-PATIENT CASES-

Medical Treatment of mRCC

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1st ESMO Asia 2015
COI Disclosure

First author: Yoshihiko TOMITA

Grant: Astra-Zeneca, Astellas, Takeda Pharm.

Honorarium: Pfizer

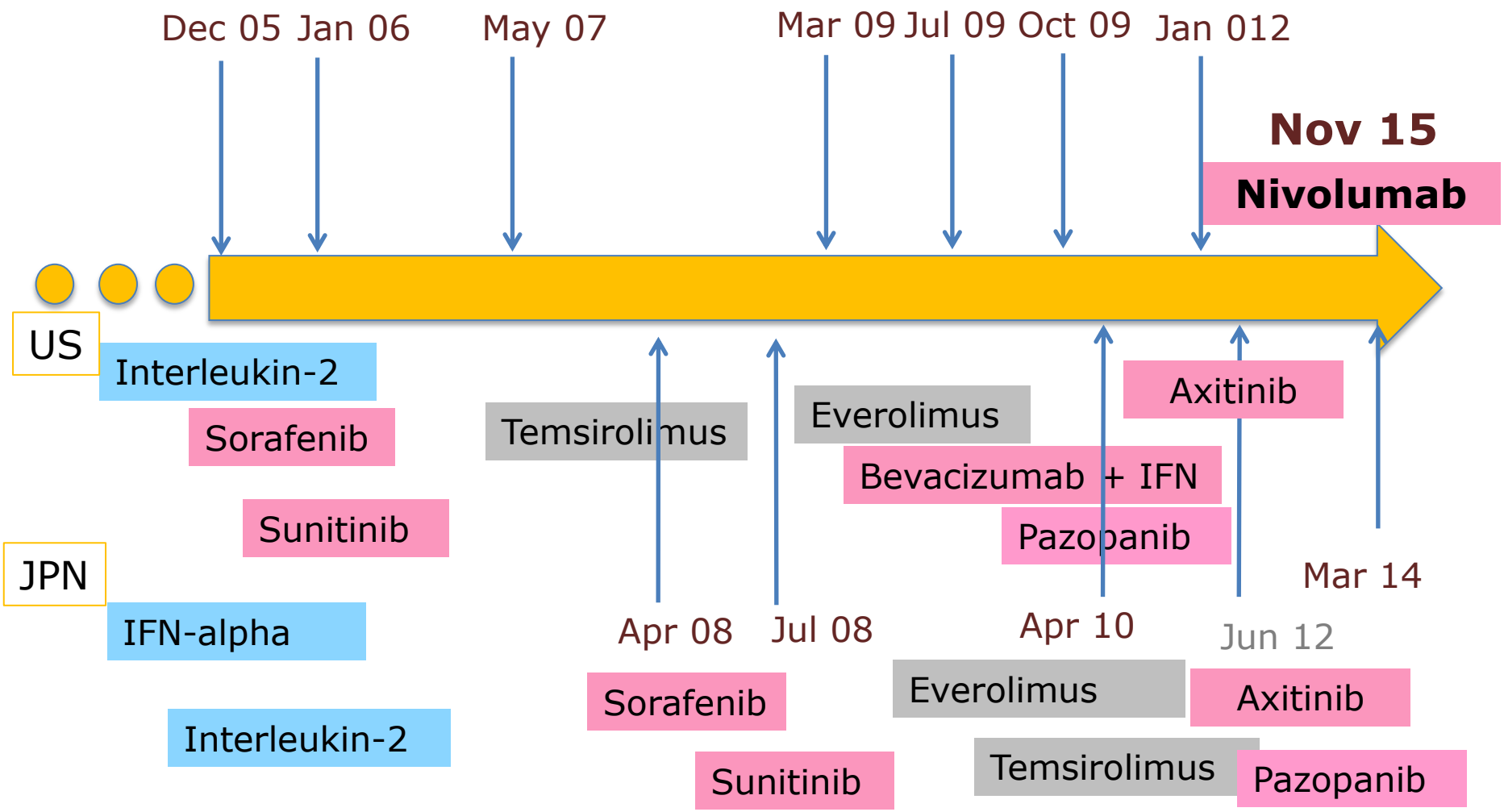
Global clinical trials GU cancer –JAPAN-

1.	RAD001	everolimus	mTOR阻害薬	10 countries
	180011	転移性腎細胞癌	第Ⅲ相	
2.	CCI779	temsirolimus	mTOR阻害薬	3
	190007	進行性腎細胞癌	第Ⅱ相	
3.	Pazopanib	pazopanib	非特異的チロシンキナーゼ阻害薬	14
	200007	転移性腎細胞癌	第Ⅲ相	
4.	Axitinib	axitinib(Ⅲ相)	VEGFR阻害薬	22
	210003	転移性腎細胞癌	第Ⅲ相	
6.	Axitinib	axitinib(Ⅱ相) 1st line	VEGFRチロシンキナーゼ阻害薬	7
	220003	転移性腎細胞癌	第Ⅱ相	
7.	RAD001	everolimus	mTOR阻害薬	11
	220006	腎細胞癌	第Ⅲ相	
8.	Pazopanib	pazopanib術後補助療法	非特異的チロシンキナーゼ阻害薬	25
	220010	腎細胞癌	第Ⅲ相	
9.	TKI258	dovitinib	VEGFRおよびFGFR,VEGFR,PDGFR阻害薬	27
	230008	腎細胞癌	第Ⅲ相	
10.	TAK-700	Orteronel(化学療法施行前)	アンドロゲン産生抑制薬	41
	230011	前立腺癌	第Ⅲ相	
11.	TAK-700	Orteronel癌(化学療法施行中・後)	アンドロゲン産生抑制薬	41
	230011	前立腺癌	第Ⅲ相	
12.	Axitinib	axitinib(Ⅲ相)術後補助療法	VEGFR阻害薬	6
	240001	転移性腎細胞癌	第Ⅲ相	
13.	ONO-4538	Nivolumab	完全ヒト型抗PD-1抗体	24
	240014	進行性又は転移性腎細胞癌	第Ⅲ相	

Ongoing Clinical Trials in Niigata Univ. Hospital

contract	company	Target	compound		Dupty	PI	Uniq. code	
April	ONO/BMS	mRCC	ONO-4538/BMS-734016	nivolumab＋ipilimumab	Yamana	Tomita	CH27-002	抗PD-1抗体＋抗CTLA-4抗体
April	MSD	UC	MK-3475	pembrolizumab	Maru	Tomita	CH27-003	抗PD-1抗体
June	Jansen	Prostate Ca	ARN-509（JNJ-56021927）			Kasahara	CH27-004	
June	Lilly	UC	LY3009806	ramucirumab	Takizawa	Tomita	CH27-005	抗VEGFR2抗体
July	ONO/BMS	UC	ONO-4538	nivolumab	Yamana	Tomita	CH27-006	抗PD-1抗体
Aug	Chugai/Rosh	mRCC	MPDL3280A (RO4876646)	atezolizumab	Anraku	Tomita	CH27-009	抗PD-L1抗体
Aug	ファイザー株式会社 Pfizer	mRCC	MSB0010718	avelumab	Tasaki	Tomita	CH27-010	抗PD-L1抗体

RCC Systemic therapy Timeline



In Clinical Practice

Q. Which is most appropriate drug to THE patient?

Balance of benefit and morbidity

Benefit

- ✓ Cure
- ✓ Longer survival with good PS

Morbidity

- ✓ Time
- ✓ Expense
- ✓ AEs
  - ✓ …sometimes too tough or even lethal.

Evidence based treatment

Pivotal trials building the evidence

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Summary of Trials to mRCC

Drug	Setting	Prev. Tx	Control	Results
sorafenib	**2nd line**	cytokine	placebo	positive
sorafenib	1st line	-	IFN-α	negative
sunitinib	**1st line**	-	IFN-α	positive
temsirolimus	**1st line**	-	IFN-α、IFN-α+temsirolimus	positive
temsirolimus	2nd line	sunitinib	sorafenib	negative
everolimus	**2nd line+**	sunitinib、sorafenib	placebo	positive
pazopanib	**1st line**	-	sunitinib	positive
axitinib	**2nd line**	sunitinib	sorafenib	positive
tivozanib	1st line	-	sorafenib	negative
dovitinib	3rd line	sunitinib、everolimus	sorafenib	negative
nivolumab	**2nd line**	sunitinib etc.	everolimus	positive
cabozantinib	**2nd line**	sunitinib etc.	everolimus	positive

First-, second-, third-line therapy for metastatic renal cell carcinoma (mRCC): benchmarks for trials design from the International mRCC Database Consortium (IMDC)

Heng DYC[1], Rini BI[2], Lee J[3], Kroeger N[1], Srinivas S[4], Harshman LC[4], Knox JJ[5], Bjarnason GA[6], MacKenzie M[7], Wood L[8], Vaishampayan UN[9], Agarwal N[10], Pal SK[11], Tan MH[12], Rha SY[13], Yuasa T[14], Donskov F[15], Bamias A[16], North S[17], and Choueiri TK[18] for the International mRCC Database Consortium

1: Tom Baker Cancer Centre, University of Calgary, Calgary, AB; 2: Cleveland Clinic Taussig Cancer Center, Cleveland, OH; 3: Asan Medical Center, Seoul, South Korea; 4: Stanford Cancer Center, Stanford, CA; 5: Princess Margaret Hospital, Toronto, Ontario; 6: Sunnybrook Odette Cancer Centre, Toronto, ON; 7: London Health Sciences Center, London ON; 8: Queen Elizabeth II Health Sciences Centre, Halifax, NS, 9: Karmanos Cancer Institute, Detroit MI; 10: Huntsman Cancer Institute, Salt Lake City, UT; 11: City of Hope Comprehensive Cancer Center; 12: National Cancer Center, Singapore; 13: Yonsei Medical University, Seoul, South Korea; 14: Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; 15: Aarhus University Hospital; Aarhus, Denmark; 16: University of Athens, Athens, Greece; 17: Cross Cancer Institute, Edmonton, AB; 18: Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

RESULTS

- Out of 2705 total patients,
  - 57% of patients received only first line therapy (n=1533)
    - Median OS from initial targeted therapy: 14.9 months
  - 27% of patients received only 2 lines of therapy (n=734)
    - Median OS from initial targeted therapy: 21.0 months
  - 16% of patients received 3 or more lines of therapy (n=438)
    - Median OS from initial targeted therapy: 39.2 months

- Or third lin tter OS 0001).

Choice of 1st line drug is imortant.

ASCO 2013: Heng, D. Y. C. et al.: 4586
Br J Cancer. 2014 Apr 15;110(8):1917-22

RCC treatment Algorithm ESMO 2014

Histology and setting	Risk group	Standard	Option
Clear-cell first line	Good or intermediate risk	Sunitinib	Cytokines (including high dose IL2)
		Bevacizumab + IFN	Sorafenib
		Pazopanib	
	Poor prognosis	Temsirolimus	Sunitinib Sorafenib
Clear-cell second line	Post-cytokines	Sorafenib Pazopanib Axitinib	Sunitinib
	Post-TKIs	Everolimus Axitinib	Sorafenib
Clear-cell third line	Post-2 TKIs	Everolimus	
Non-clear-cell histology			Temsirolimus Sunitinib Sorafenib

NCCN guide line 2016 ver. 1.0
1st line for stage IV disease

- **Sunitinib ★ category 1**
- **Temsirolimus ★ cat. 1 poor risk**
  cat. 2B selected other risk group
- **Bev. + IFN ★ cat. 1**
- **Pazopanib ★ cat. 1**
- High dose IL-2 cat. 2A selected
  pts. With good PS
- Axitinib cat. 2A
- Sorafenib cat. 2A selected pts.

Benefit

- ✓ Cure
- ✓ Longer survival with good PS

Recent experience of High dose IL-2 therapy 'SELECT' trial

Characteristics	$n = 120$
Median age, y (range)	56 (28–70)
ECOG performance status[a] 0/1, %	72/24[b]
Prior nephrectomy, %	99
MSKCC risk factors, n (%)	
0 (favorable)	23 (19)
1–2 (intermediate)	84 (70)
≥3 (poor)	13 (11)

Clear Cell Histology 96%

Clin Cancer Res; 21(3); 561–8 2015.

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CR experienced approx. 5% of pts.

Table 2. Clinical activity of HD IL2

Objective response[a]	***N*** **(%)**	
Patients with measurable disease (*n*)	120 (100)	
Assessment	Independent	Investigator
ORR	30 (25.0; 95% CI, 17.5–[illegible]%)	34 (28.3; 95% CI, 20.5–[illegible]%)
CR	3 (2.5)	9 (7.5)
PR	27 (22.5)	25 (20.8)
SD (>6 mo)	9 (7.5)	9 (7.5)

Clin Cancer Res; 21(3); 561–8 2015.

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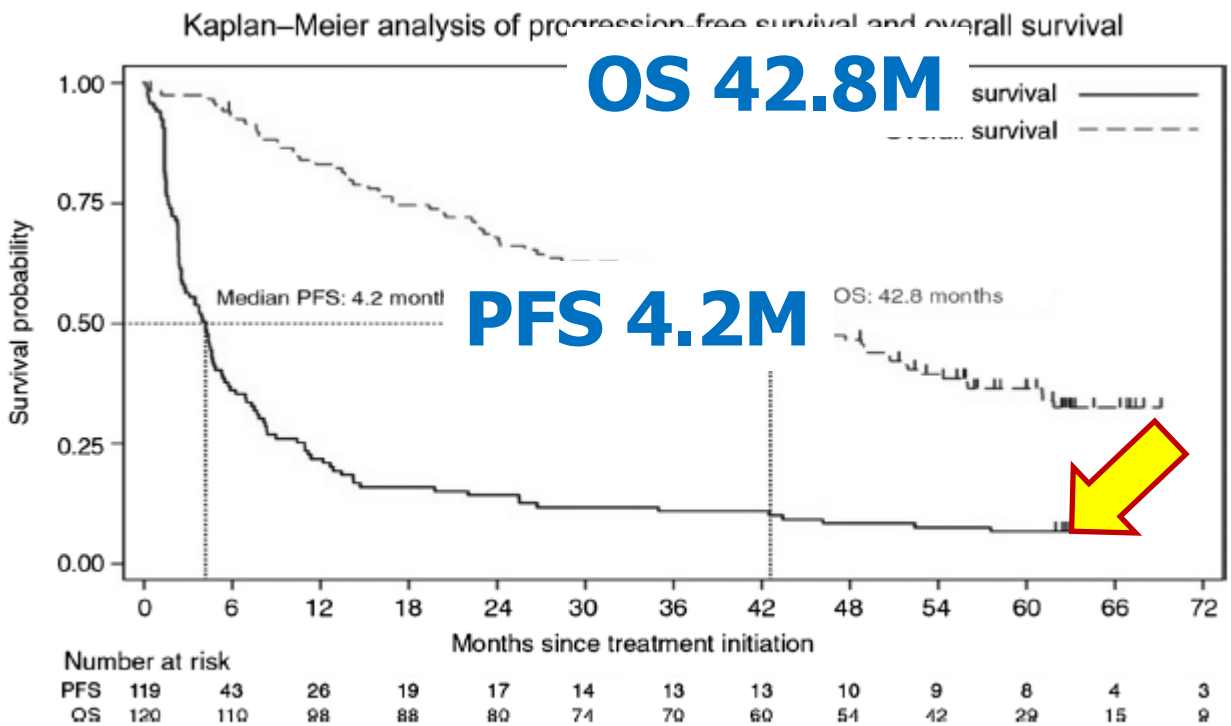
Approximate 10% pts. did not show progression at 60 months after Tx



Clin Cancer Res; 21(3); 561–8 2015.

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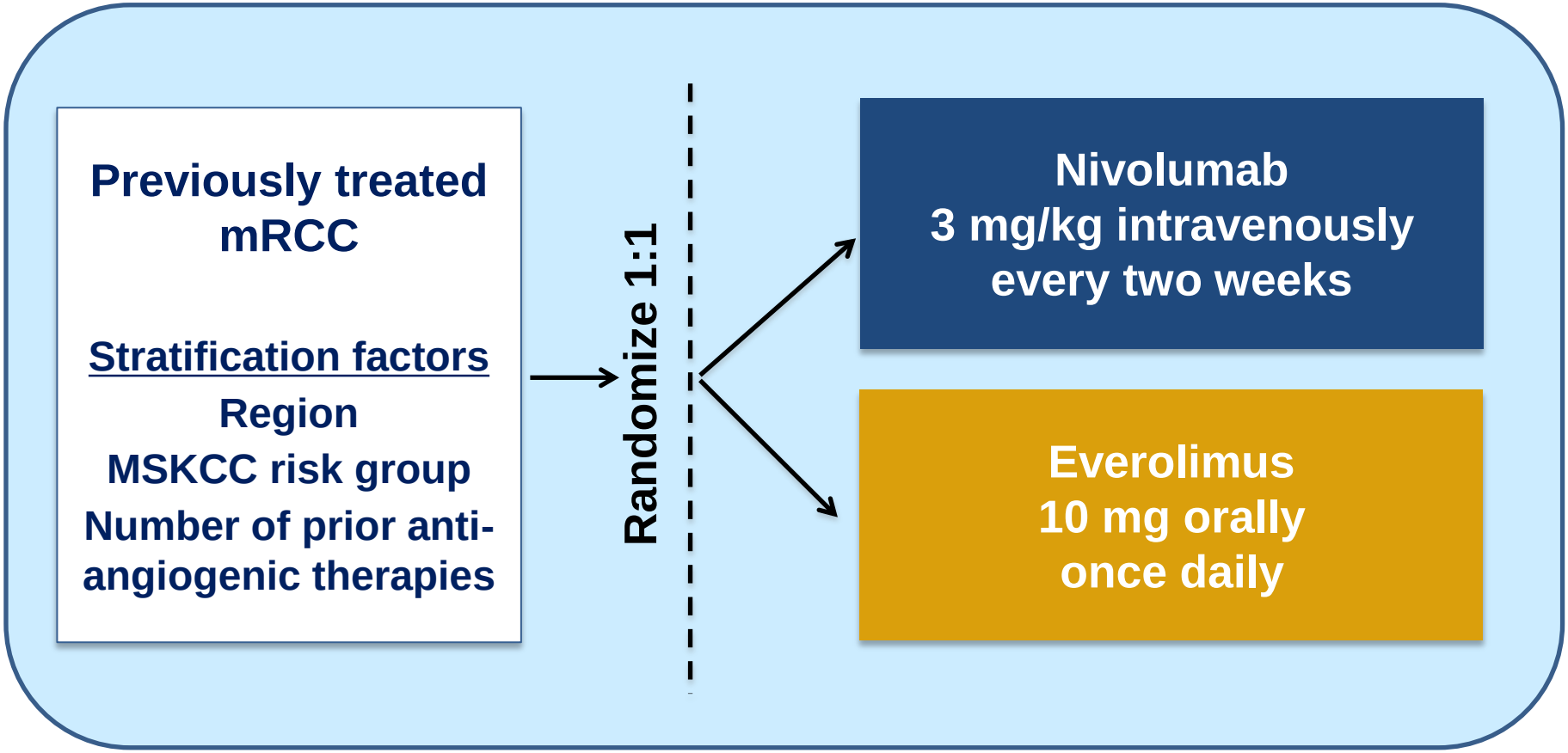
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

Study design



- Patients were treated until progression or intolerable toxicity occurred
- Treatment beyond progression was permitted if drug was tolerated and clinical benefit was noted

MSKCC, Memorial Sloan-Kettering Cancer Center.

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	24	55
Progr		
Not e		
Median months		1.2)
Median months (range)		2.2)
Ongoing response, n/N (%)	49/103 (48)	10/22 (45)

Imm. Check point inhibitor may not give durable CR like IL-2 therapy.

*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.

Benefit

✓ Cure

✓ Long[illegible]ival with [illegible]d PS

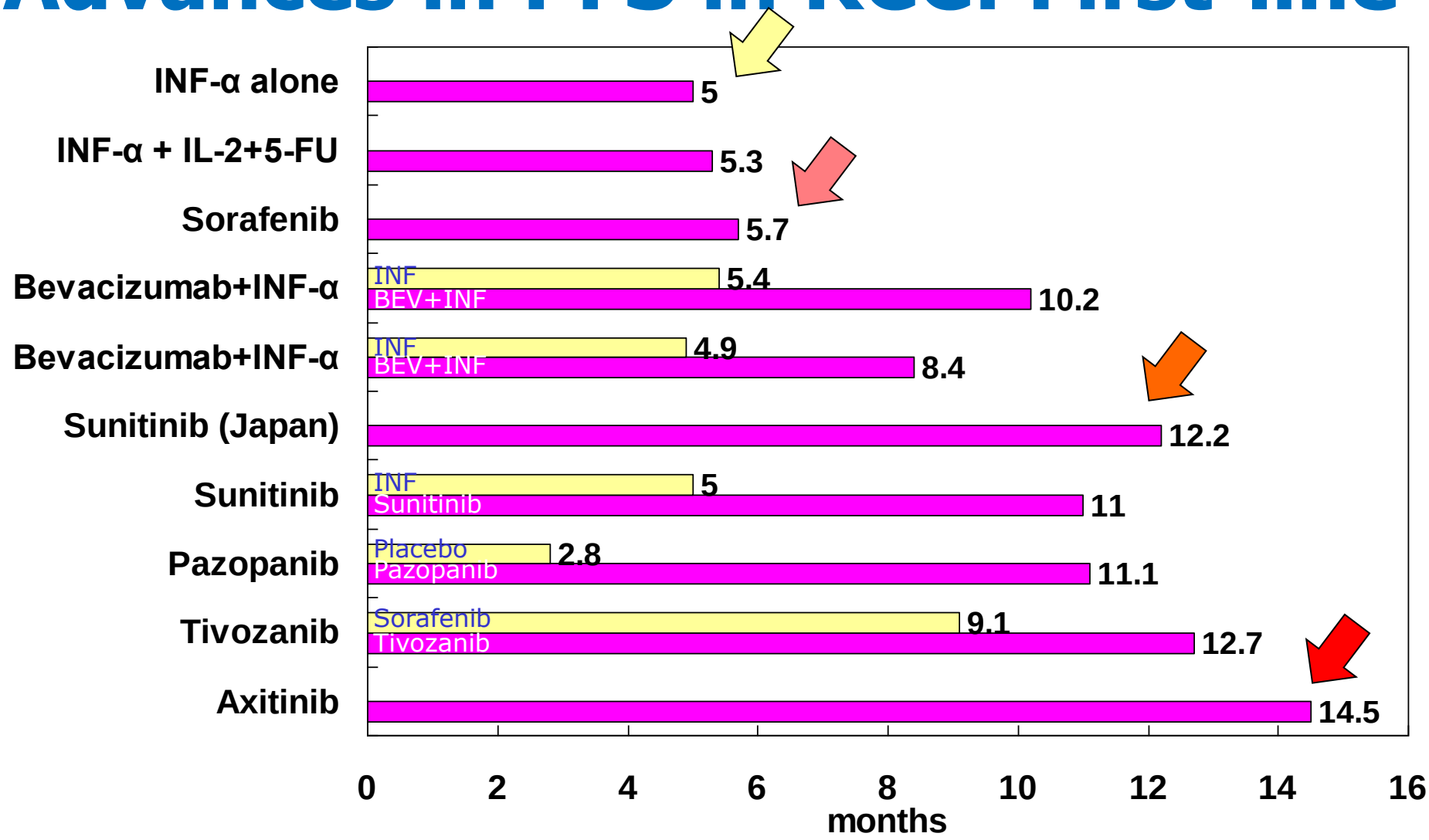
But, durable CR might be still harboring IL-2.

Needs IO+IO, or T drug combination?

Benefit

- ✓ Cure
- ✓ **Longer survival with good PS**

Advances in PFS in RCC: First-line

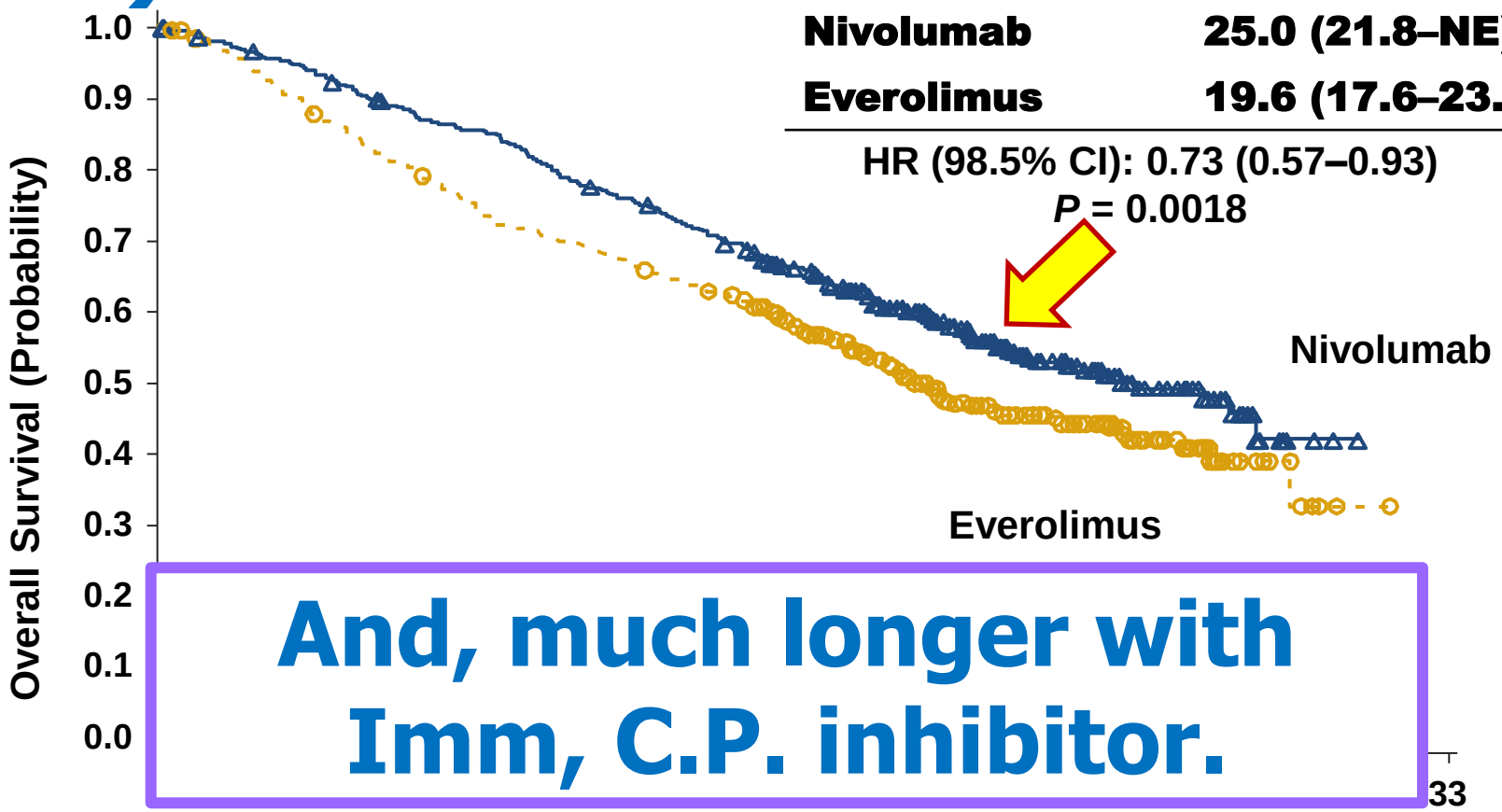


1. Kane et al. *Clin Cancer Res*. 2006;12:7271. 2. Gore et al. ASCO; 2008. Abstract 5039. 3. Nexavar PI 4. Escudier ASCO; 2008. Abstract 5025. 5. Rini et al. ASCO; 2009. Abstract LBA5019. 6. Tomita JJCO 2010. 7. Motzer. JCO. 2009 8. Sternberg et al. ASCO; 2009. Abstract 5021. 9. Motzer, ASCO 2012 10. Rini, ASCO 2012

Survival benefit from nivolumab (OS)

Median OS, months (95% CI)	
Nivolumab	**25.0 (21.8–NE)**
Everolimus	**19.6 (17.6–23.1)**

HR (98.5% CI): 0.73 (0.57–0.93)
P = 0.0018



And, much longer with Imm, C.P. inhibitor.

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.

Benefit

- ✓ Cure
- ✓ Longer survival with good PS

Yes, we have longer survival with targeted drugs!

And, much longer with Imm, C.P. inhibitor.

Morbidity

- ✓ Time
- ✓ Expense
- ✓ AEs
  - ✓ …sometimes too tough or even lethal.

Co-morbidity of pts. taken into consideration

	Renal	Liver	Pulmonary	Heart	DM	Infection	Hemato-logical	GI	general
Sunitinib	✔			✔			✔		(✔)
Pazopa									
Temsirolimus		(✔)	✔		(✔)	✔			

Choose the drug to avoid higher grade AEs!

Further consideration

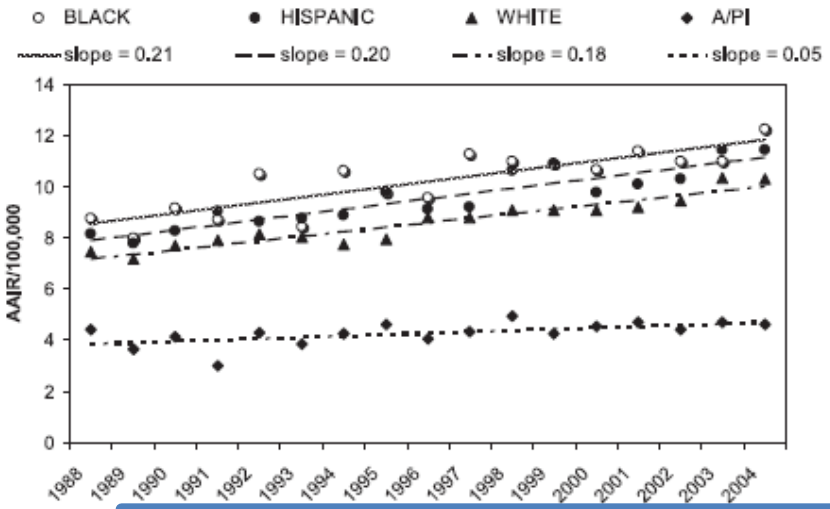
- ✓ Patints
  - ✓ Financial status
  - ✓ Family

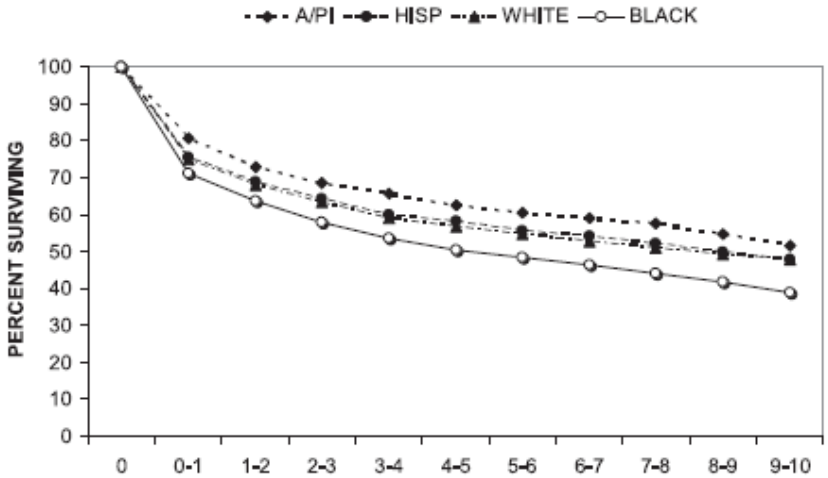
Racial difference?

- ✓ Tumor character

Racial disparities in RCC Incidence & Survival

- Data from the California Cancer Registry shows a lower incidence **and higher survival rate among Asians / Pacific Islanders in RCC** compared to whites, blacks, and Hispanics (cytokine era).





Racial difference to cytokine therapy?

Stafford H et al. *J Urol.* 2008;179:1704

OS in cytokine era
Japan vs. US

Yamagata Univ.
Dept. Urology

Prognosis mRCC (Motzer, JCO., 2003)

- IFN-alpha as a first line treatment. 463pts
  - over all response rate 11%
  - ***3-year survival 19%***
- multi-modality treatment

  over 21-year period 670pts.
  - survivor grater than ***5 year*** 30/670pts. ***4%***
  - disease free 12/670pts.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

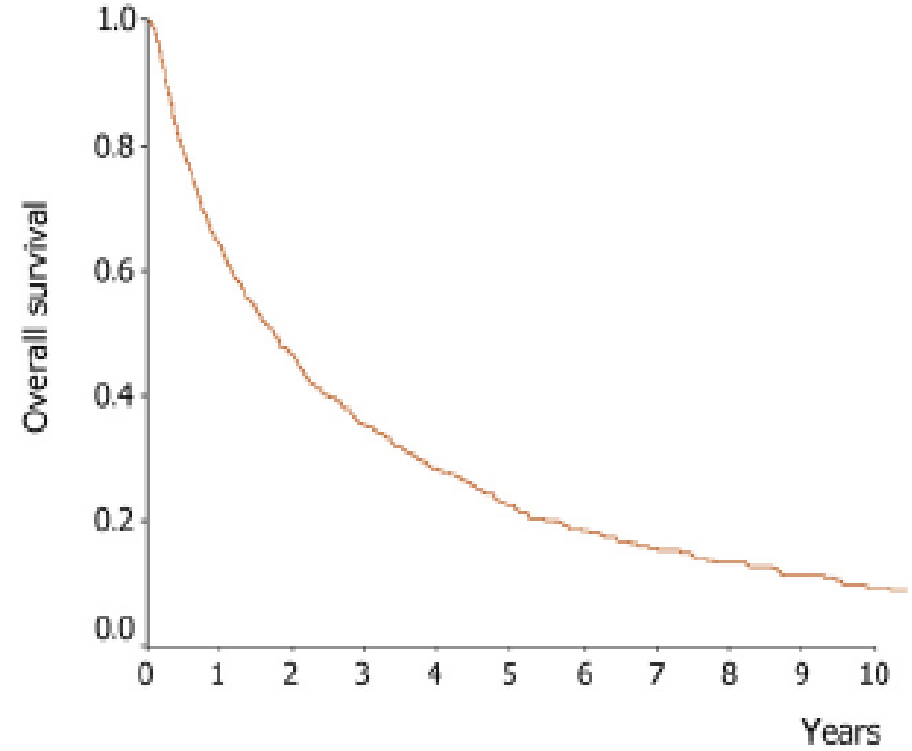
European Association of Urology

Kidney Cancer

Prognosis of Japanese Metastatic Renal Cell Carcinoma Patients in the Cytokine Era: A Cooperative Group Report of 1463 Patients

Sei Naito[a], Naoki Yamamoto[b], Tatsuya Takayama[c], Masatoshi Muramoto[d], Nobuo Shinohara[e], Kenryu Nishiyama[f], Atsushi Takahashi[g], Ryo Maruyama[h], Takashi Saika[i], Senji Hoshi[j], Kazuhiro Nagao[k], Shingo Yamamoto[l], Issei Sugimura[m], Hirotsugu Uemura[n], Shigehiko Koga[o], Masayuki Takahashi[p], Fumio Ito[q], Seiichiro Ozono[c], Toshiro Terachi[r], Seiji Naito[s], Yoshihiko Tomita[a,*]

Overall survival



Events	Number of patients at risk										
1029	1463	840	543	362	244	165	108	81	59	41	24

Median Survival 642 ± 33days

（Motzer 306days）

JPN vs US

	JPN		USA
• 1 yr survival	65%	VS	30%
• 3			%
• 5			%

So many difference of background.
But racial difference of response to cytokine can not be denied.

Further consideration

- ✓ Patints
  - ✓ Financial status
  - ✓ Family

- ✓ Tumor character

Speed of Progression

Character of mRCC pts. with long (>5yrs) NED period after radical Nx

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Late (>5yrs NED) & Early Recurrence out of 657 pts. (1981-2008, cytokine era)

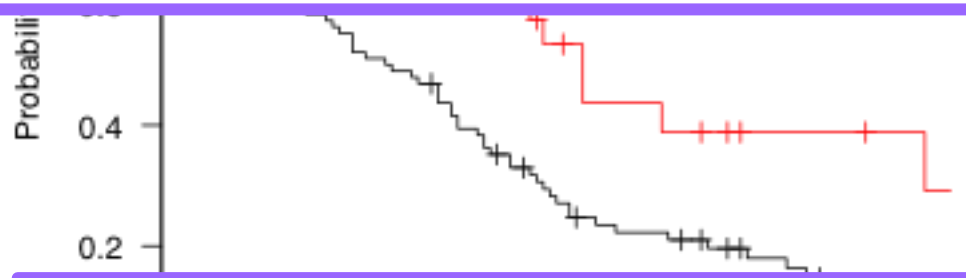
	Early recurrence	Late recurrence
Number of recurrence	96/647 (14.6%)	41 /657 (6.2%) 5-10y 24 (3.6%) >10y 17 (2.6%)
Time to recurrence [month], median (range)	17 (1-57)	101 (63-254)

Kobayashi K et. al., Int. J Urol., in press

OS after recurrence

Over than 5yrs. Survival can be expected in pts. of late recurrence.

	Median OS [months]	5y-OS
	34.5	27.1%
	64.0	53.4%
	P=0.008	



Targeted therapy for >10Yrs ?

Number at risk

0	96	58	45	24	16	9	7
1	41	34	23	13	8	5	3

Kobayashi K et. al., Int. J Urol., in press

Drug therapy

+surgery

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A Real Case

Representative of series of patients -Cytokine plus surgery to ‘surgical CR’-

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68 year old man

- Jun. 2003 p/o lung deposits in screening chest X-ray.
- CT others, >T3aN0M1 lt. RCC.
- Sep. 2003 laparoscopic lt. radical Nx

  pT3aNxM1, clear cell carcinoma, G2, INF-beta, v(+).

Chest CT scan

Jun. 8, 2003

68 year old man

- Jun. 2003 p/o lung deposits in screening chest X-ray.
- CT others, >T3aN0M1 lt. RCC.
- Sep. 2003 laparoscopic lt. radical Nx (HALS)
  - pT3aNxM1, clear cell carcinoma, G2, INF-beta, v(+).
- IFN-alpha+ IL-2+Tegafur uracil (2 courses, every 8 weeks)

68 year old man

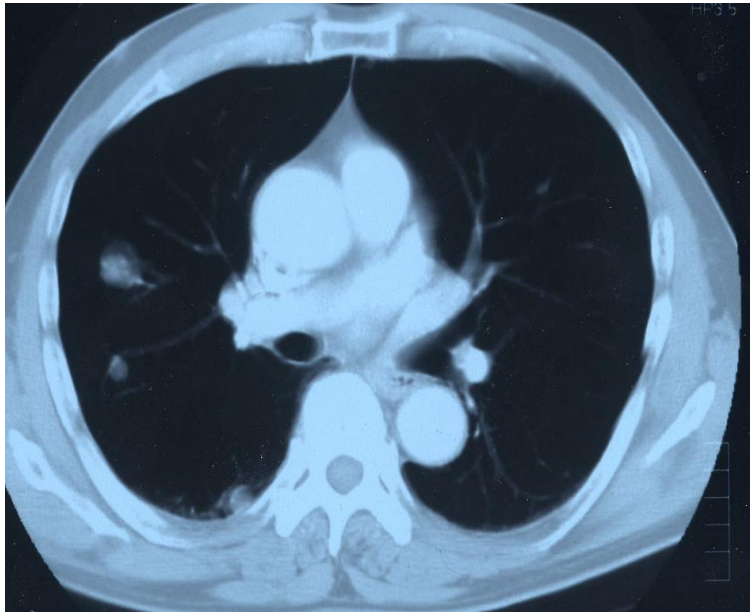
- Jun. 2003 p/o lung deposits in screening chest X-ray.
- CT others, >T3aN0M1 lt. RCC.
- Sep. 2003 laparoscopic lt. radical Nx (HALS)
  - pT3aNxM1, clear cell carcinoma, G2, INF-beta, v(+).
- IFN-alpha+ IL-2+Tegafur uracil (2 courses, every 8 weeks)
- **Progression of Disease at the end of 2 course of the cytokine therapy.**

Chest CT scan

Subjected to very low dose IL-2 maintenance Tx.

Jan. 8, 2004
16w

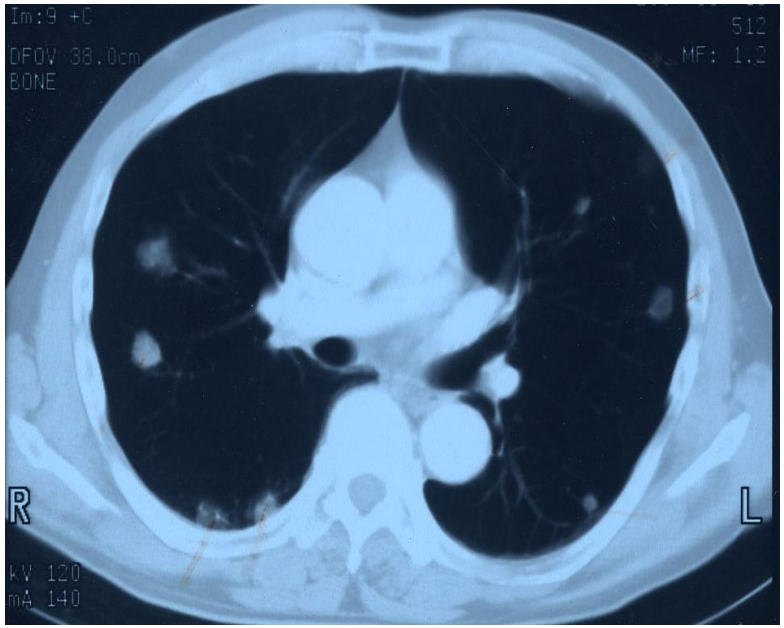
PD

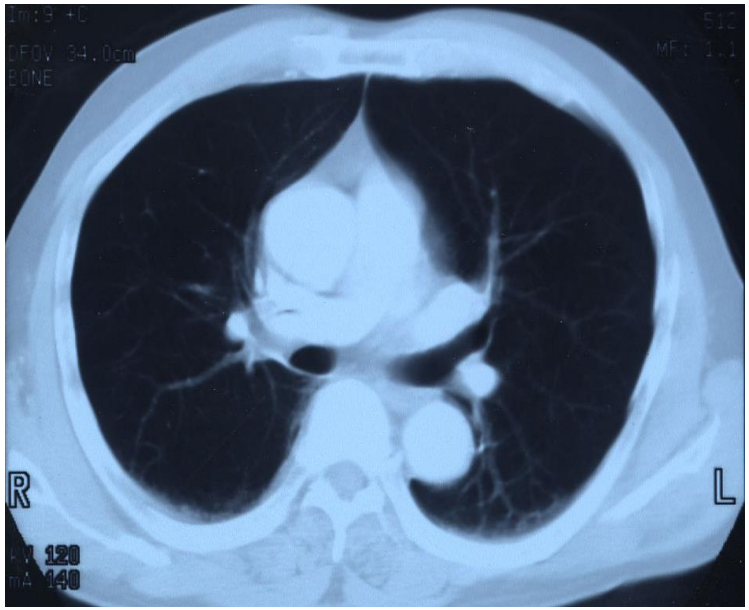


Apr. 6, 2004
40w

PD

Chest CT scan





Oct. 19, 2004
57w

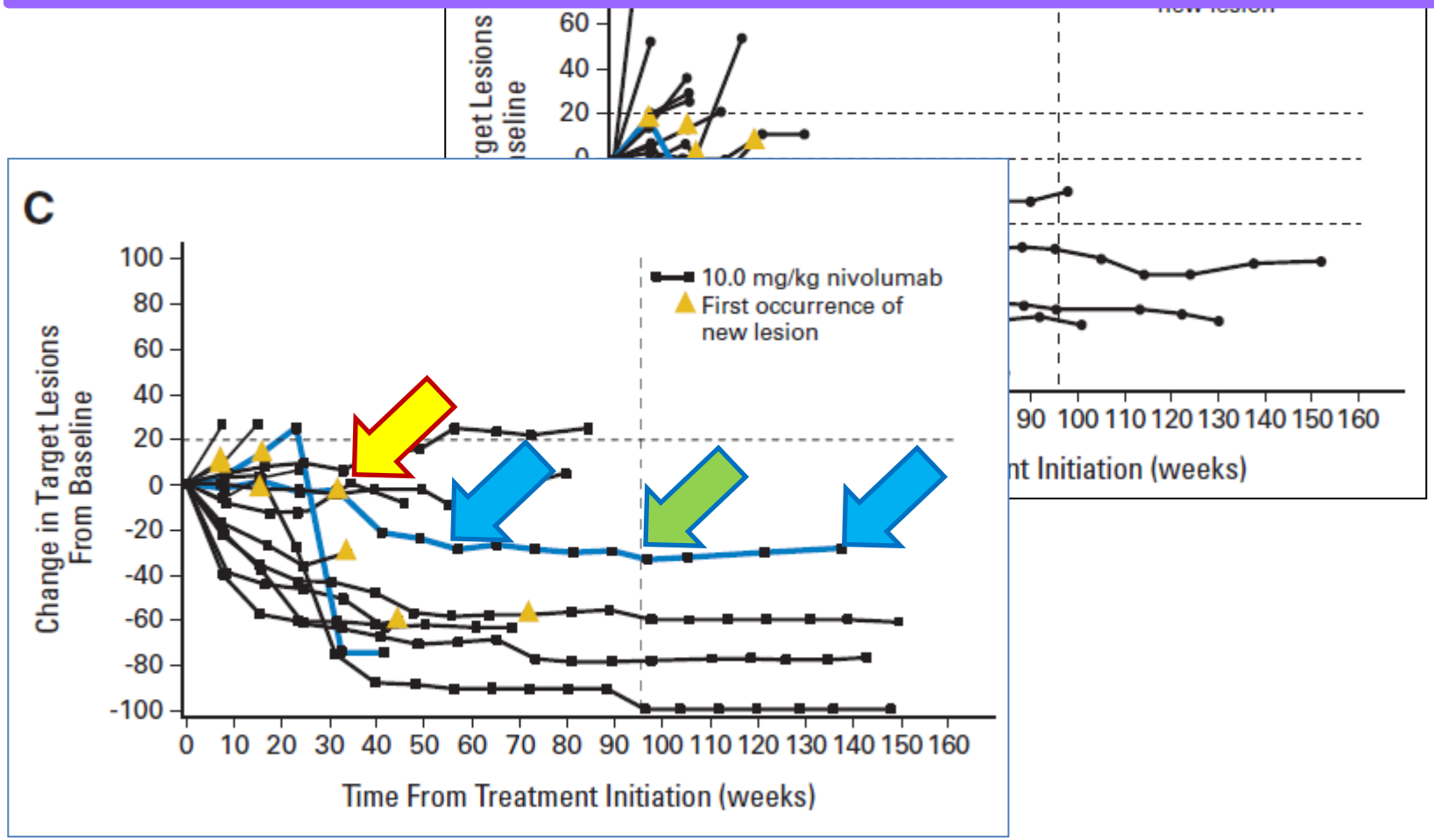
PD

Apr. 26, 2005
83w

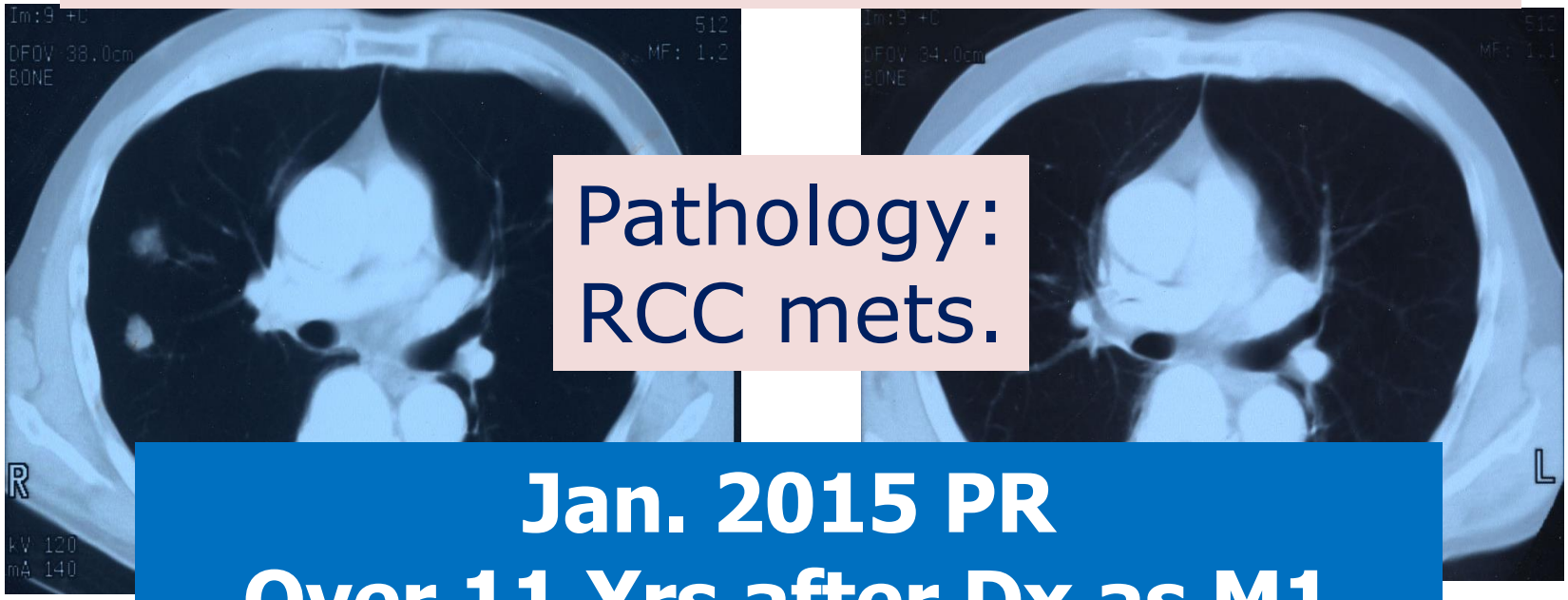
PR

Spider plot 1mg and 10mg/kg

Tumor flare, 'pseudoprogression'



He was subjected to
VATS.@Nov. 2014
for ONE growing lesion in lt. lung.



Pathology:
RCC mets.

Jan. 2015 PR
Over 11 Yrs after Dx as M1

Now On Maintenance Therapy

57w PD 83w PR

It’s kind of anecdote, but…

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Poor Predictive factor in IAT Tx
UMIN 00222 N=28

	Odds R	P value
Primary T≧3	21.50 （1.08-429.00）	**0.0444**
LDH≧230 U/l	5.43 （0.29-102.00）	0.2590
Ca≧9.0 mg/dl	2.37 （0.07－84.60）	0.6370
Sum of diameter ≧30mm	1.28 （0.09-18.20）	0.8580
P>=1	0.89 （0.01-71.20）	0.9570

Poor Predictive factor in IAT Tx

UMIN 00222 N=28

	Odds R	P value

HIGHLY selected mRCC pts.

- ✓ Lung mets. Only
- ✓ T1 or 2 primary
- ✓ Long NED after Nx
- ✓ Good PS

… still candidate for cytokine therapy at least in Japan

Poor Predictive factor in IAT Tx

UMIN 00222 N=28

	Odds R	P value

HIGHLY selected mRCC pts.

- ✓ Lung mets. Only
- ✓ T1 or 2 primary
- ✓ Long NED after Nx
- ✓ Good PS

… still candidate for cytokine therapy at least in Japan

2nd Line?

Abstract No. 20067

Phase III AXIS trial of axitinib vs sorafenib in patients with metastatic renal cell carcinoma: Asian subgroup analysis

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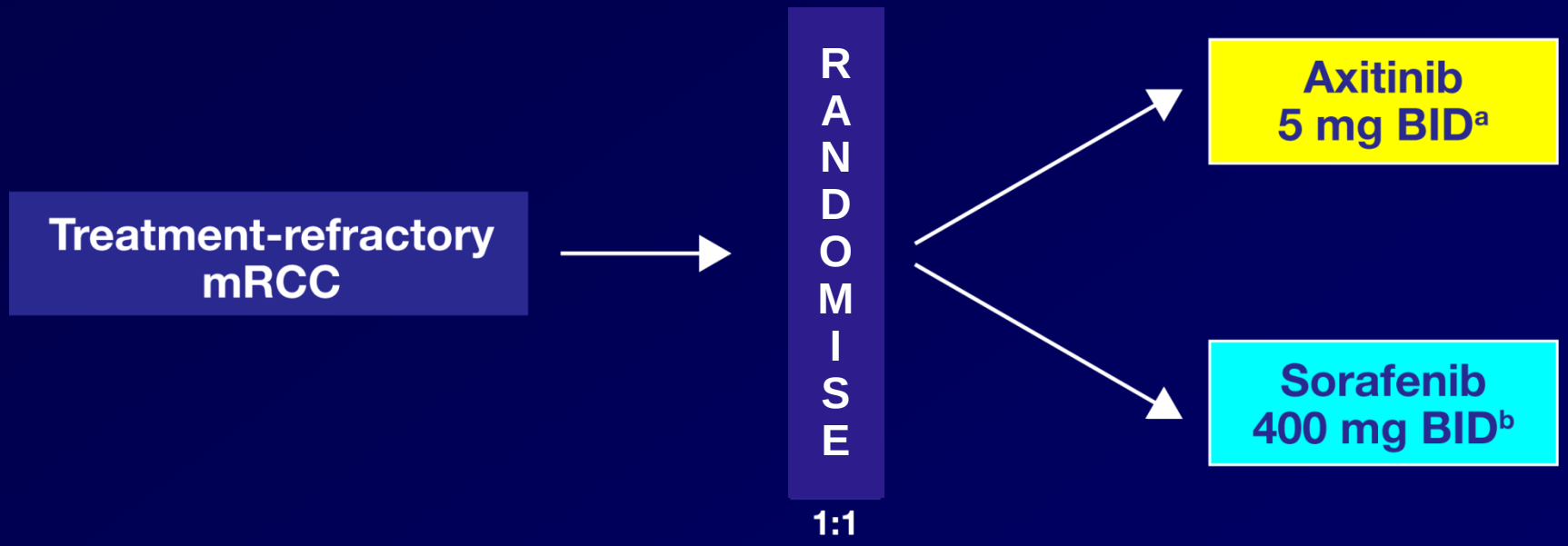
Study Design



Randomisation stratified by ECOG PS and type of prior treatment.

[a] Starting dose 5 mg BID, with option for stepwise dose increase to 7 mg BID and then 10 mg BID, or dose reduction, based on patient tolerability.
[b] Only dose reduction was permitted, if necessary.

Demographics of Asian Patients

	Axitinib n=77	Sorafenib n=81	Total n=158
Ethnicity, n			
Japanese	26	29	55
Chinese	28	23	51
Korean	11	16	27
Indian	11	13	24
Southeast Asian	1	0	1

PFS (IRC Assessment) by Prior Regimen

Prior Treatment Regimen	Asian		Non-Asian	
	Axitinib	Sorafenib	Axitinib	Sorafenib
Cytokines	n=43	n=42	n=83	n=83
mPFS, mo	12.1	6.4	12.0	6.6
HR (*P* value [a])	0.390 (0.0045)		0.523 (0.0020)	
Sunitinib	n=31	n=34	n=163	n=161
mPFS, mo	4.5	4.7	4.8	3.4
HR (*P* value [a])	0.775 (0.2057)		0.741 (0.0184)	

[a] One-sided log-rank test stratified by ECOG PS.

RCC treatment Algorithm ESMO 2014

Niigata JPN 2015

Histology and setting	Risk group	Standard	Option
Clear-cell first line	Good or intermediate risk	Sunitinib	Cytokines (including high dose IL2)
		~~Bevacizumab~~ + IFN	Sorafenib
	Cytokine Tx	Pazopanib	
	Poor prognosis	Temsirolimus	Sunitinib Sorafenib
Clear-cell second line	Post-cytokines	Sorafenib Pazopanib Axitinib	Sunitinib
	Post-TKIs	Everolimus **Nivolumab**	Sorafenib
Clear-cell third line	Post-2 TKIs	Everolimus	
Non-clear-cell histology			Temsirolimus Sunitinib Sorafenib

Conclusive remarks

- ✓ Take everything into consideration. Especially data of YOUR patients in YOUR country.
- ✓ Chose best drug and most suitable way of treatment to each patients.

FOR YOUR PATIENTS & THEIR FAMILY!

Back up

新潟大學
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NCCN guide line 2016 ver. 1.0
1st line for stage IV disease

- **Sunitinib ★ category 1**
- **Temsirolimus ★ cat. 1 poor risk**
  cat. 2B selected other risk group
- **Bev. + IFN ★ cat. 1**
-
-
-
- Sorafenib cat. 2A selected pts.

'NCCN International Programs – Asia Consensus Statement'
In progress