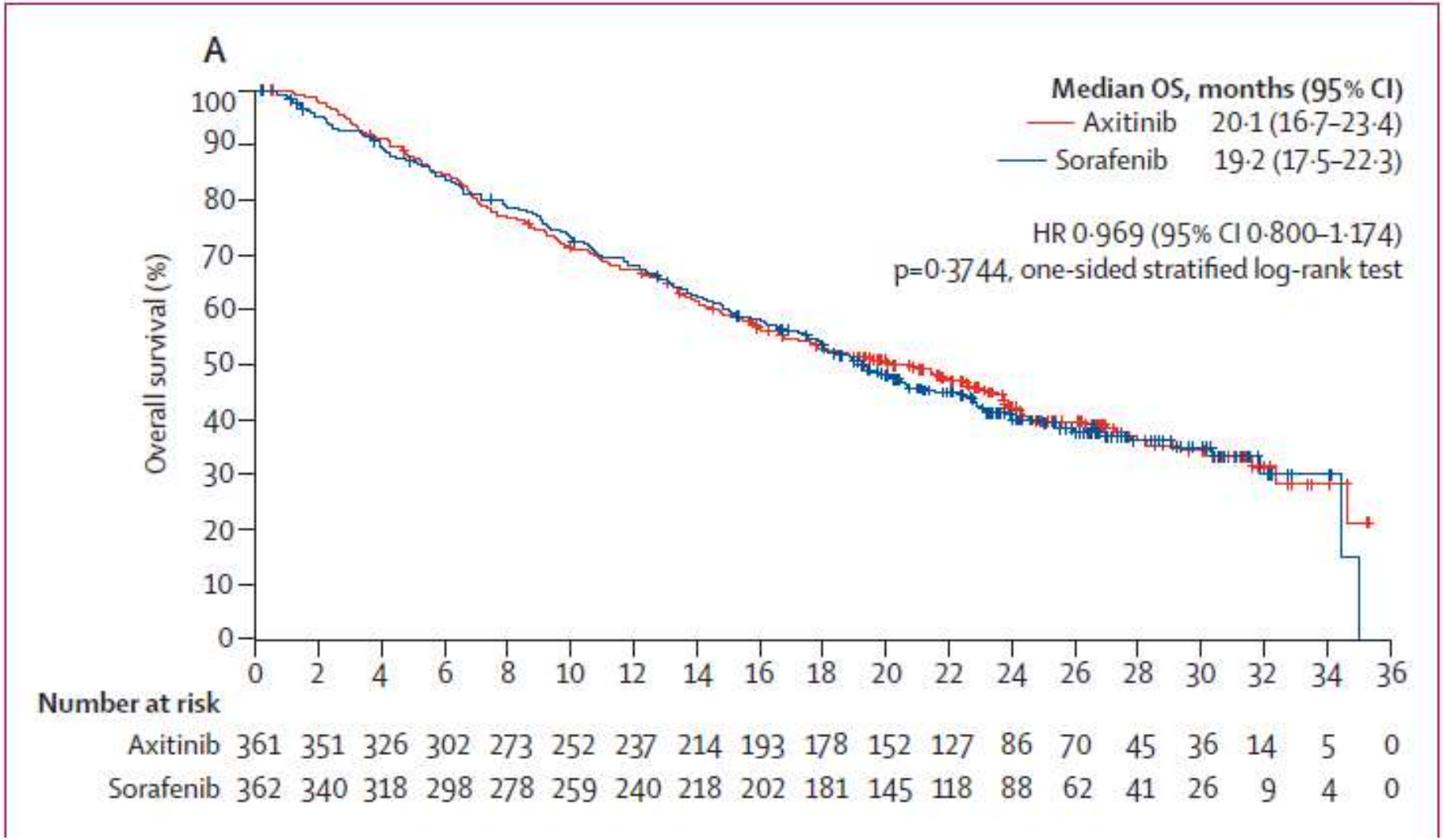
Med OS 21.4 vs 16.5 mo



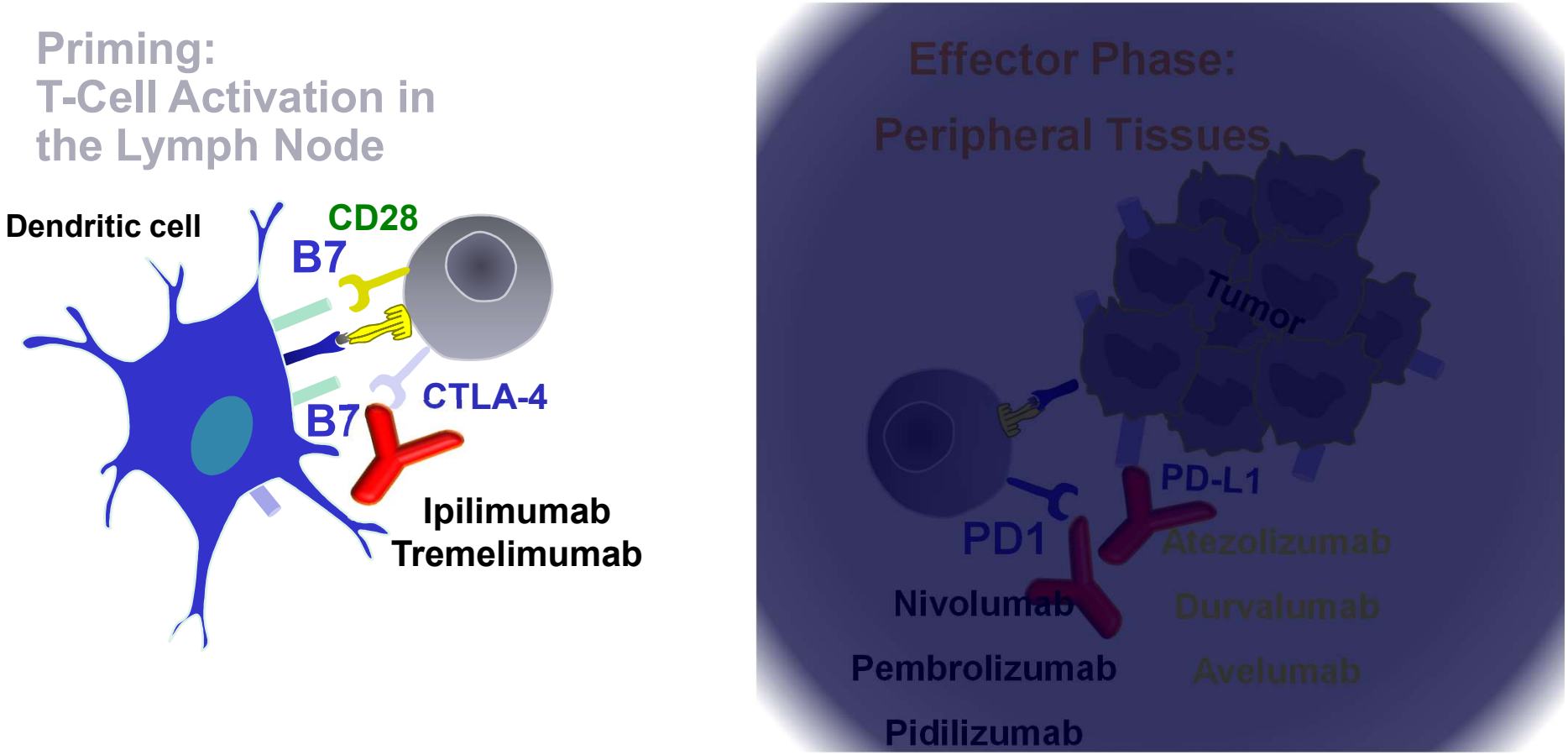
RR 17% vs 3%

Lancet Oncol 2016: 17:917-927

Flere 2 og 3 linje behandlingsmuligheder: Axitinib og sorafinib

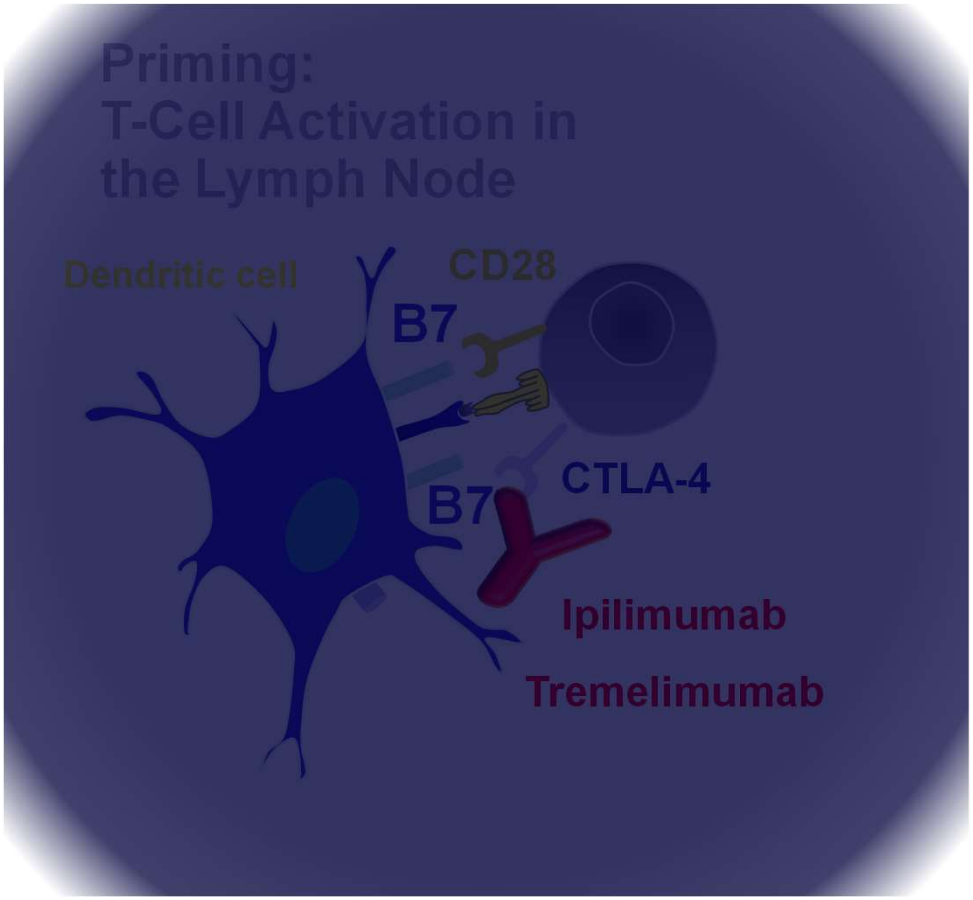


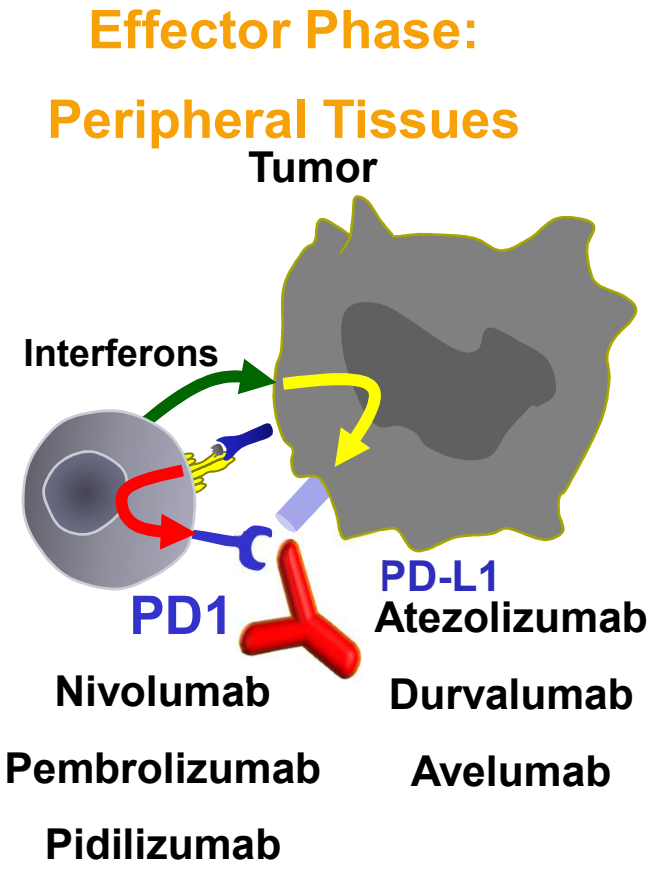
Checkpoint immunterapi



1. Ribas A. *N Engl J Med.* 2012;366:2517-2519.
2. Spranger S, Gajewski T. *J Immunother Cancer*. 2013;1:16.

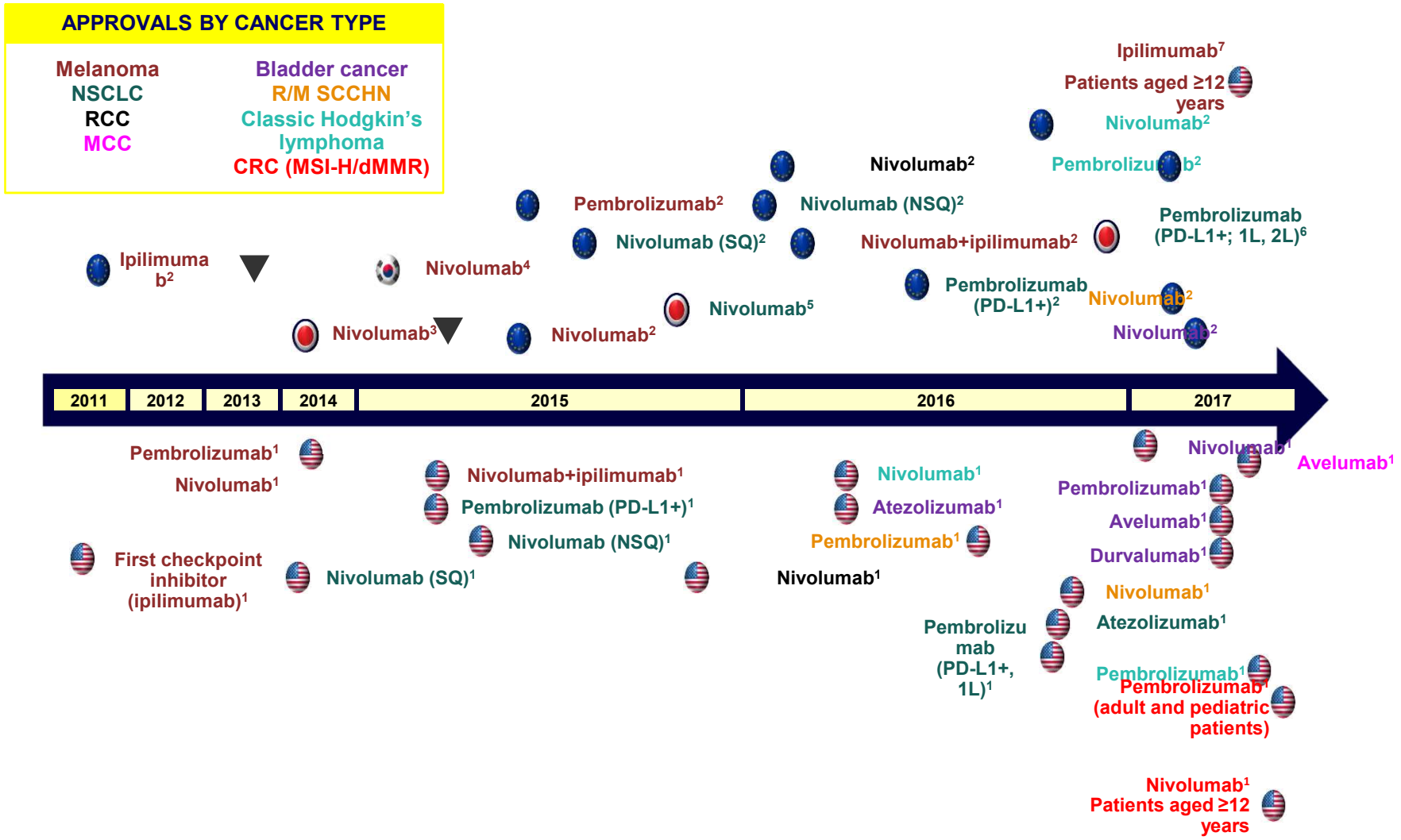
Checkpoint immunterapi





1. Ribas A. *N Engl J Med.* 2012;366:2517-2519.
2. Spranger S, Gajewski T. *J Immunother Cancer*. 2013;1:16.

History of Checkpoint Inhibitors: Key Milestones



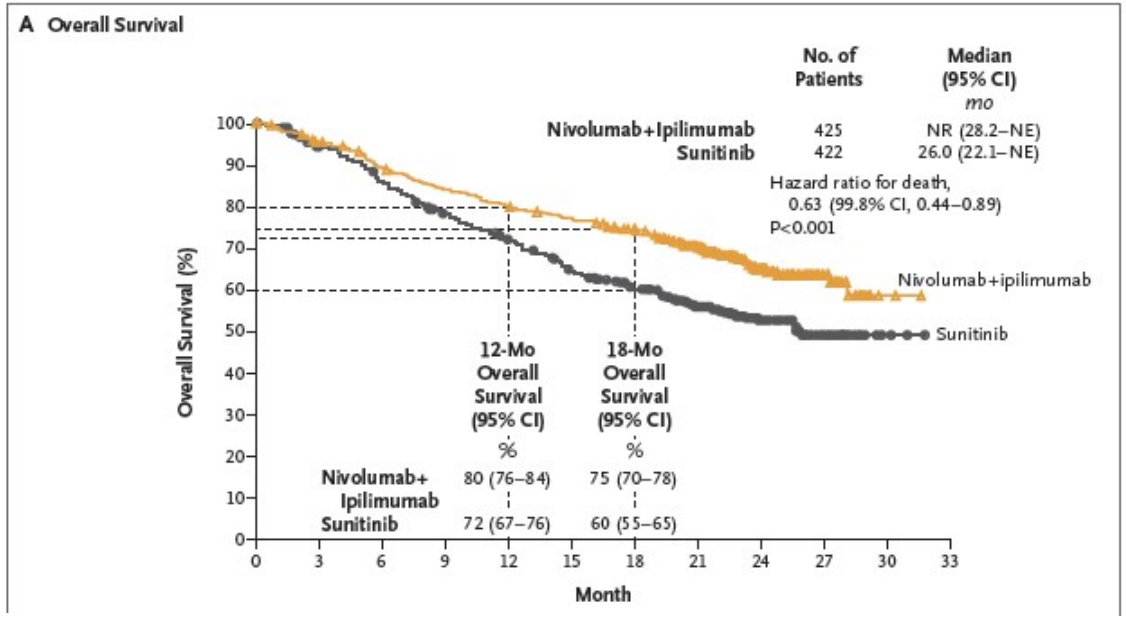
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 5, 2018 VOL. 378 NO. 14

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.-O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B.I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators*

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma



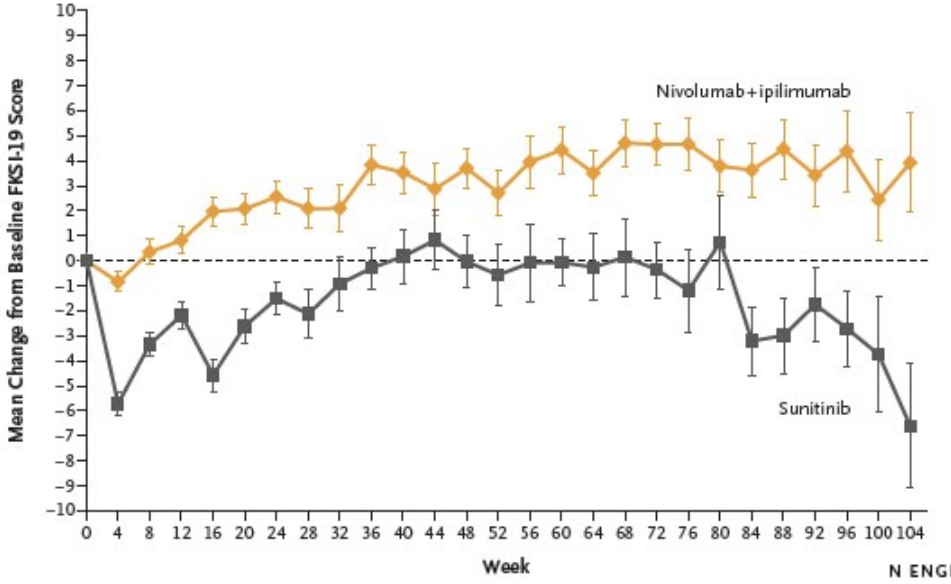
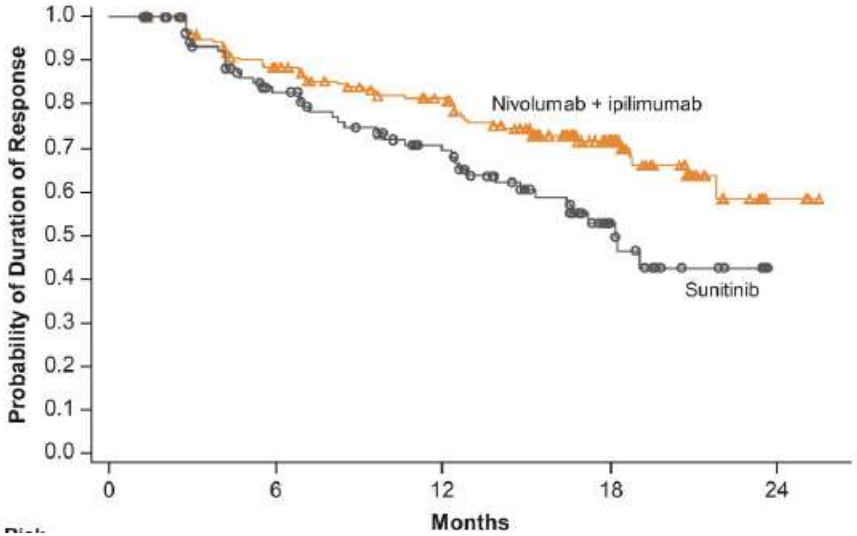


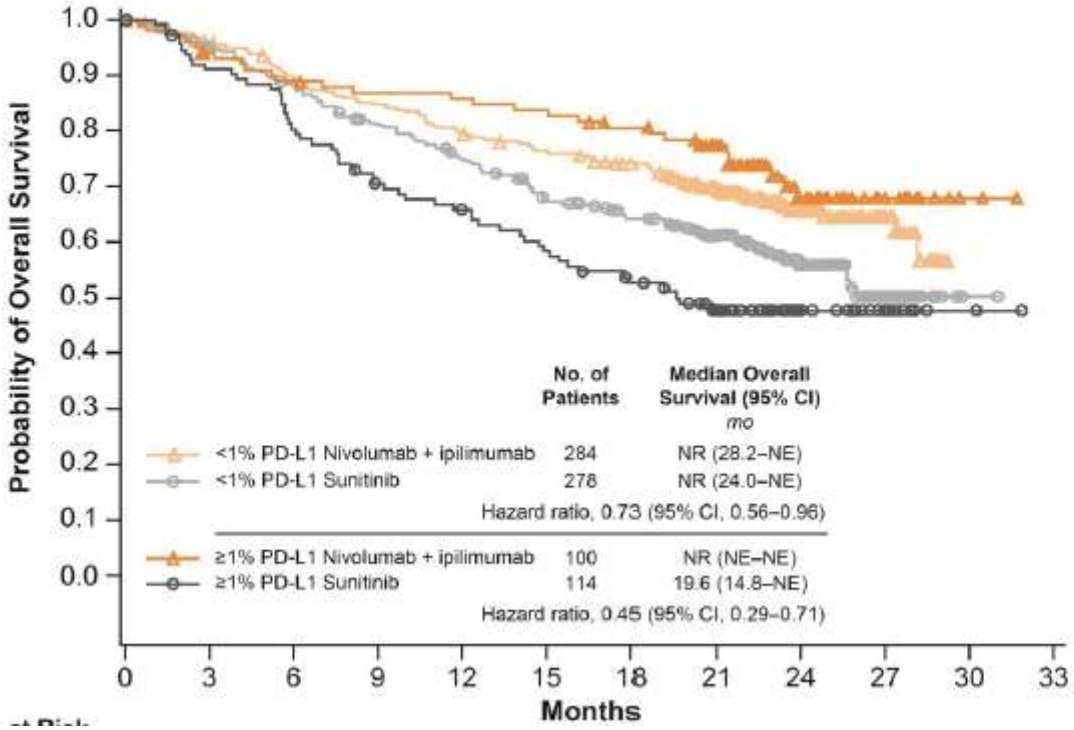
Figure S2. Duration of Response in IMDC Intermediate- and Poor-risk Patients. IPI denotes ipilimumab; NIVO, nivolumab; SUN, sunitinib

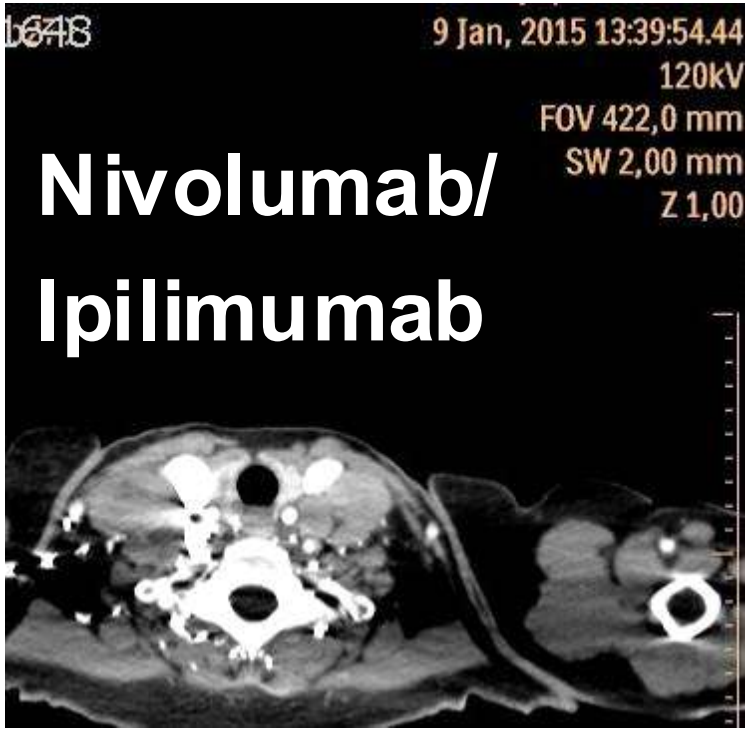


RR 42% vs 27%

CR 9% vs 1%

Figure S4. Kaplan–Meier Curves for Overall Survival According to PD-L1 Expression Level in IMDC Intermediate- and Poor-risk Patients

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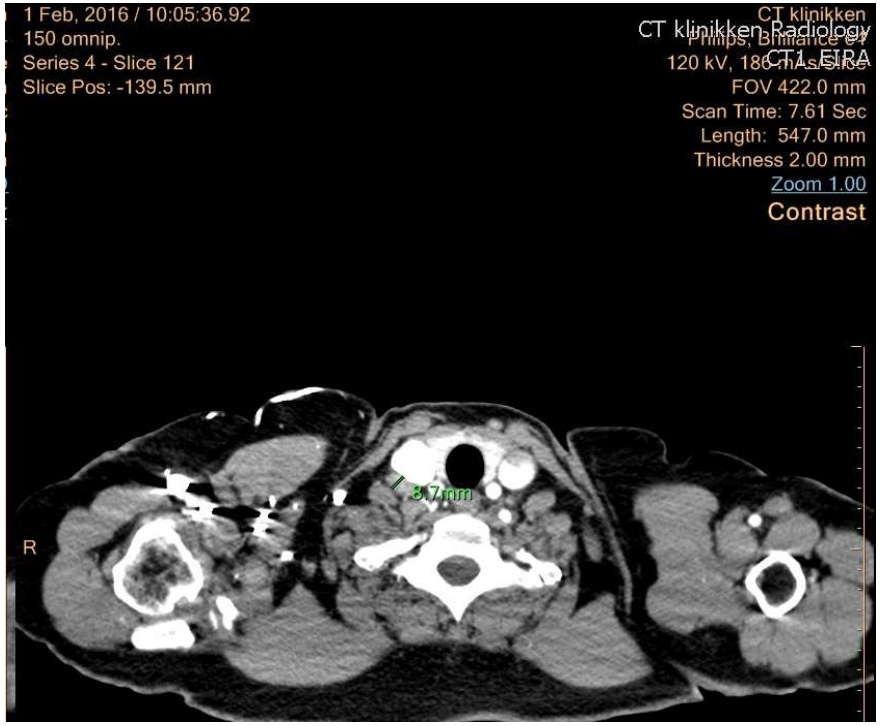
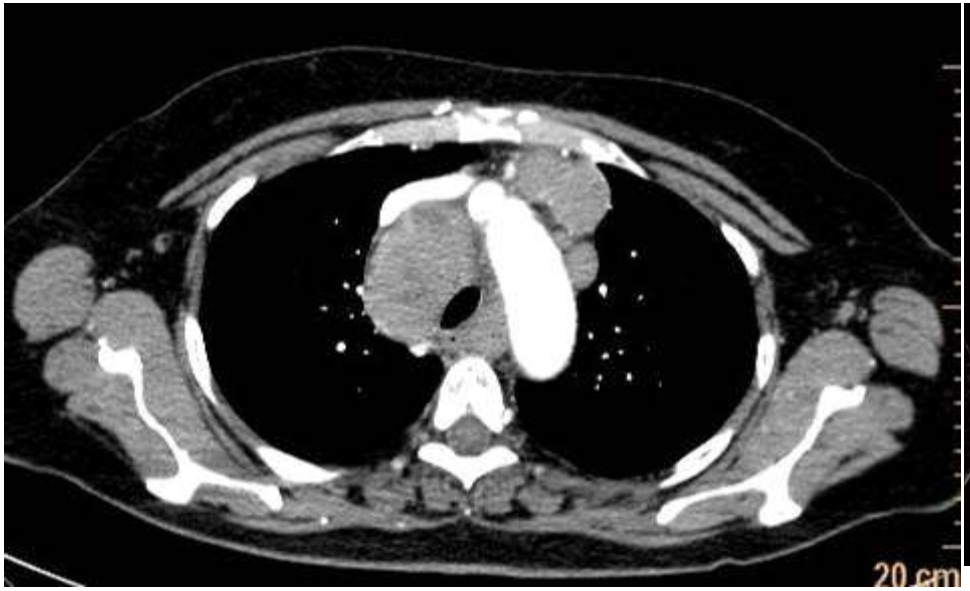
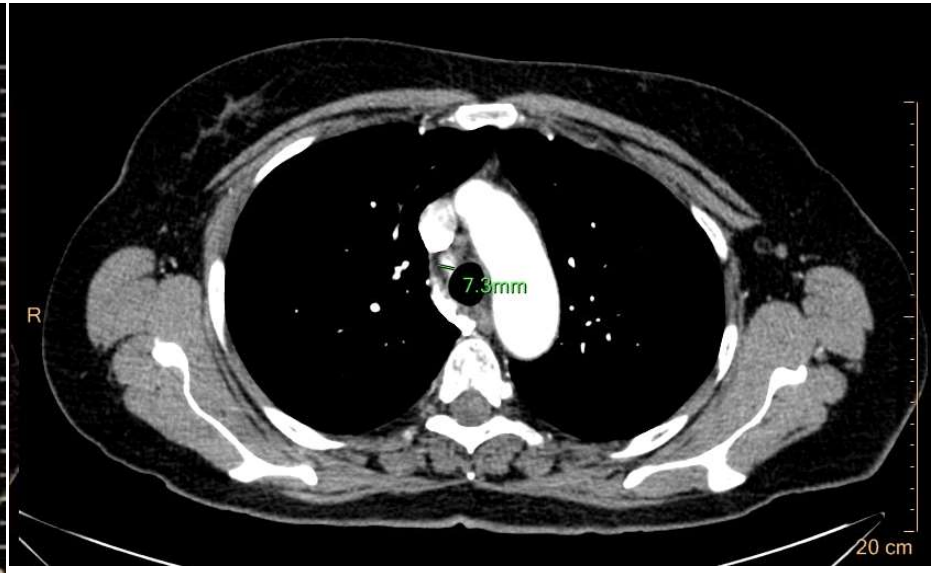
120kV
FOV 422,0 mm
SW 2,00 mm
Z 1,00
Nivolumab/
Ipilimumab


1 Feb, 2016 / 10:05:36.92
150 omnip.
Series 4 - Slice 121
Slice Pos: -139.5 mm
CT klinikken
CT klinikken Radiology
FOV 422.0 mm
Scan Time: 7.61 Sec
Length: 547.0 mm
Thickness 2.00 mm
Zoom 1.00
Contrast
8.7mm
R


20 cm


7.3mm
R
20 cm

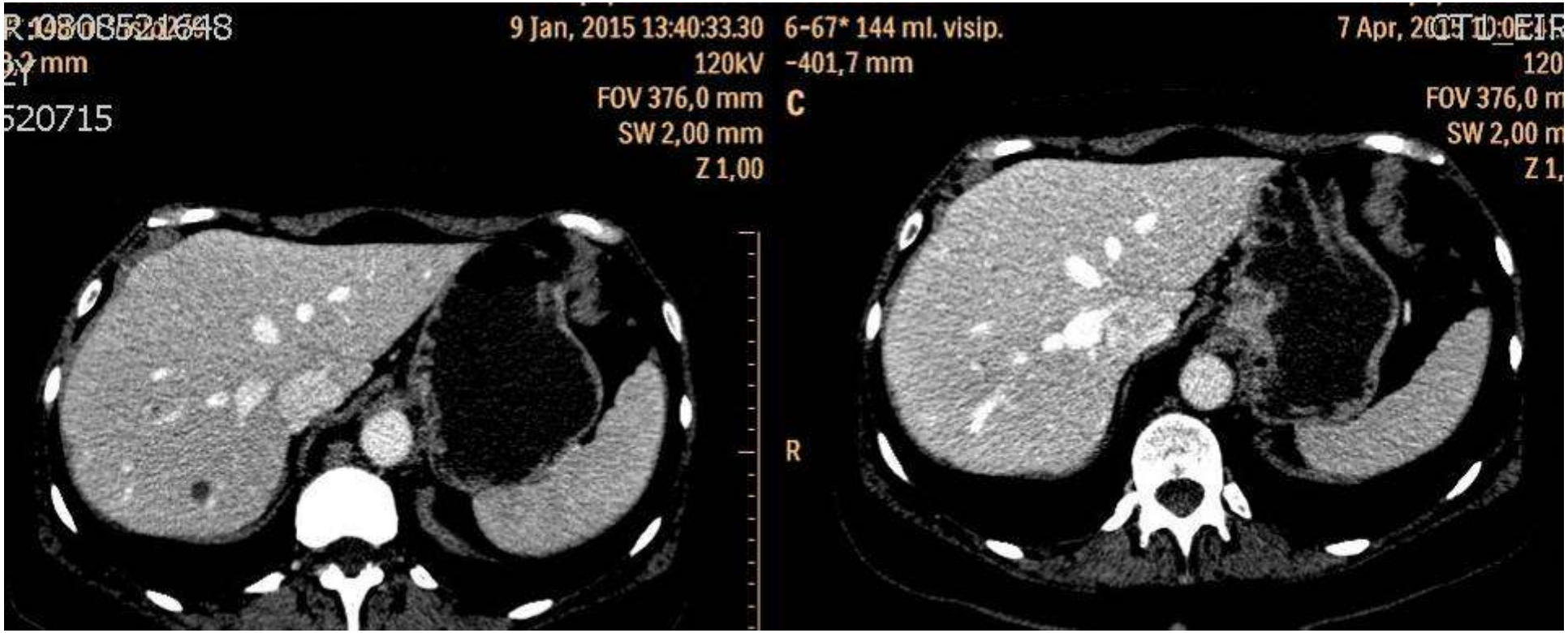

9 Jan, 2015 13:40:33.30
120kV
FOV 376,0 mm
SW 2,00 mm
Z 1,00
6-67* 144 ml. visip.
-401,7 mm
C
R

Table 3. Treatment-Related Adverse Events Occurring in 15% or More of Treated Patients in Either Group.*

Event	Nivolumab plus Ipilimumab (N=547)		Sunitinib (N=535)	
	Any Grade†	Grade 3 or 4	Any Grade‡	Grade 3 or 4
	number of patients (percent)			
All events	509 (93)	250 (46)	521 (97)	335 (63)
Fatigue	202 (37)	23 (4)	264 (49)	49 (9)
Pruritus	154 (28)	3 (<1)	49 (9)	0
Diarrhea	145 (27)	21 (4)	278 (52)	28 (5)
Rash	118 (22)	8 (1)	67 (13)	0
Nausea	109 (20)	8 (1)	202 (38)	6 (1)
Increased lipase level	90 (16)	56 (10)	58 (11)	35 (7)
Hypothyroidism	85 (16)	2 (<1)	134 (25)	1 (<1)
Decreased appetite	75 (14)	7 (1)	133 (25)	5 (<1)
Asthenia	72 (13)	8 (1)	91 (17)	12 (2)
Vomiting	59 (11)	4 (<1)	110 (21)	10 (2)
Anemia	34 (6)	2 (<1)	83 (16)	24 (4)
Dysgeusia	31 (6)	0	179 (33)	1 (<1)
Stomatitis	23 (4)	0	149 (28)	14 (3)
Dyspepsia	15 (3)	0	96 (18)	0
Mucosal inflammation	13 (2)	0	152 (28)	14 (3)
Hypertension	12 (2)	4 (<1)	216 (40)	85 (16)
Palmar–plantar erythrodysesthesia	5 (<1)	0	231 (43)	49 (9)
Thrombocytopenia	2 (<1)	0	95 (18)	25 (5)

* These events were considered by investigators to be related to treatment.

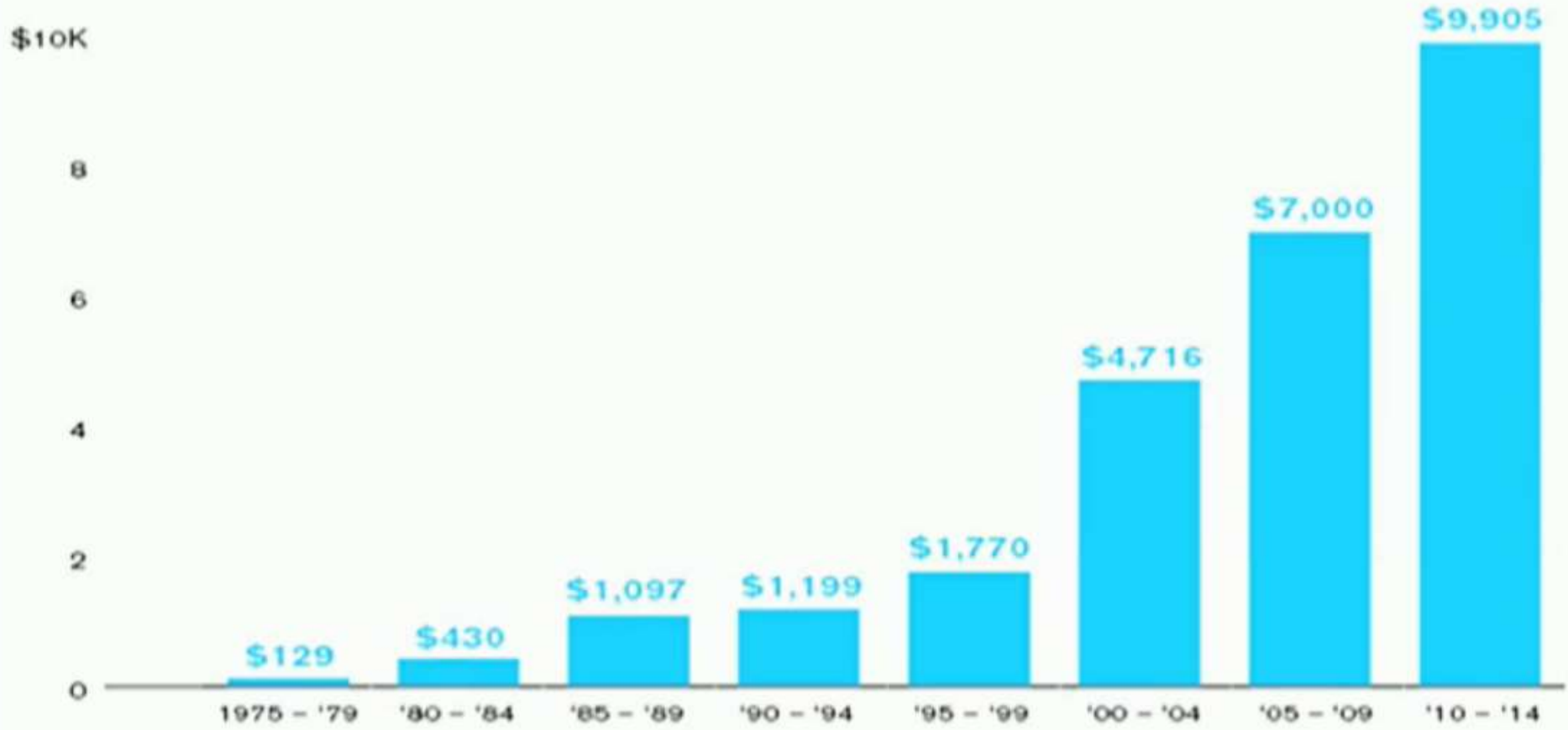
† There were eight treatment-related deaths in the nivolumab-plus-ipilimumab group: one each due to pneumonitis, pneumonia and aplastic anemia (the cause of death in this case was updated after the database lock to treatment-related), immune-mediated bronchitis, lower gastrointestinal hemorrhage, the hemophagocytic syndrome, sudden death, liver toxic effects, and lung infection.

‡ There were four treatment-related deaths in the sunitinib group: two due to cardiac arrest and one each due to heart failure and multiple organ failure.

Cancer Drugs Hit Market at Ever-Higher Prices

U.S. prices for new cancer drugs have soared since the 1970s despite an increasing number of available brands.

Median monthly cost for new cancer drugs during the five-year period



Number of new drugs introduced	5	3	6	14	30	18	21	33

Note: Costs are monthly Medicare prices for each drug the year it was introduced, adjusted for inflation.

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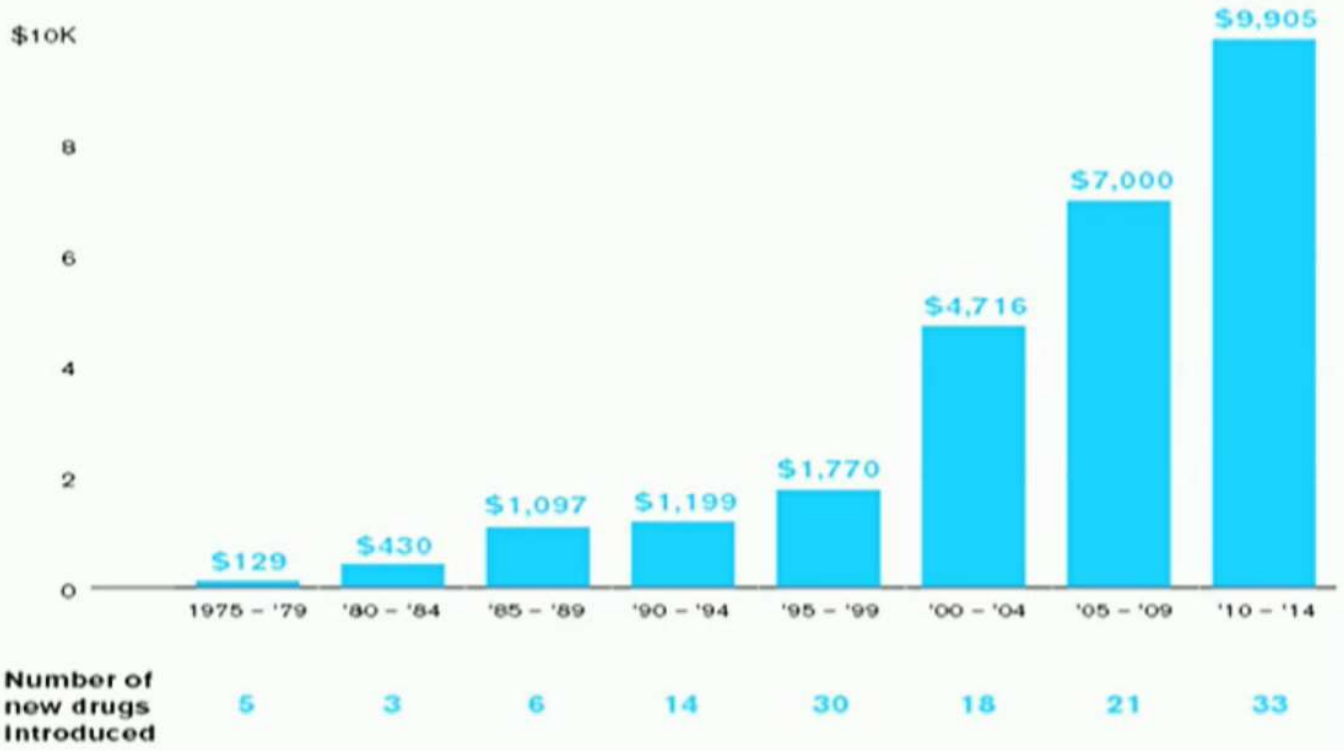

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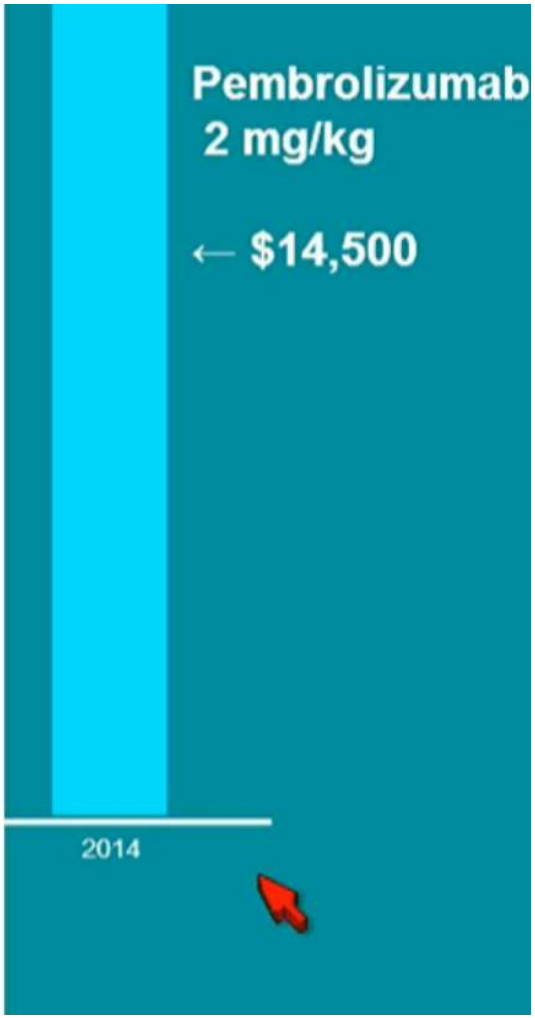


Pembrolizumab AWP
(Redbook online): $51.792 / mg

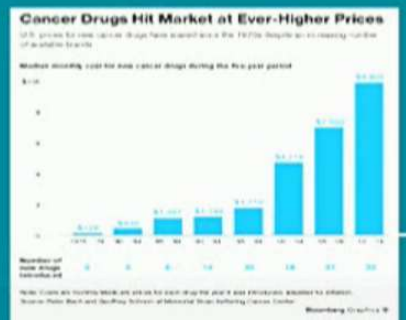
$51.792 x 10 mg/kg x 75 kg x 26 doses/year =

$1,009,944 per patient / per year

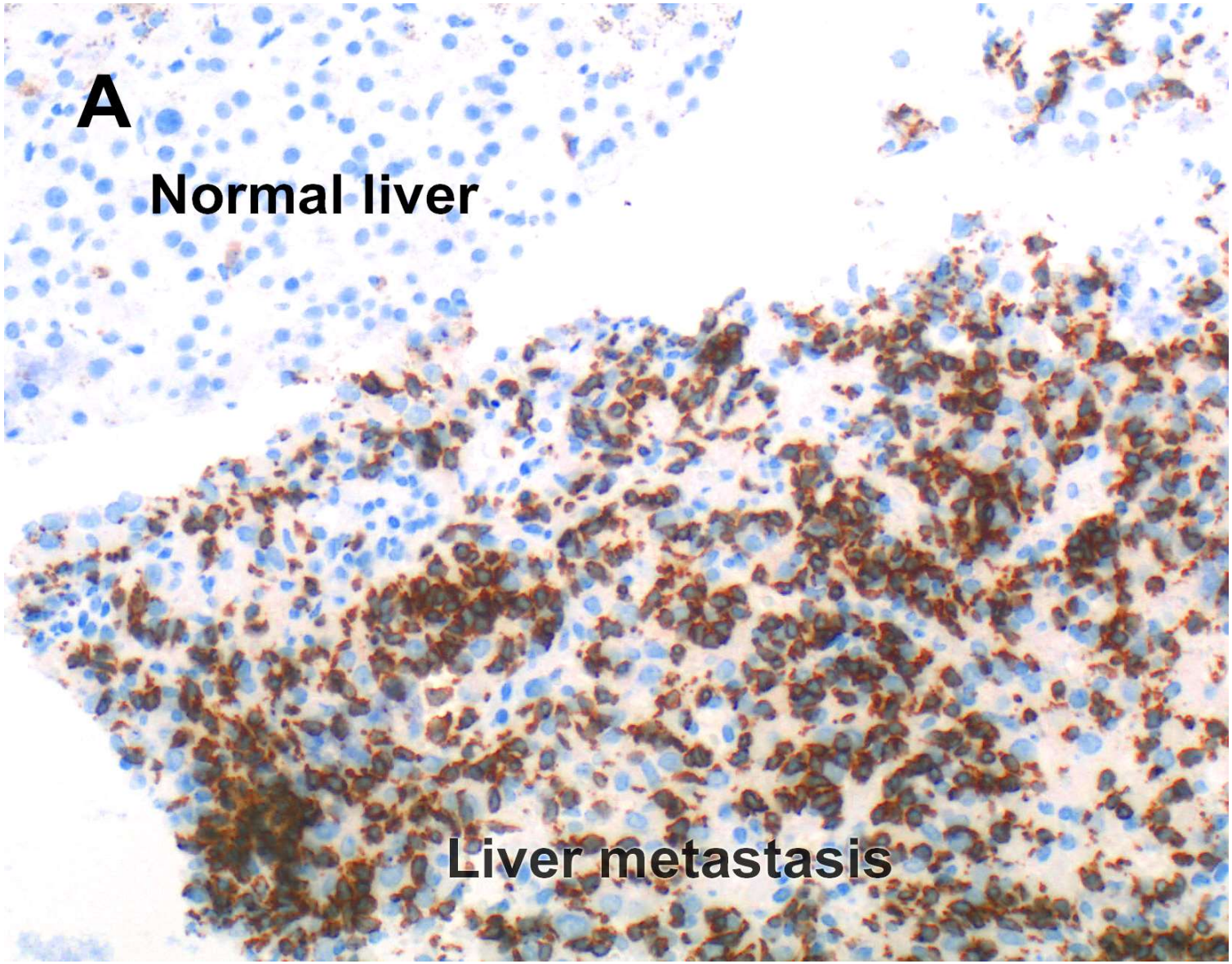
Selection of 2015 ASCO abstracts
using Pem 10 mg/kg q 2 wks:

abstract # 4010 (esophageal ca)
abstract # 5510 (ovarian ca)
abstract # 7502 (Small cell Lung ca)
abstract # 8035 (non-small cell lung ca)
abstract # 9040 (melanoma)

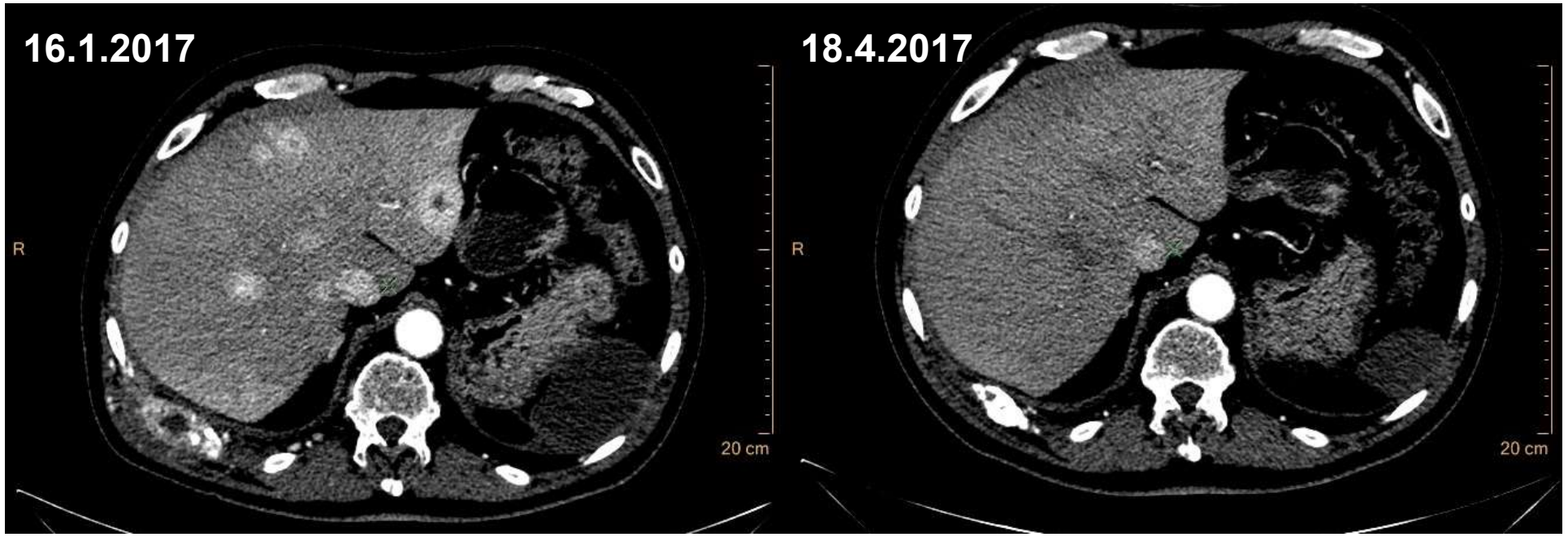
←Pembrolizumab 10 mg/kg
q 2 weeks
$83,500/month

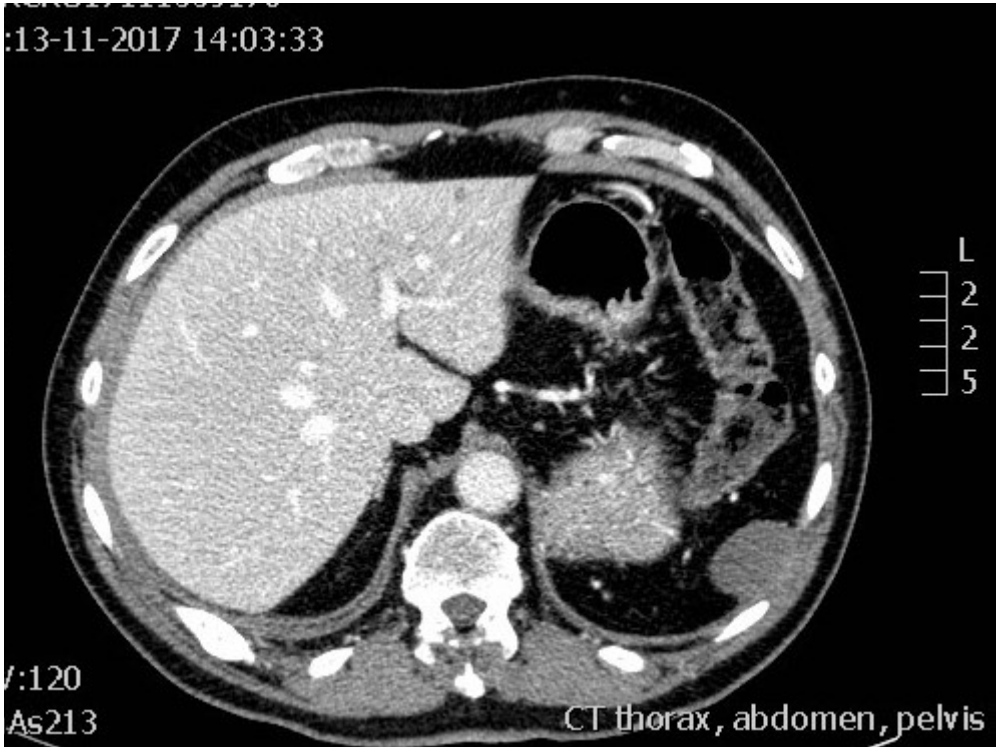


←Pembrolizumab 2 mg/kg
q 2 weeks
$16,700/month



Donskov F, Cancer Immunol Immunotherapy 2004


16.1.2017
R
20 cm
18.4.2017
R
20 cm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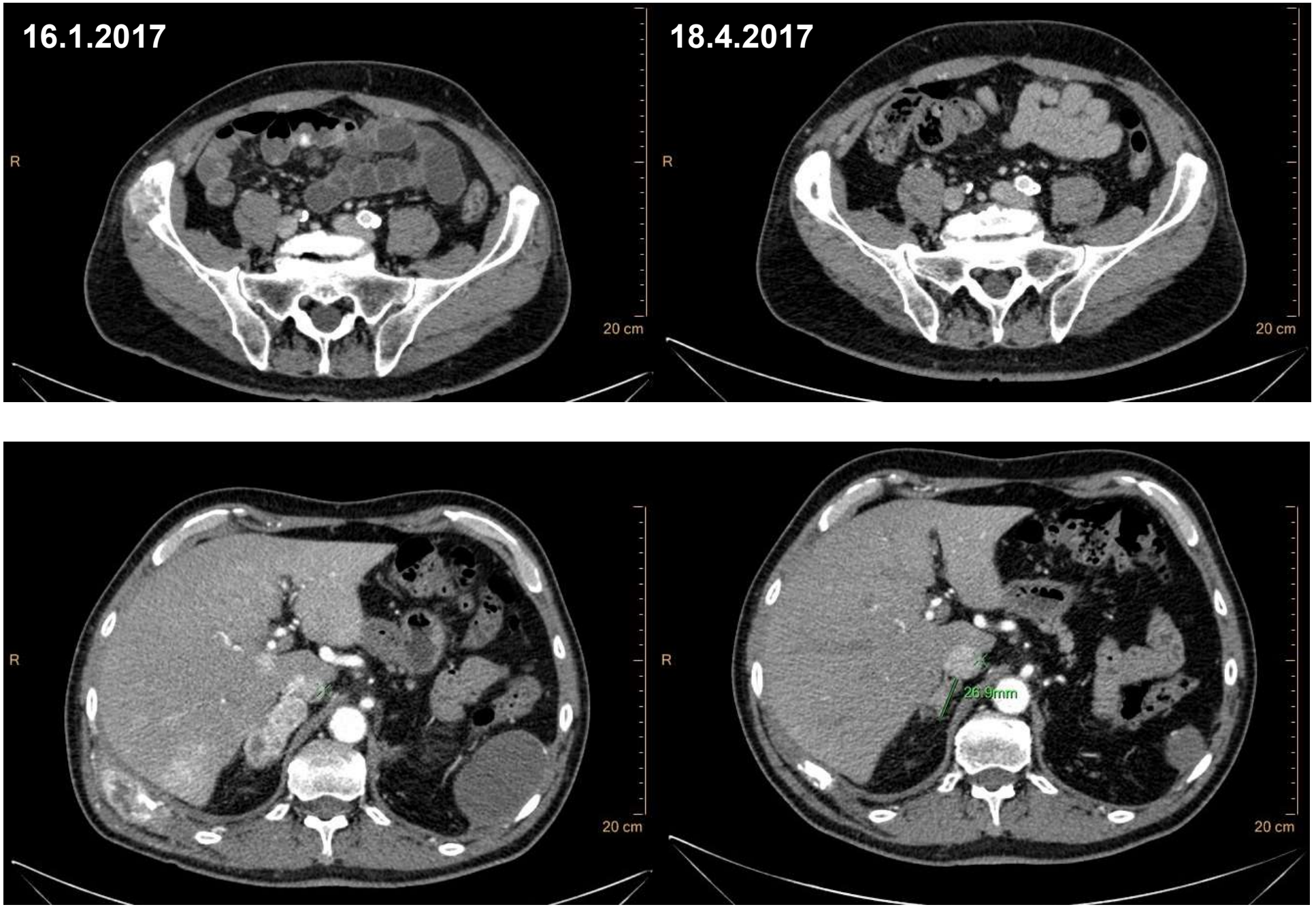
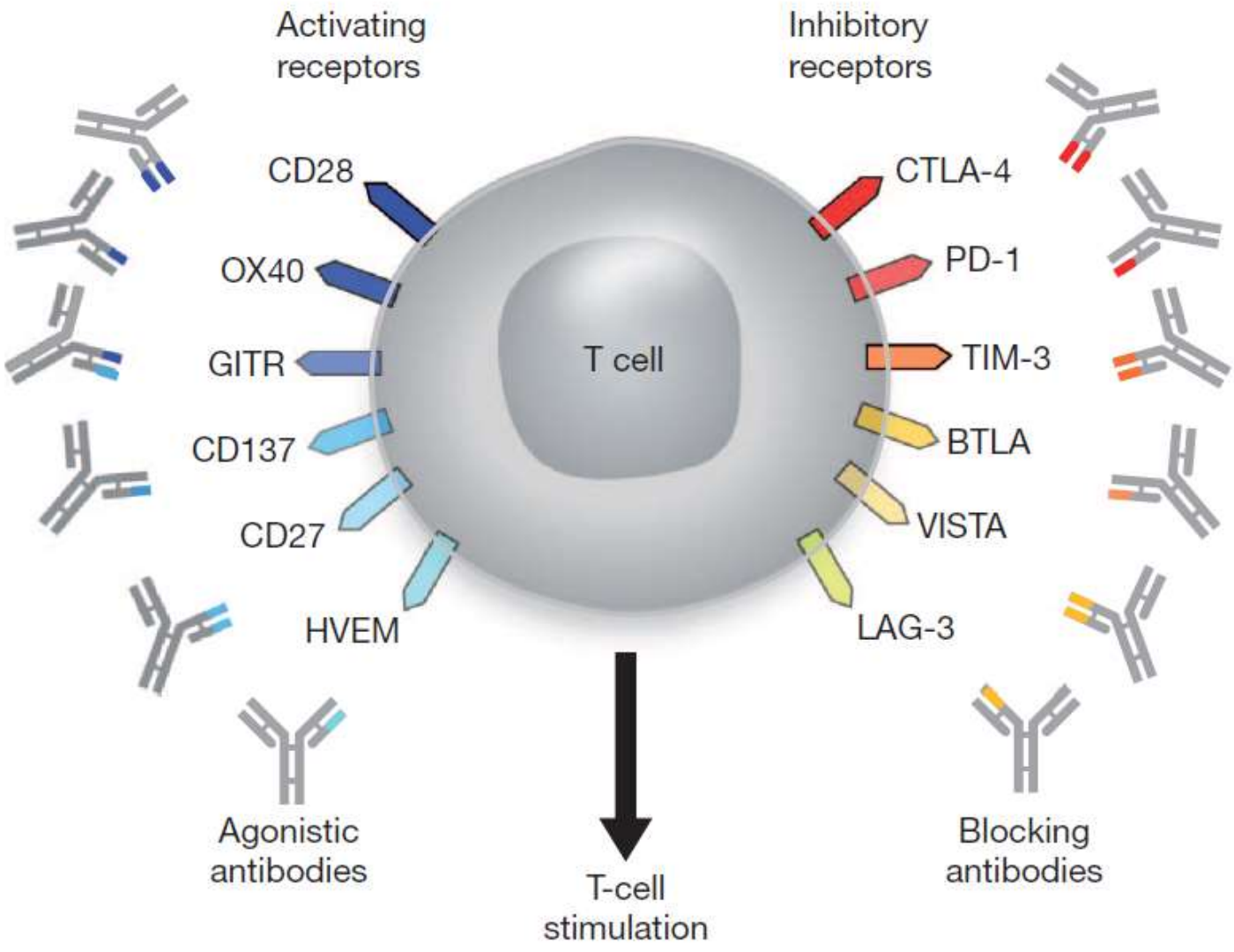
L
2
2
5
:120
As213
CT thorax, abdomen, pelvis


16.1.2017
R
20 cm
18.4.2017
R
20 cm
R
20 cm
R
26.9mm
20 cm

PD1/PDL-1 is just the beginning



Konklusioner

- **Flere & bedre behandlingsmuligheder for mRCC**
- **Alle pt med mRCC kan få behandling**
- **Fokus på forebyggelse**