Carcinome rénal et nouvelles thérapies ~~Association canadienne~~ du cancer du rein

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Hématologue et oncologue médical

CHUM

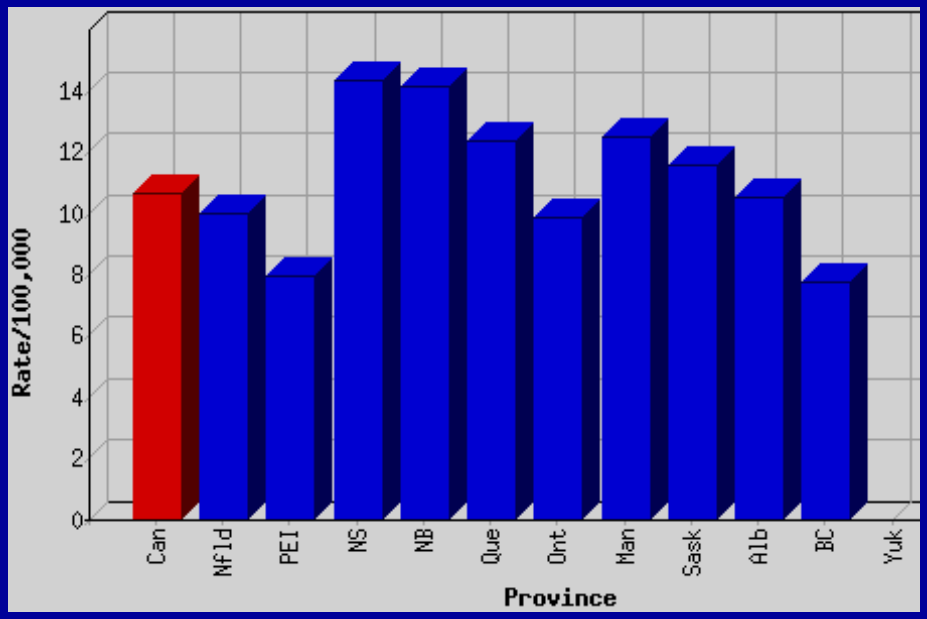
Objectifs:

- Données préalables
- Retour rapide sur les cytokines
- Éléments des génétique
- vHL, VEGF et carcinome rénal
- Nouvelles thérapies
  - Bevacizumab (Avastin®)
  - Sorafinib (Nexavar®)
  - Sunitinib (Sutent®)
  - CCI-779 (Temsirolimus)
  - RAD001 (everolimus

Carcinome rénal

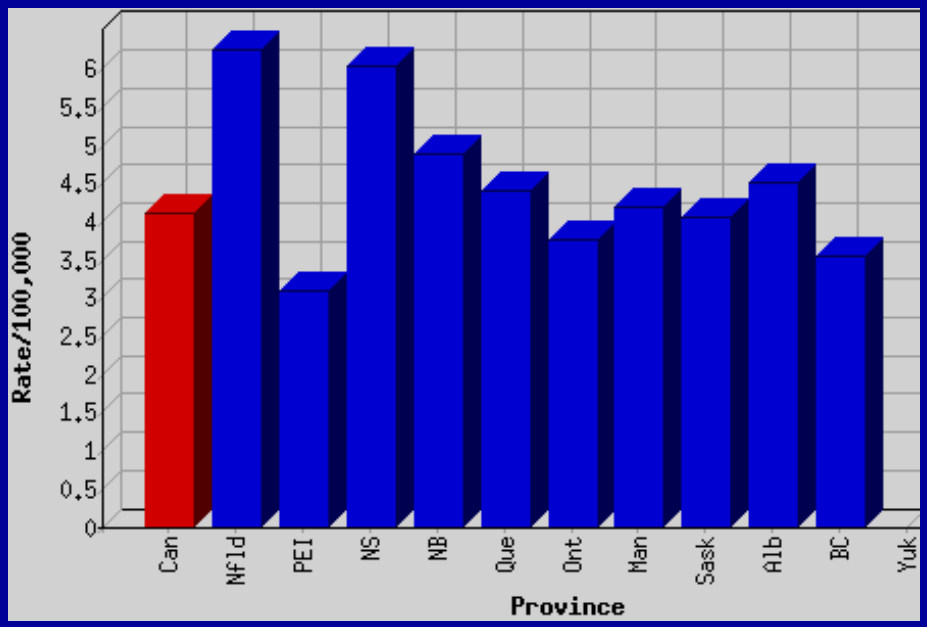
Incidence spécifique par province ou territoire

Cancer of the Kidney, Both Sexes Combined, All Ages, 2001
Age-Standardized Incidence Rate per 100,000



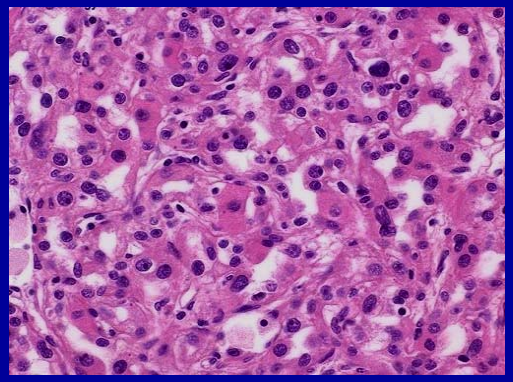
Mortalité spécifique par province ou territoire

Cancer of the Kidney, Both Sexes Combined, All Ages, 2001
Age-Standardized Incidence Rate per 100,000

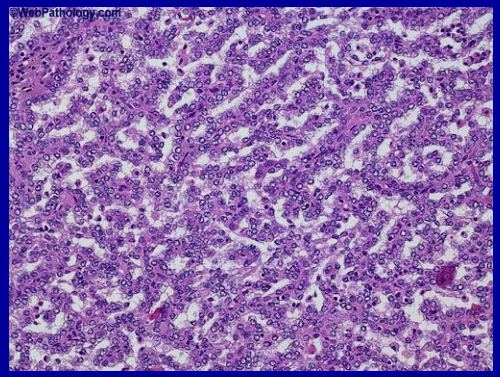


Cancer Statistics Canada 2006

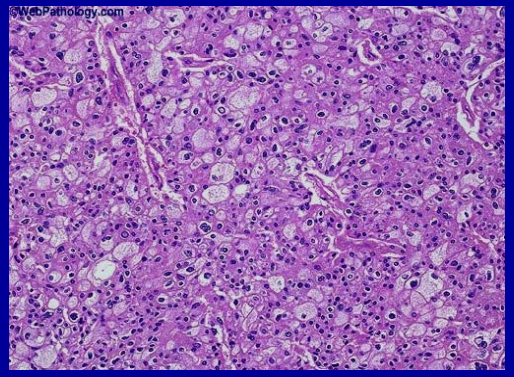
Carcinome rénal: histologie



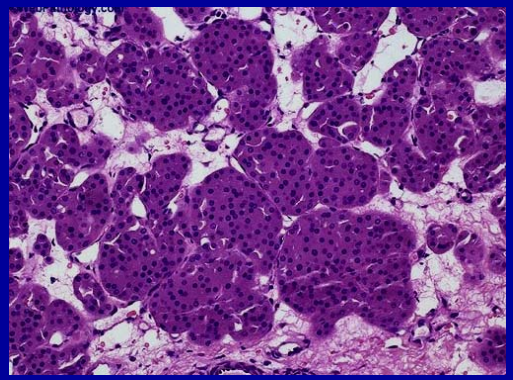
Cellules claires 75-80%



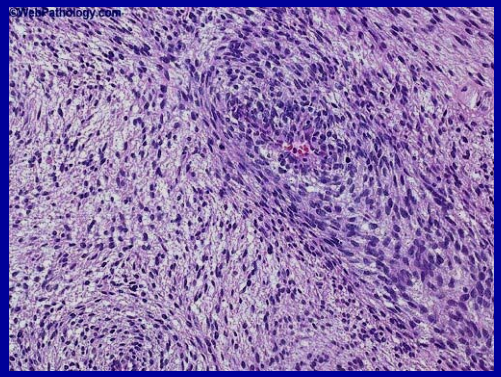
Papillaire 7-14%



Chromophobe 5-8%



Oncocytome 2-5%



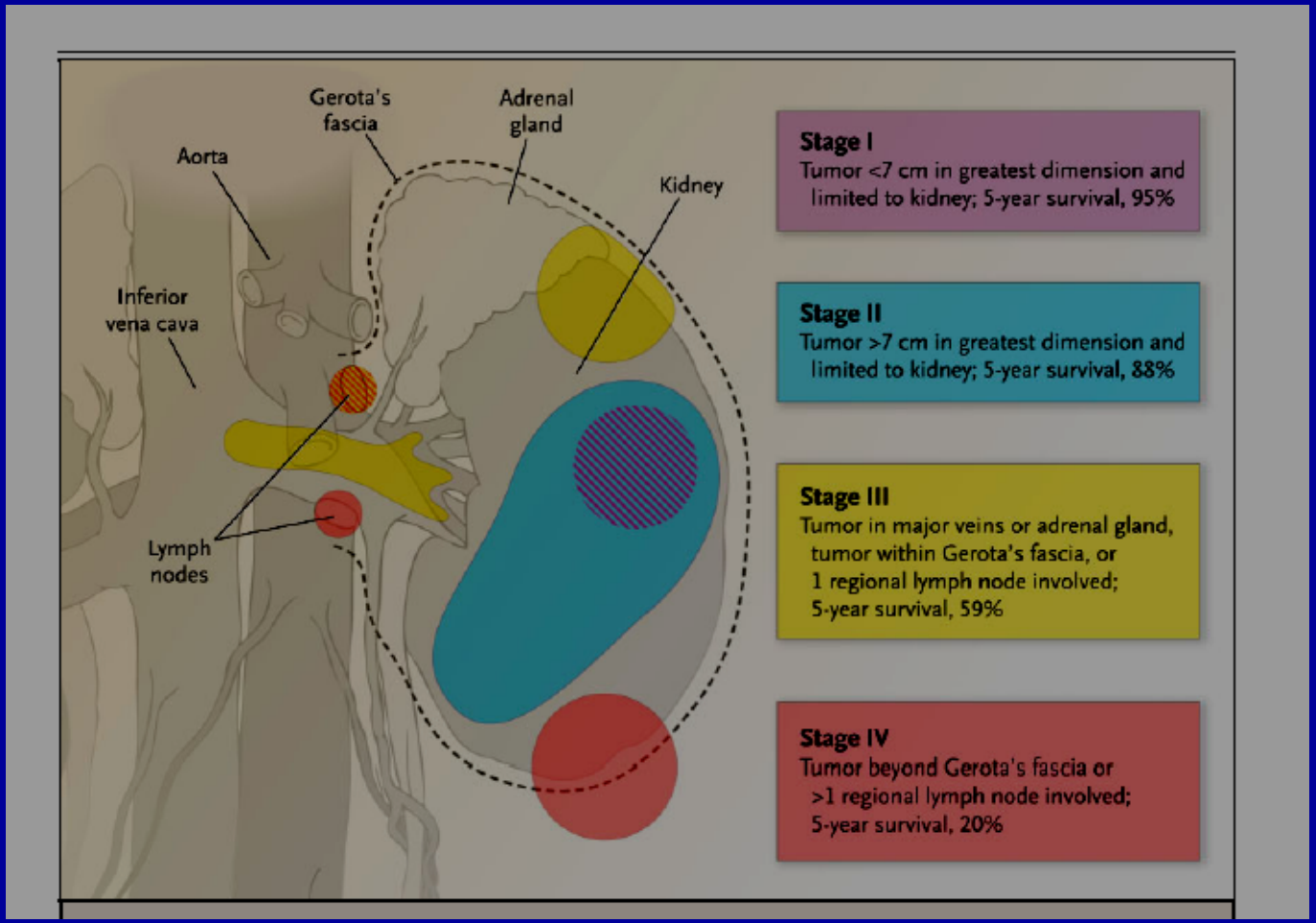
Sarcomatoïdes/ Autres 1-2%

Groupes hétérogènes

États mixtes rapportés

Carcinome rénal

Pronostic



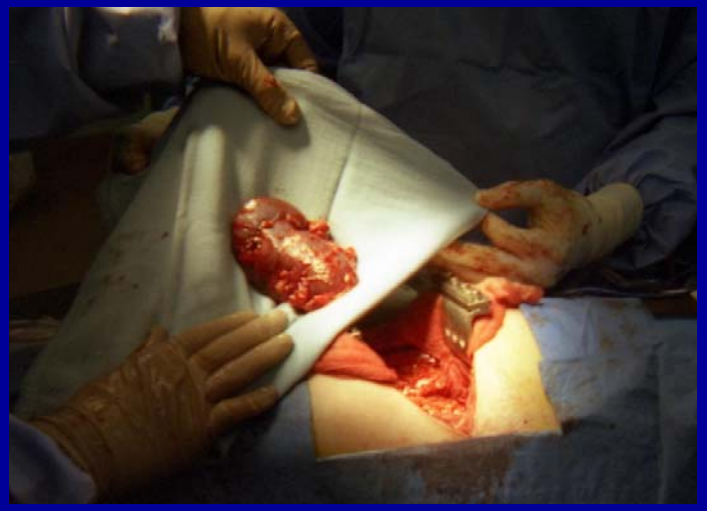
→ ***Facteur pronostic le plus important: stade***

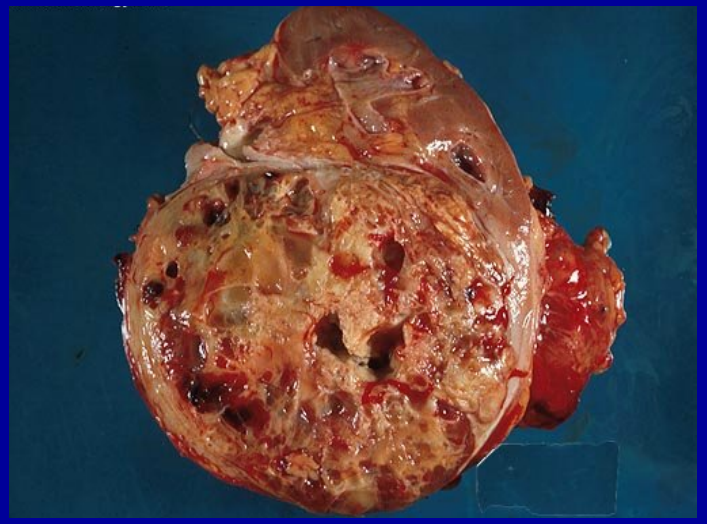
Cohen NEJM 2005

Carcinome rénal

Considération de l'oncologue

- ***Résection complète est la seule option pour une cure***
- Métastasectomie de sites uniques/localement récidivant à considérer en premier lieu
- Pas de rôle défini à thérapie adjuvante ou néo-adjuvante
- Résistance à la chimiothérapie
- Thérapies systémiques limitées
- Options standards autres:
  - interleukines low-dose
  - interferon low-dose



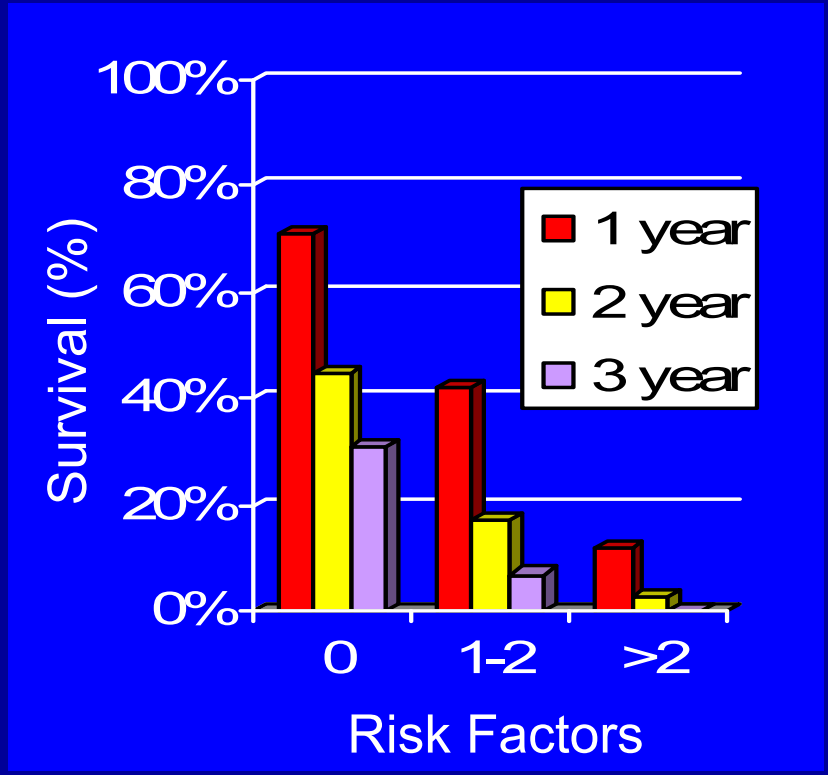


Principes de traitement

- Primum non nocere
  - Avantages vs inconvénients
  - Capacité à contrer les effets secondaires
    - Formation
      - Personnel
      - Corps médical
    - Participation à des études cliniques

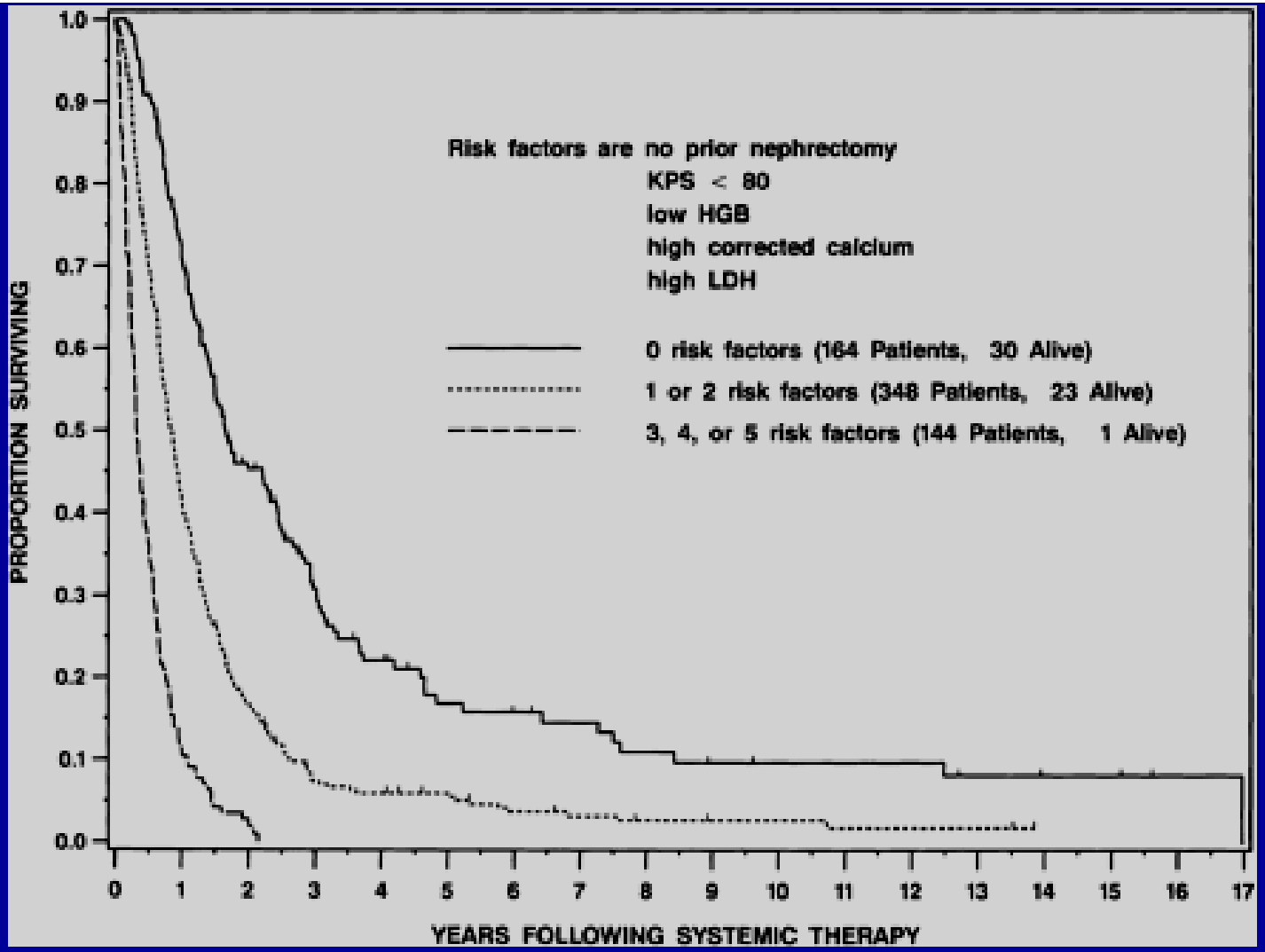
Facteurs pronostics pour la survie chez patients jamais traités avec carcinome rénal avancé

- Analyse multivariée rétrospective (670 pts)
- **Facteurs de risque:**
  - KPS bas (≤70)
  - Hb basse (< LLN)
  - LDH élevés (> 1.5 x ULN)
  - HyperCa (> 2.5 mmol/L)
  - Pas de néphrectomie



Motzer JCO 1999;17: 2530

Facteurs pronostics pour la survie chez patients jamais traités avec carcinome rénal avancé



Motzer JCO 1999;17: 2530

Cytokine Therapy – Interferon-α

Treatment	n	Overall Response Rate	Complete Response (CR)	Median Survival (months)
IFN-α vs. medroxyprogesterone[1]	335	13% vs. 7%	2% vs. 0%	8.5 vs. 6 (*P* = .017)
IFN-α + vinblastine vs. vinblastine[2]	160	16.5% vs. 2.5%	8.9% vs. 1.2%	15.8 vs. 8.8 (*P* = .0049)
Meta-analysis (Cochrane Database Review) [3]	4216	12.9% vs. 2.5%	Not reported	3.8 mo improvement vs. control (*P* = .0005)

1. Medical Research Council Renal Cancer Collaboration. *Lancet.* 1999;353:14-17.
2. Pyrhonen S, Salminen E, Ruutu M, *et al. J Clin Oncol.* 1999;17:2859-2867.
3. Coppin C, Porzsolt F, Awa A, *et al. Cochrane Database Syst Rev.* 2004;1:CD001425.

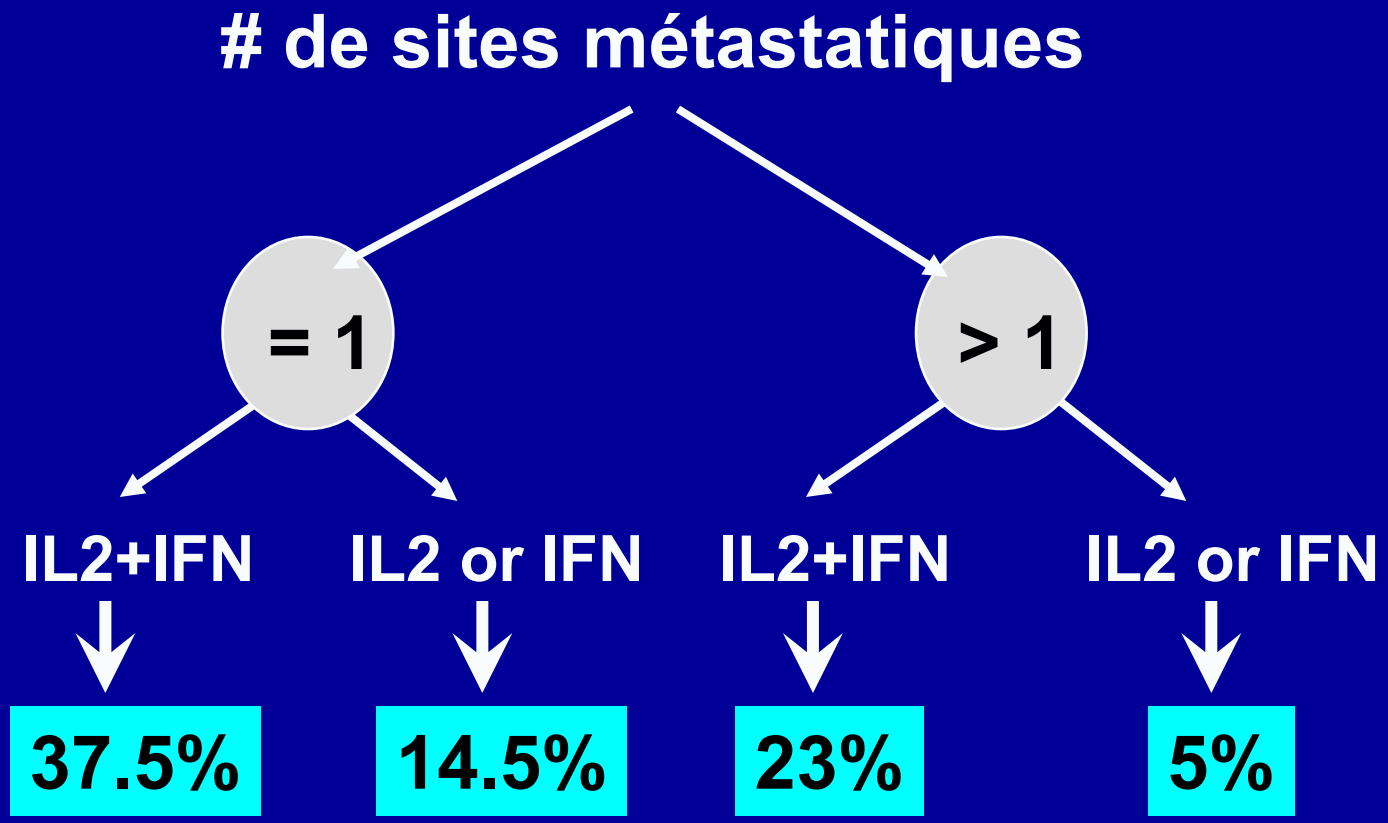
CRECY Trial

	IL2	IFN	IL2+IFN	Total
n	138	147	140	425
CR				3
PR				43
SD				106
PD				240
NE				33
RR			%)	36

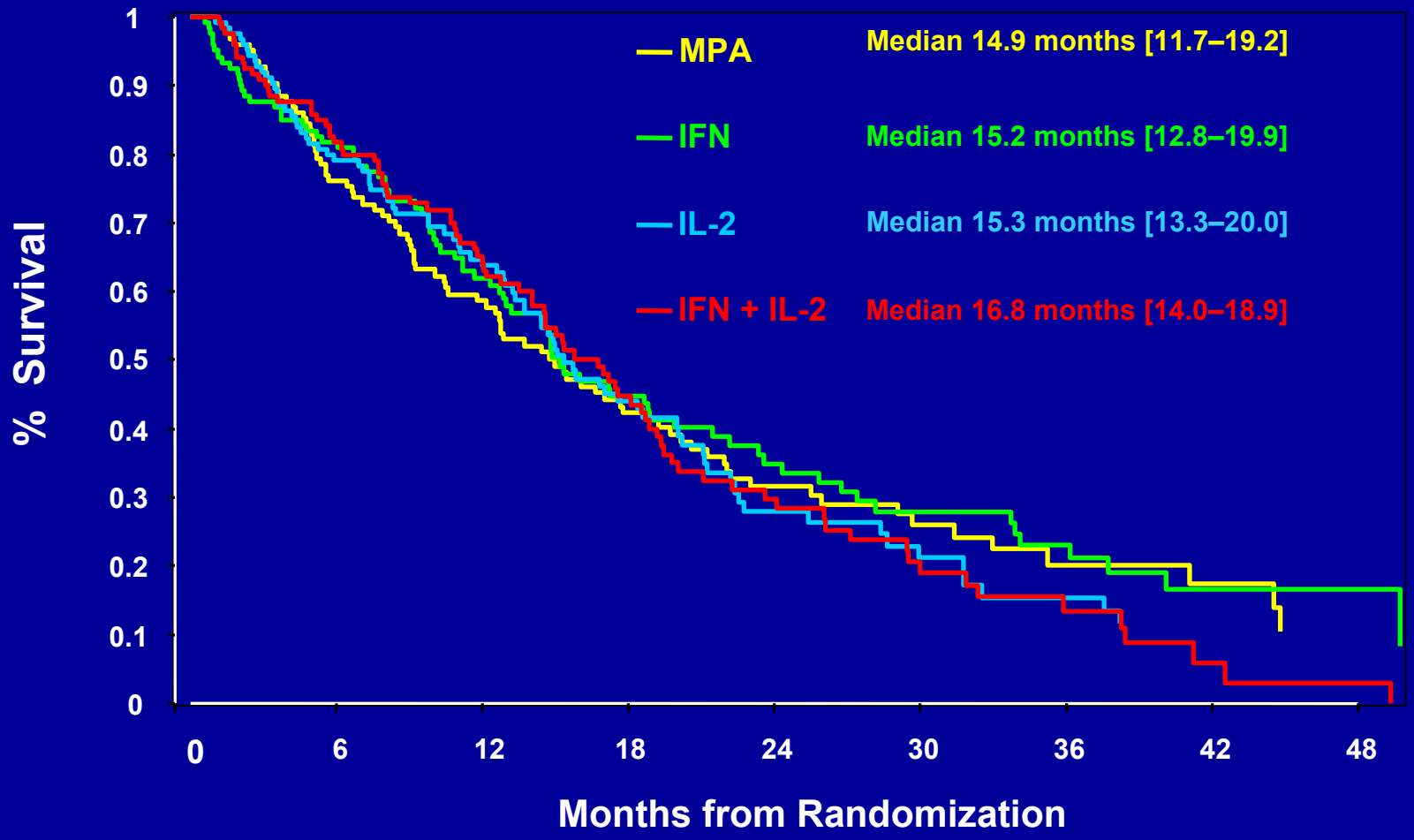
Aucun avantage de survie

Les preuves!!!!

Probabilité de réponse au traitement



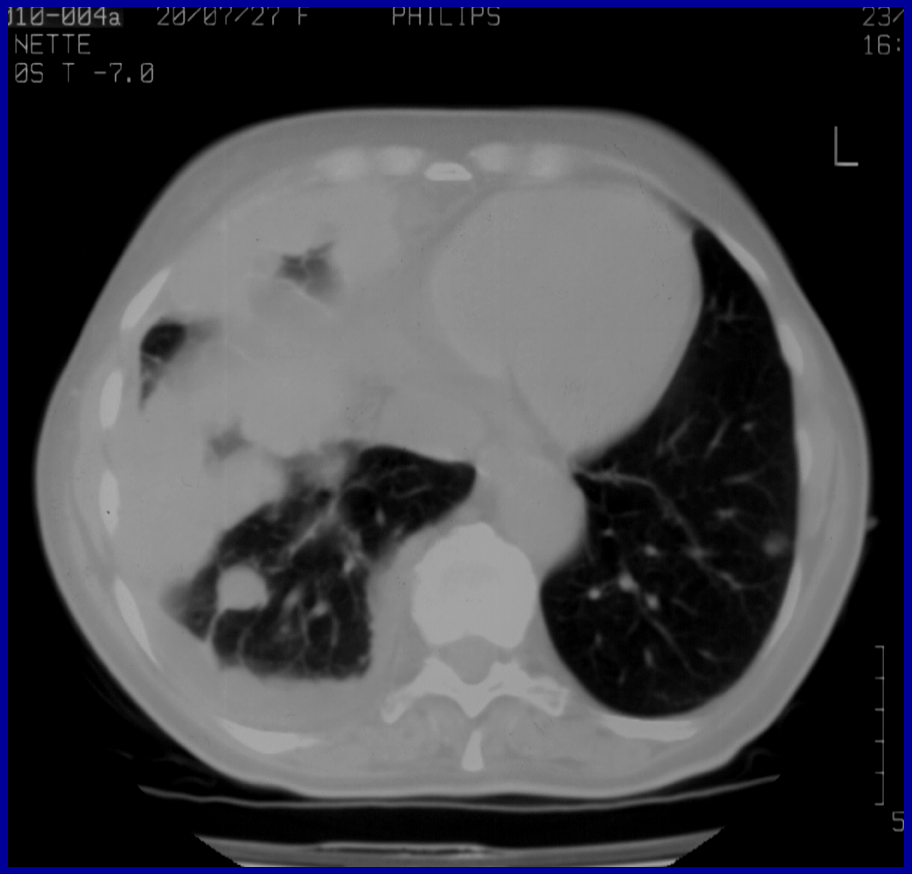
PERCY Quattro Trial: Overall Survival Similar Across Treatment Arms



Negrier S, Perol D, Ravaud A, *et al. J Clin Oncol.* 2005;23(suppl 16):4511.

Carcinome rénal

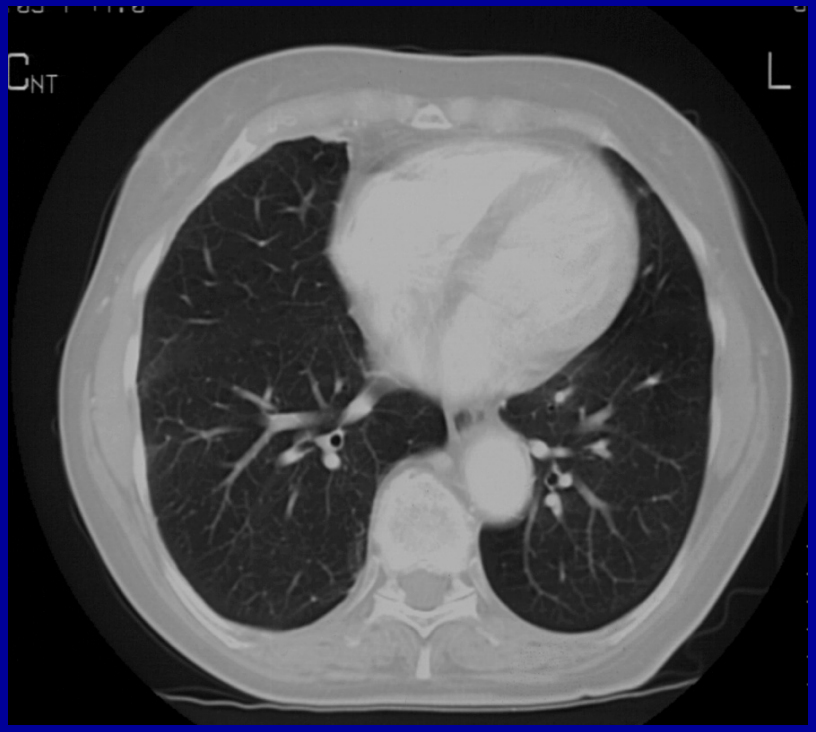
Maladie capricieuse ou subtile…….



11/2000

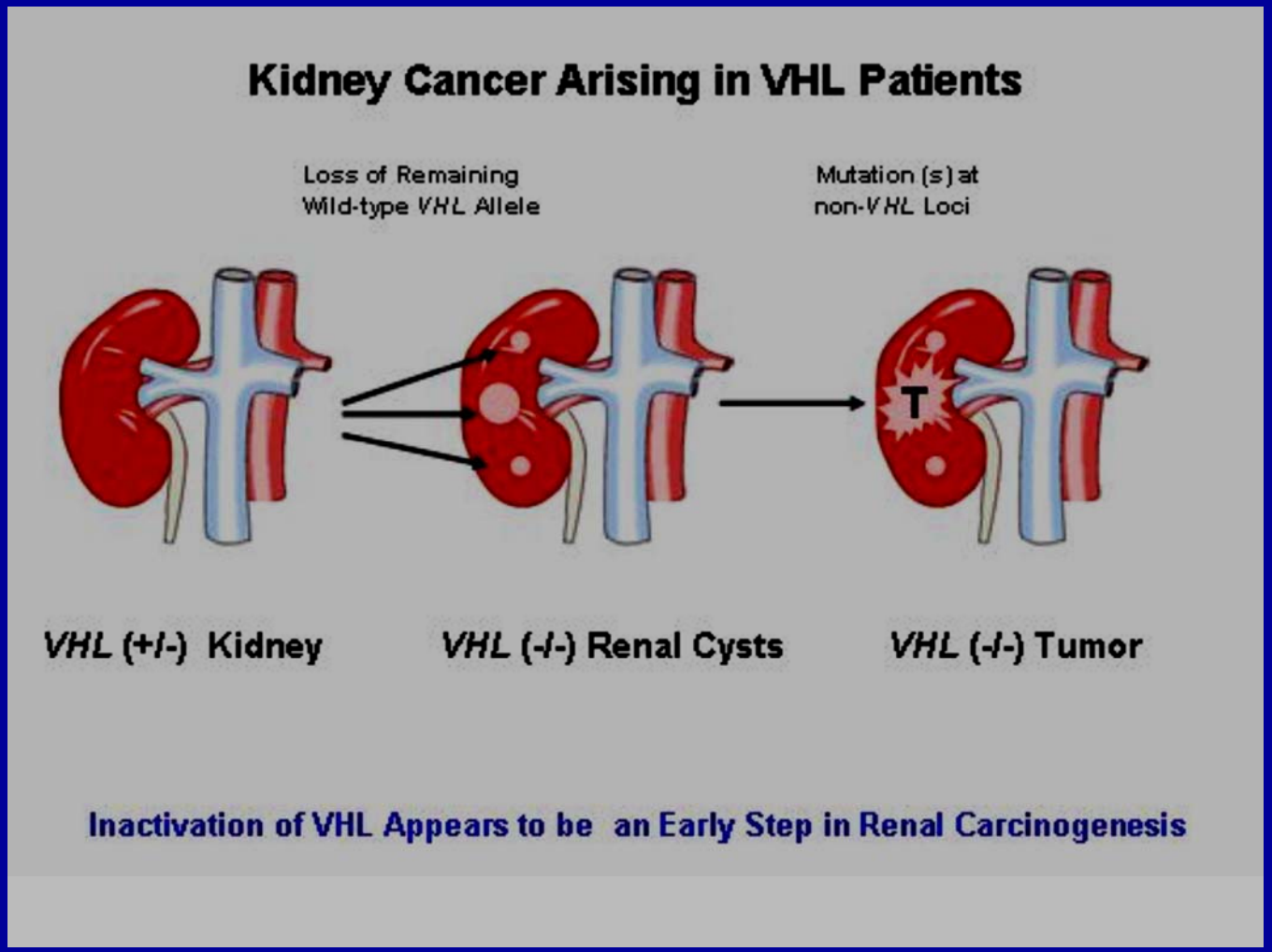
Nephrectomie 12/2000

2/2002

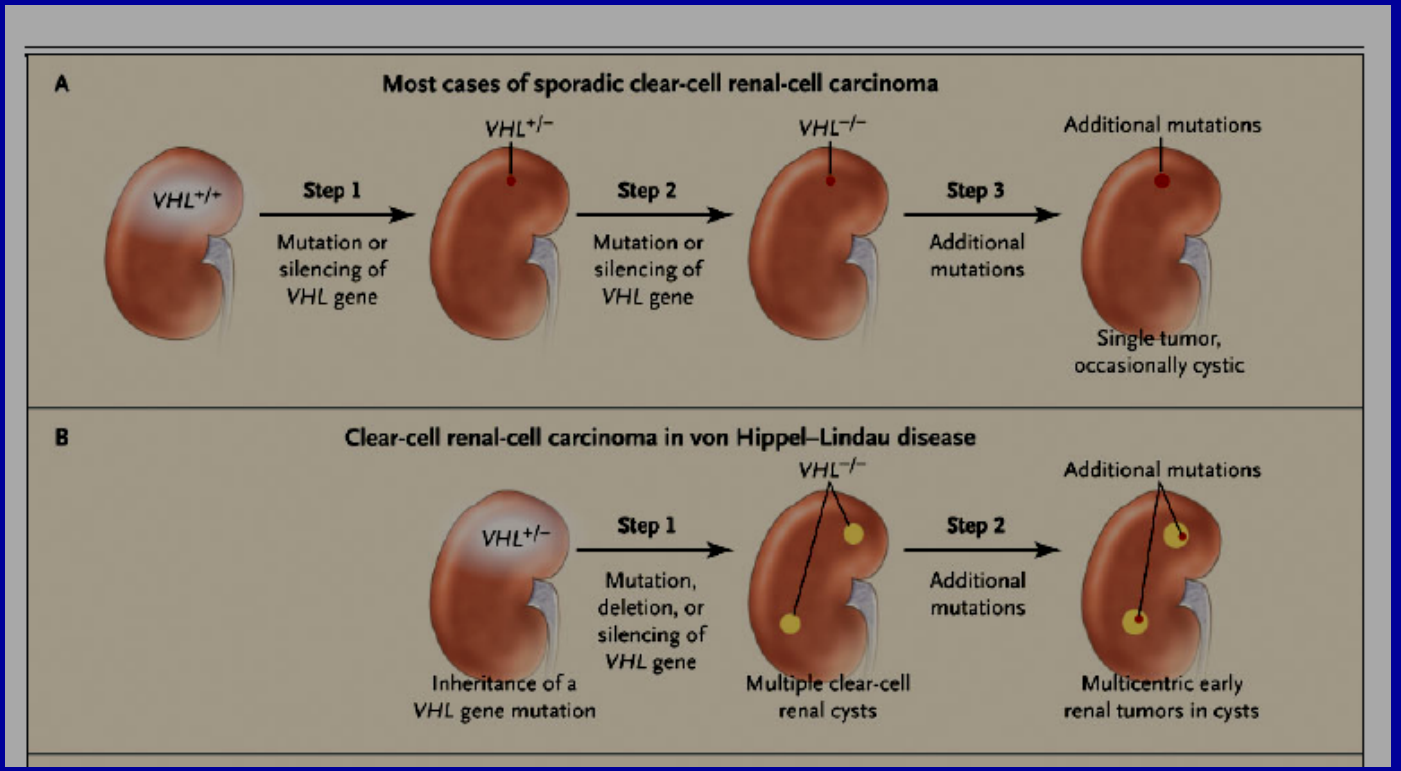


Génétique du gène VHL

- Désordre autosomal dominant
- ~50% risque de CR; souvent bilatéral et multifocal



Génétique du VHL



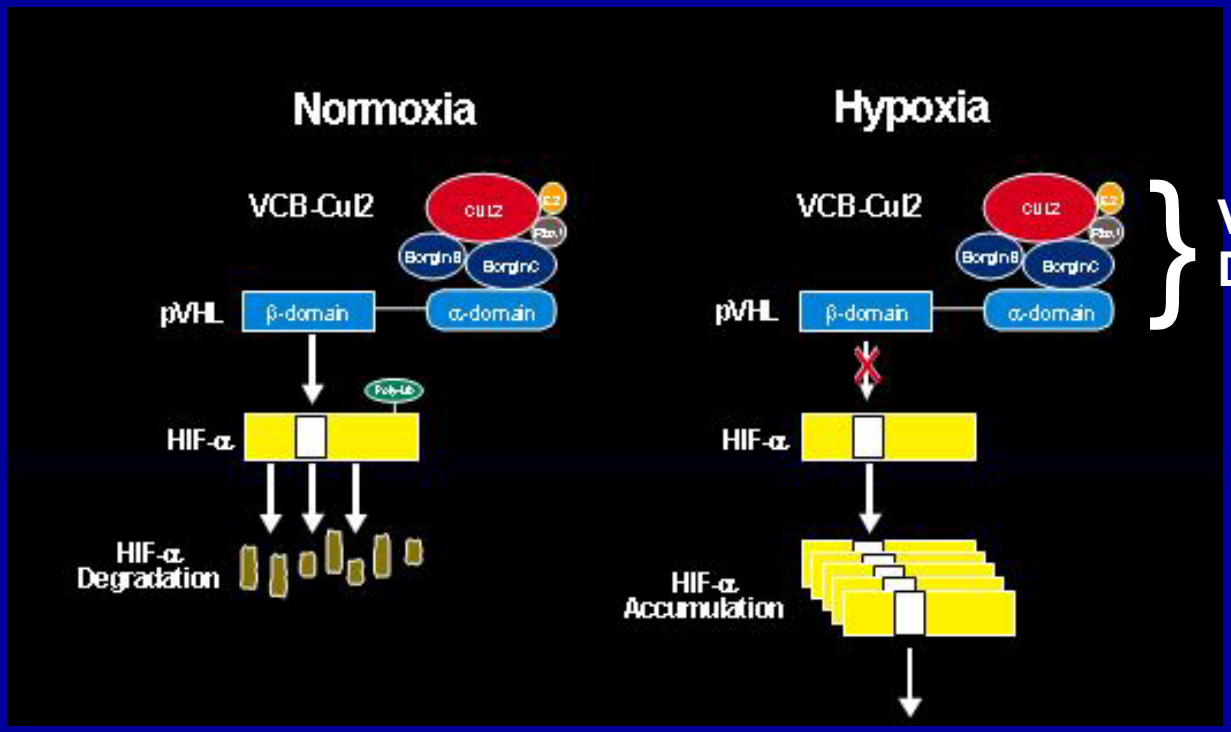
Cohen NEJM 2005

- **CCC sporadique: 2 hit theory**
  - **84-98% délétion d'un allèle (LOH)**
  - **mutations dans 34-57% de l'autre allèle**
  - **méthylation in 5-19%**

⇒ plus de 80% CCC: mutation du gène VHL

Rini JCO 2005

Fonction du gène VHL: molécule associée (pVHL)

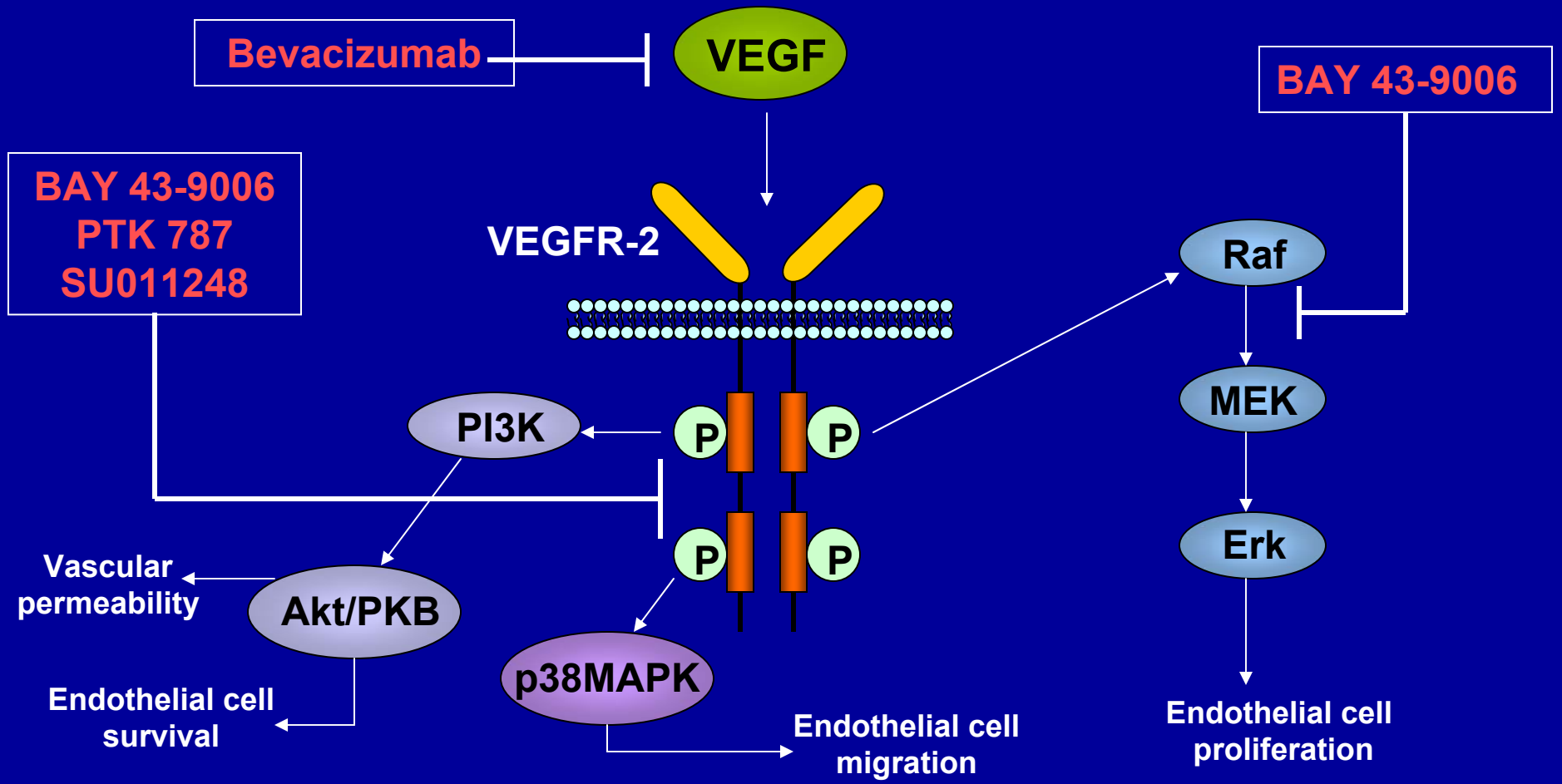


VEGF	PDGF	TGF-α,
VEGFR	PDGFR	EGFR
Angiogenesis	*Endothelial Stabilization*	*Autocrine Growth Stimulation*

Thérapie ciblée anti-angiogénique pour le CC

- Bevacizumab
- Sorafenib
- Sunitinib
- CCI-779 (Temsirolimus)
- RAD001 (everolimus)

Inhibition du VEGF(R)

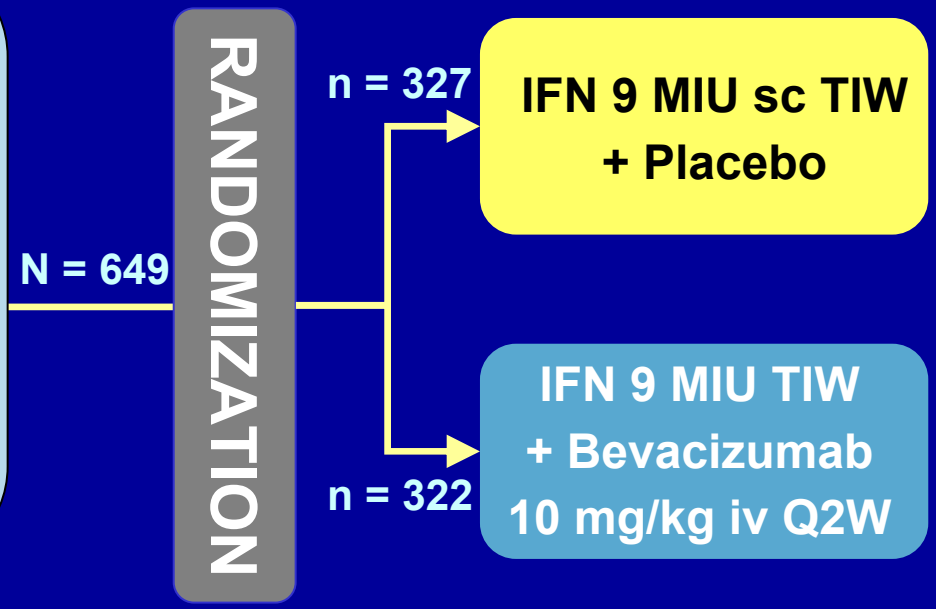


Rini JCO 2005

Bevacizumab and Interferon-α AVOREN

Eligibility Criteria

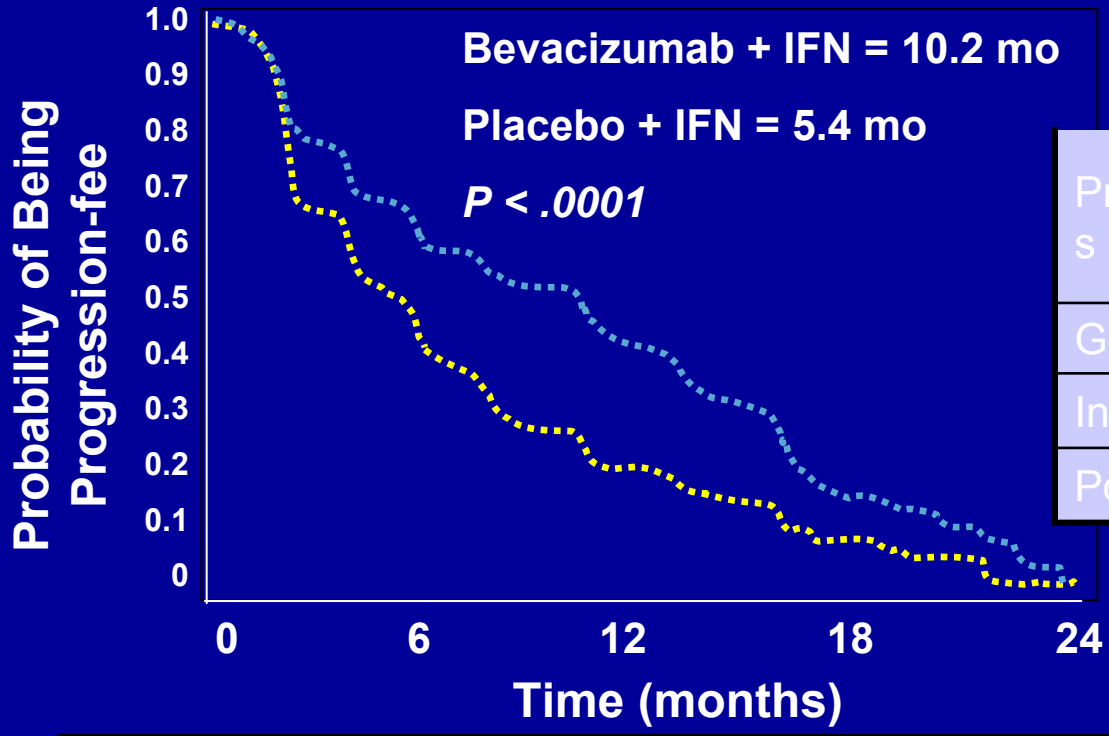
- Histologically confirmed mRCC
- Clear cell histology
- No prior systemic therapy
- Nephrectomy
- Karnofsky PS ≥ 70
- Measurable disease
- No CNS metastasis
- MSK prognosis: All groups



- Primary Objective: Overall survival
- Secondary Objectives: Progression-free survival, time to treatment failure, overall response, safety, pharmacodynamics, and pharmacokinetics

Escudier B, Koralewski P, Pluzanska A, *et al. J Clin Oncol.* 2007;25(suppl 18):3.

Bevacizumab and Interferon Provide Superior Outcomes



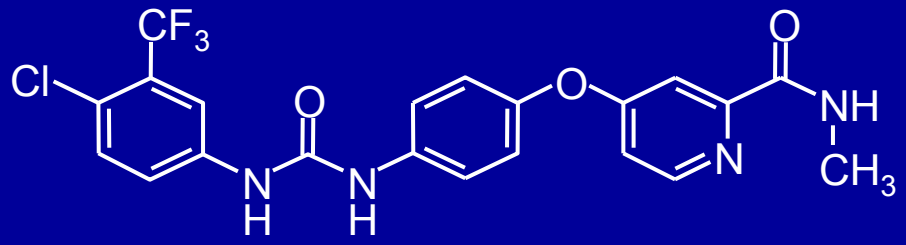
Prognosis	IFN + Placebo	IFN + Beva	*P* Value
Good	7.6	12.9	.004
Int	4.5	10.2	< .001
Poor	2.1	2.2	.457

**P* < .001

End Point	IFN + Placebo	IFN + Bevacizumab
ORR	13%	31%*
CR / PR	2 / 11	1 / 30
Overall survival (median)	19.8 mo	Not yet reached

Escudier B, Koralewski P, Pluzanska A, *et al. J Clin Oncol.* 2007;25(suppl 18):3.

Sorafenib (BAY 43-9006)
inhibiteur semi-sélectif de TK

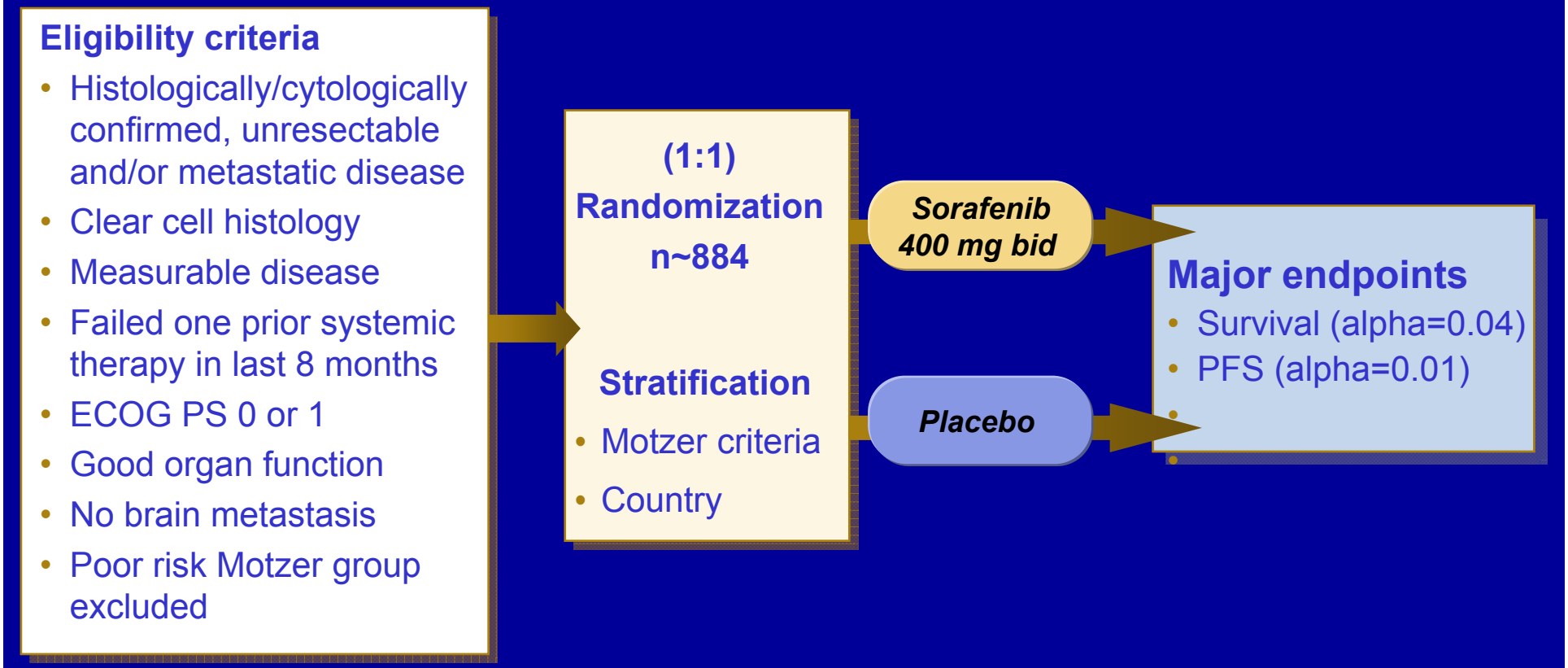


- Identifié dans contexte de recherche d'inhibiteurs de RAF-1, une sérine- thréonine kinase
- Activité démontrée contre B-RAF, VEGFR-2, PDGFR, FLT-3 et c-kit
- Activité contre de multiples types tymoraux en modèles xénografts, incluant le CR
- Phase II randomisées:
  PFS médiane 24 weeks vs. 6 weeks (p=0.009)

Ratain ASCO 2005

Sorafenib (BAY 43-9006) – Phase III

International, multi-centre, randomized placebo-controlled trial of BAY 43-9006 as second-line treatment in met RCC



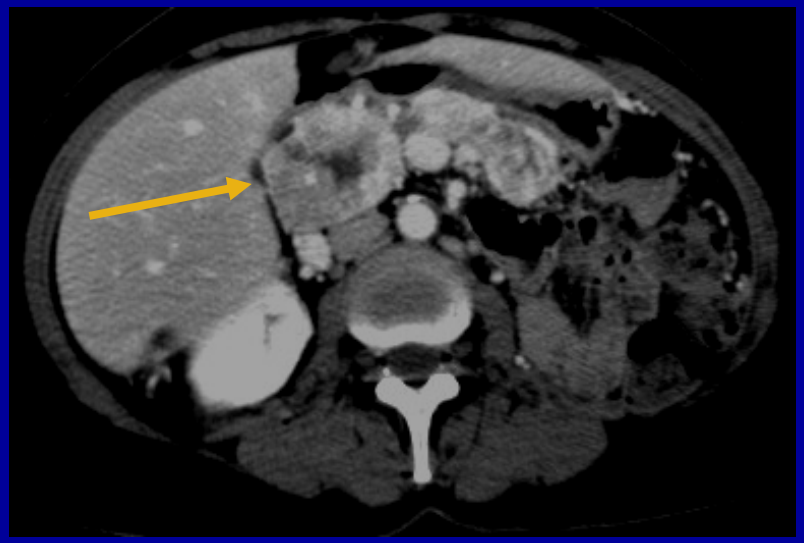
Escudier ECCO 2005

Sorafenib (BAY 43-9006) – Phase III Results

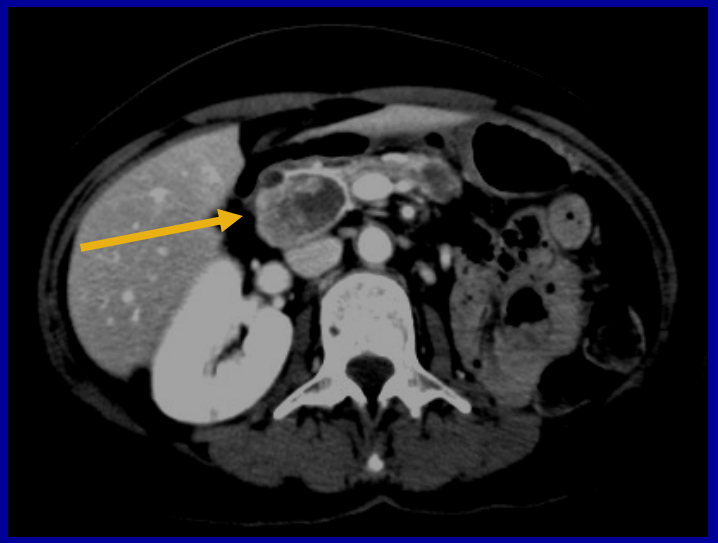
Best response (RECIST)	Sorafenib (n=384)	Placebo (n=385)
CR	0	0
PR	7(2%)	0 (0%)
SD	261 (78%)	186 (55%)
PD	29 (9%)	102 (30%)
missing	38 (11%)	49 (15%)
Median PFS	**24 weeks**	**12 weeks**
	HR 0.44 p < 0.000001	

Escudier ASCO 2005

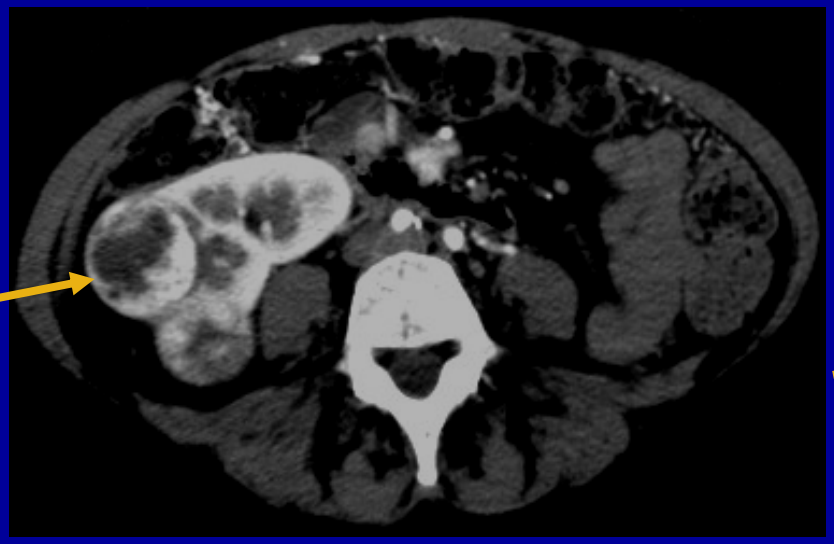
Sorafenib Patient 251-050

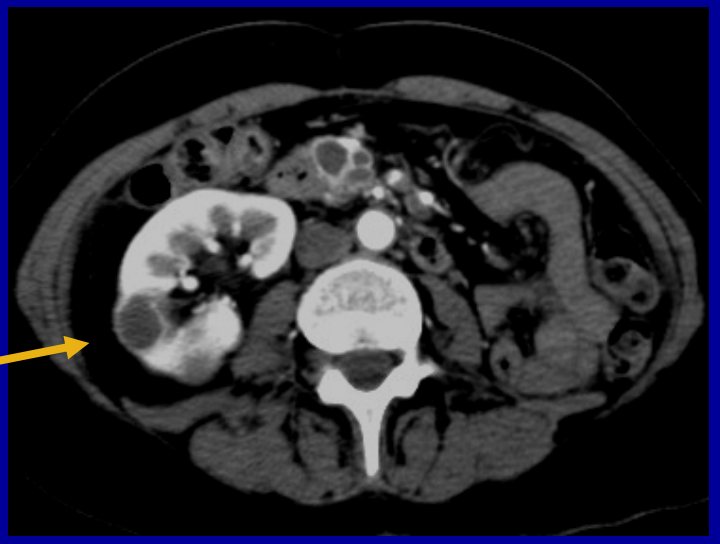


21 June 2005



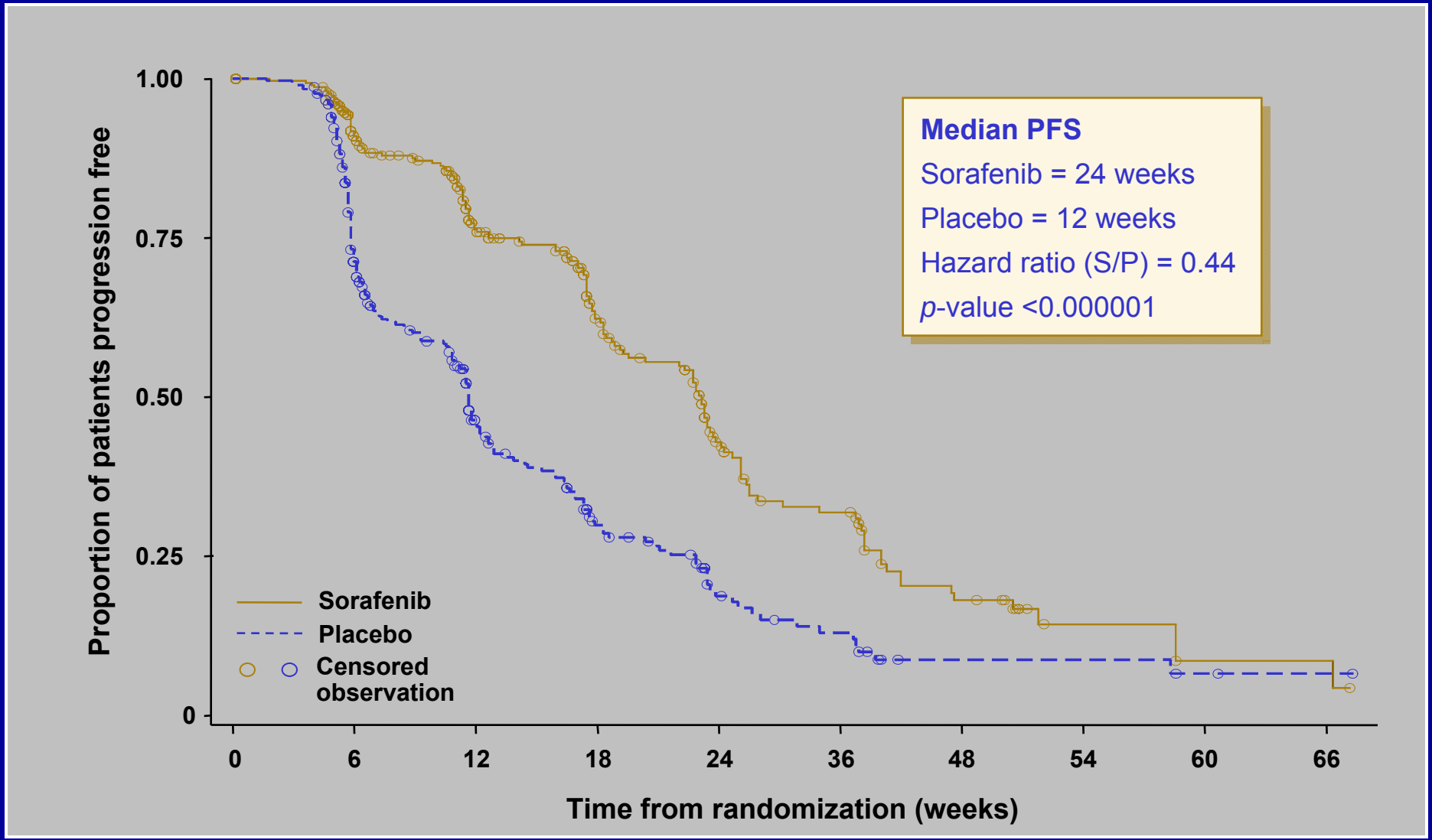
17 October 2005





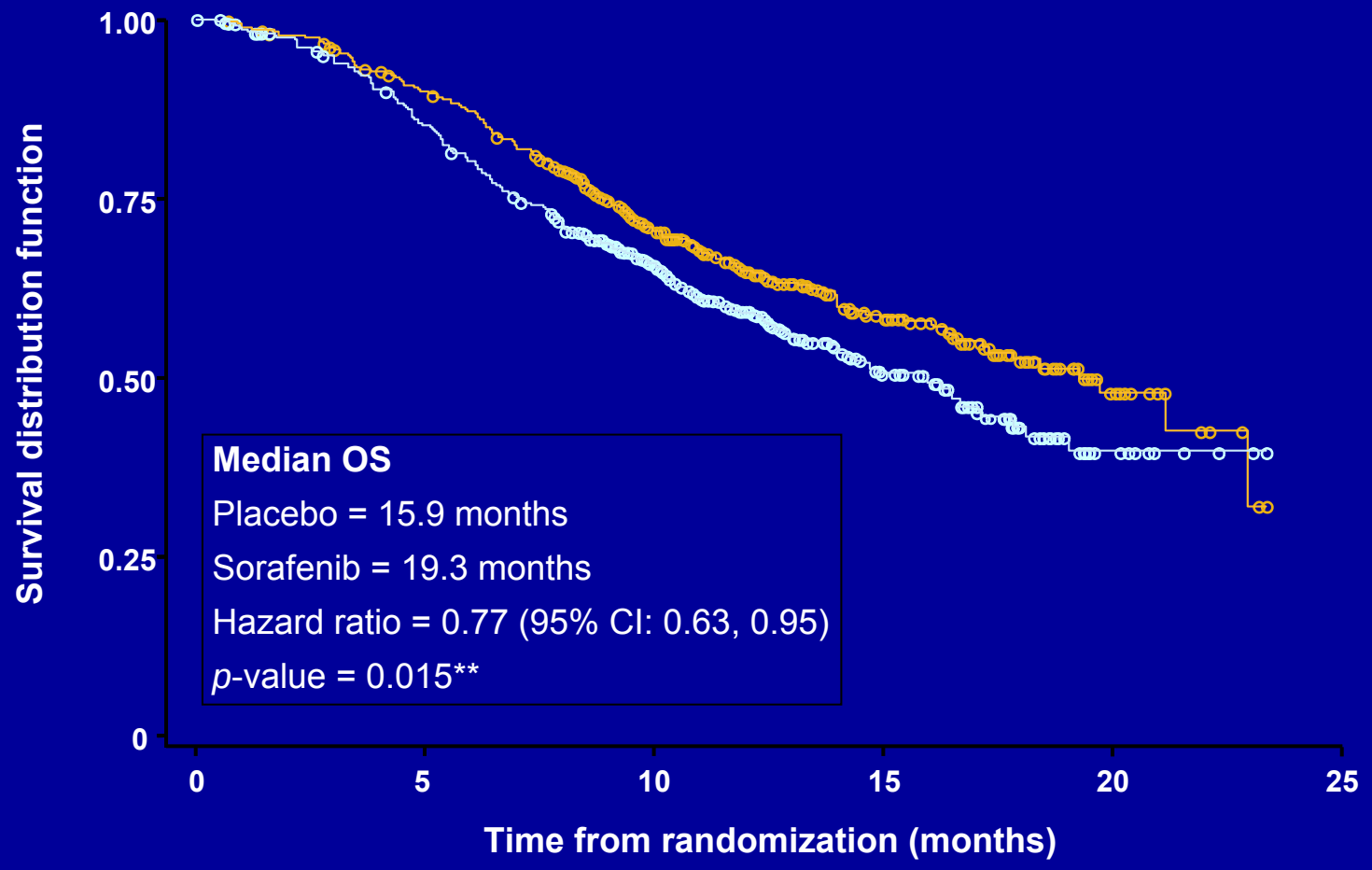
Slide Courtesy of Dr. Escudier

Sorafenib (BAY 43-9006) – Phase III
Résultats – PFS (évaluation indépendante)



Escudier ECCO 2005

TARGETs
Survie globale: Analyse 6 mois post-crossover*

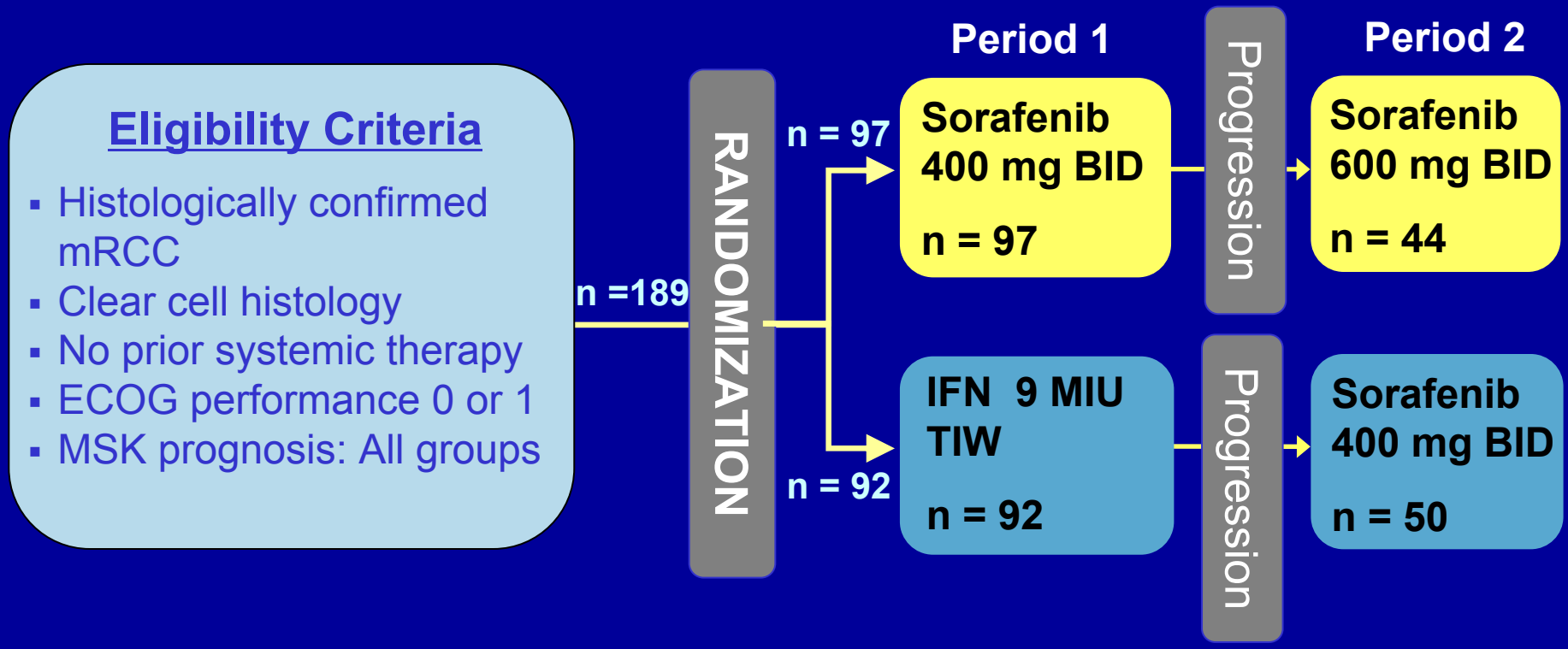


Of 367 events, a total of 122 deaths were reported in the low-risk and 245 in the intermediate-risk groups

*At 367 events, Nov. 30, 2005

**O'Brien-Fleming stopping boundary for significance was $p<0.0094$

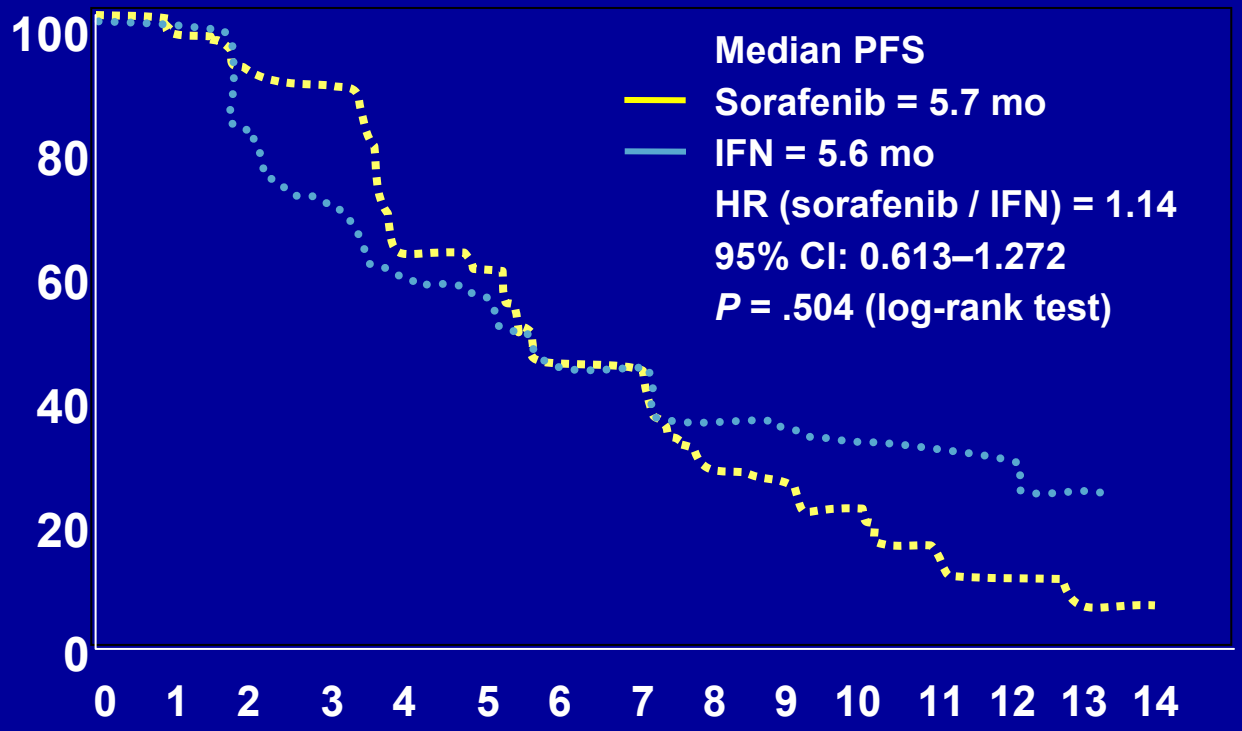
Progression-free Survival Comparable for Sorafenib and Interferon



- Primary Objective: Progression-free survival
- Secondary Objective: Quality of life

Szczylik C, Demkow T, Staehler M, *et al. J Clin Oncol*. 2007;25(suppl 18):5025.

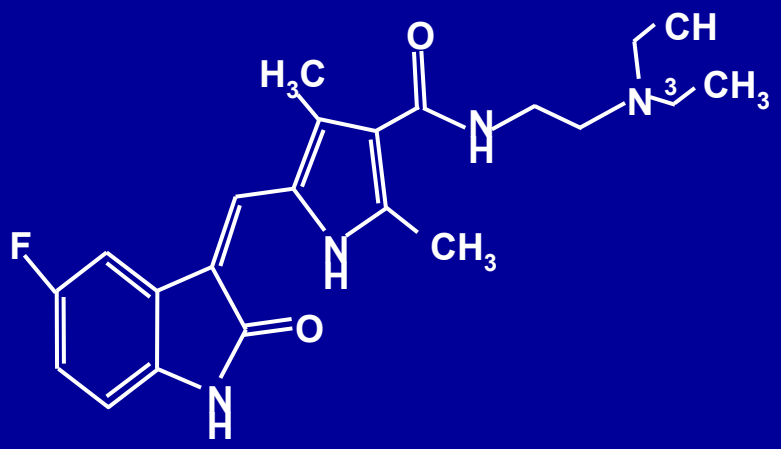
Progression-free Survival Similar Between Sorafenib and IFN-α



Patients who were dose escalated to 600 mg BID after progression had disease stabilization for a further 3.6 months

Szczylik C, Demkow T, Staehler M, *et al. J Clin Oncol*. 2007;25(suppl 18):5025.

SU011248 - Sunitinib



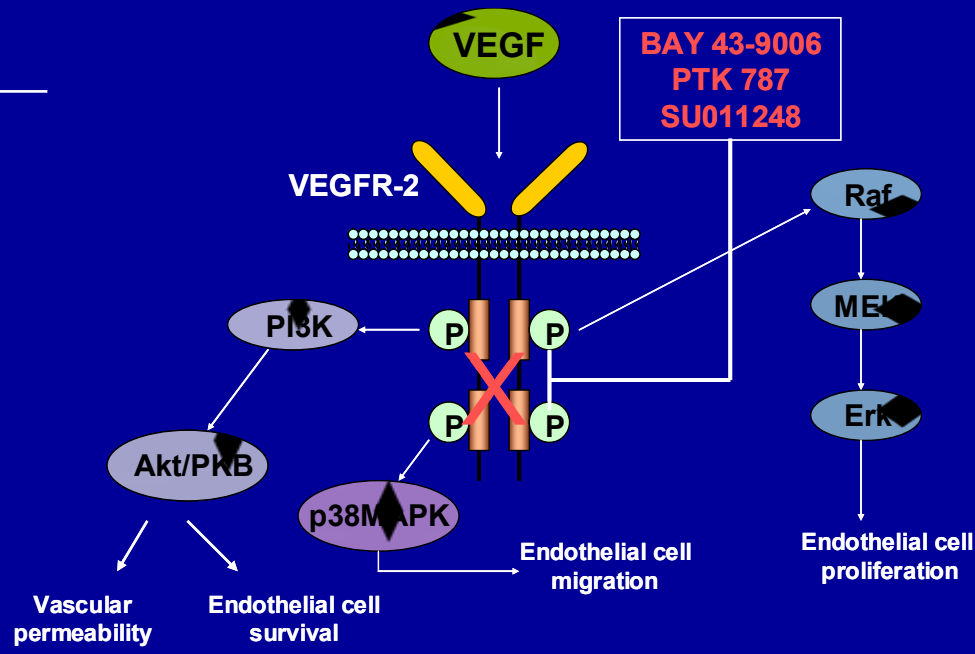
- TKI
- 50mg par jour 4 sem – 2 sem nil
- Bonne biodisponibilité sans effet de la nourriture
- Métabolisé par CYP4503A4
- ($t_{1/2}$ 40hr, métabolite 80 hr)
- Interactions potentielles CYP4503A4
- Métabolite actif SU012662
- PK linéaire (25-150mg)
- Compétitif direct du site ATP
  - Se lie au domaine kinase pour empêcher la phosphorylation des substrats

Sun L, et al. *J Med Chem*. 2003;46:1116-1119.

SU011248 - Sunitinib

Inhibition sélective: KIT, PDGFR, VEGFR, FLT3

Receptor Tyrosine Kinase (RTK)	Cellular IC50* (µM)
VEGFR2	0.004
VEGFR1	ND; K_i = 0.002
VEGFR3	ND; K_i = 0.017
PDGRF-α	0.069
PDGFR-β	0.039
KIT	0.002
FLT3 ITD	0.001 - 0.01
FLT3	0.25
RET	0.05



Activité mixte anti-angiogénique et anti-tumorale

Sun L, et al. *J Med Chem*. 2003;46:1116-1119
Rini et al JCO 2005.

SU011248 – 2 Phase II en 2ème ligne pour CR

- Objectif premier: TR
- Critères d'inclusion:

  Trial 1: ***toute*** histologie, échec aux cytokines, maladie mesurable, PS OK, absence de co-morbidités signif

  n = 63

  Motzer JCO 2006

  Trial 2: ***cellules claires*** seulement, échec aux cytokines, documentation radiologique de progression, néphrectomisés, maladie mesurable, PS OK, absence de co-morbidités signif

  n = 106

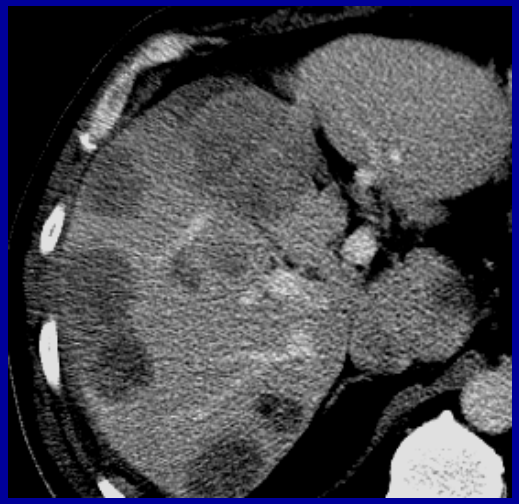
  Motzer ASCO 2005

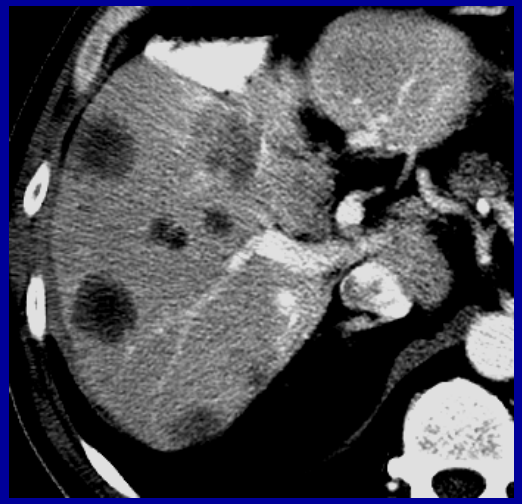
SU011248 – 2 Phase II
Résultats – best response selon RECIST

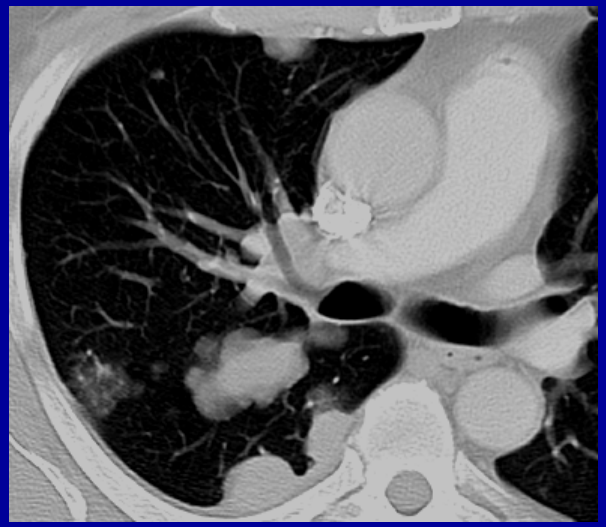
Response	Trial 1 No (%)	Trial 2 No (%)
No Patients	63	106
Overall response	**25 (40%)**	**41 (39%)**
CR	0	1(1%)
PR	25 (40%)	40 (38%)
SD ≥ 3 months	**17 (27%)**	**25 (23%)**
PD or SD < 3 months	16 (25%)	33 (31%)
Med. Duration of PR	**12.5 months**	**NA**
Median TTP	**8.7 months**	**NYR**
Median OS	**16.4 months**	**NYR**

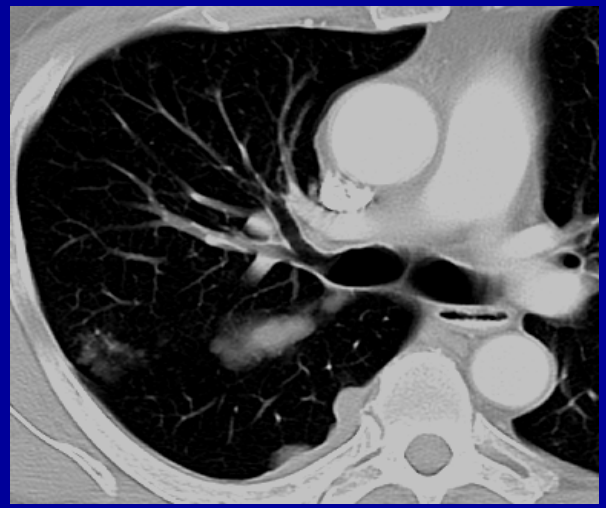
Motzer JCO 2006
Motzer JAMA 2006

Sutent







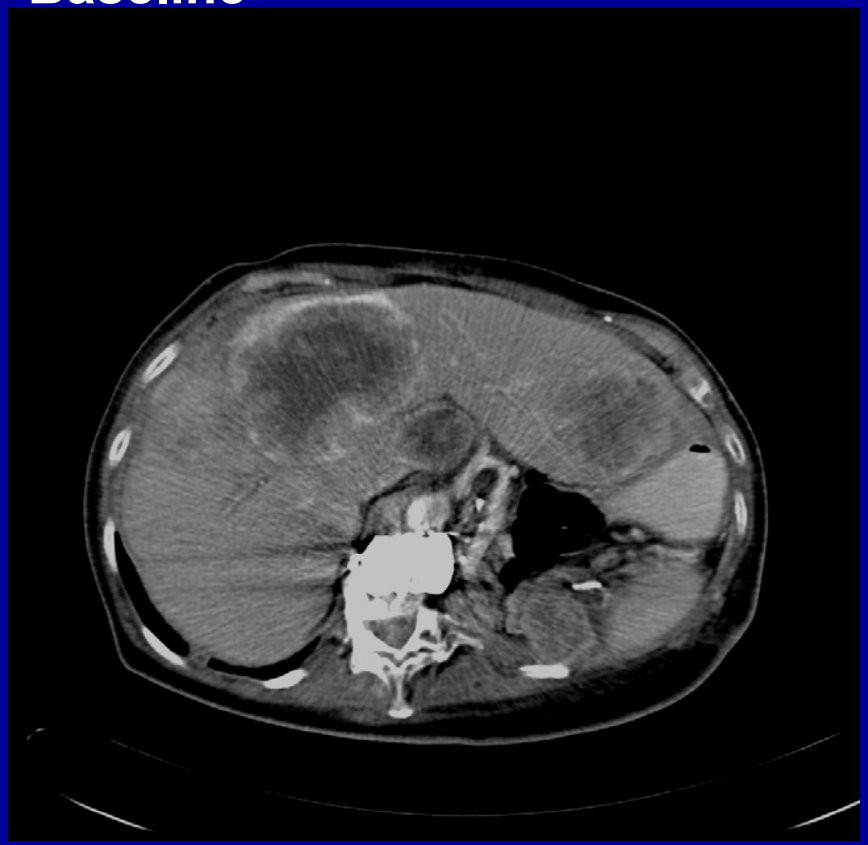


Slide Courtesy of Dr. Motzer, New York

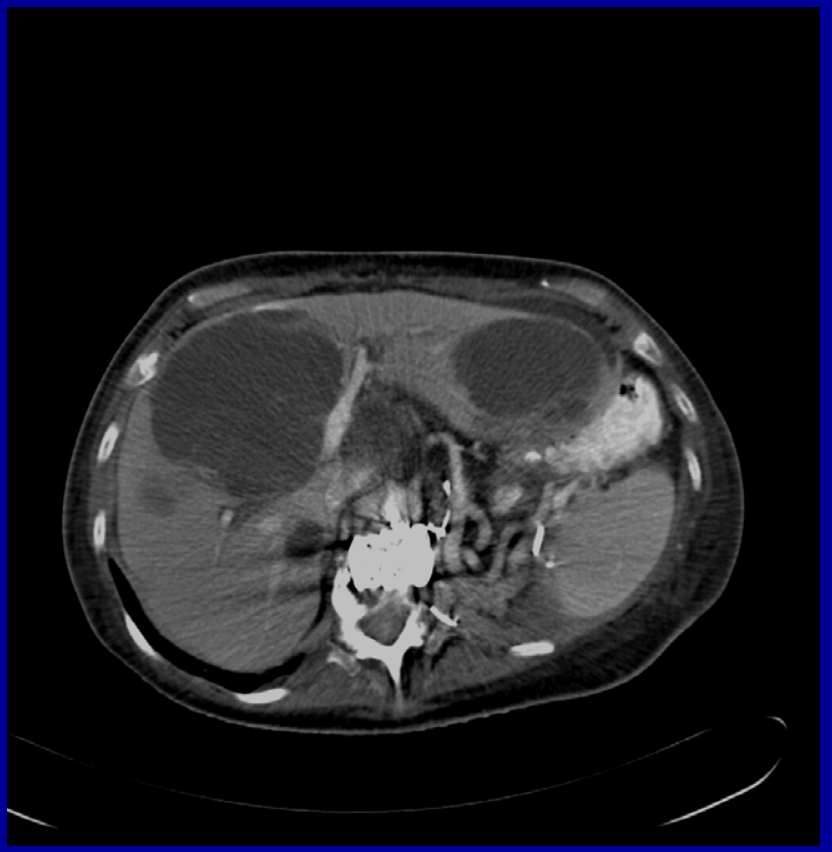
Nécrose tumorale sous SU11248

63-yr female with metastatic RCC with multiple large liver mets

Baseline



Week 4



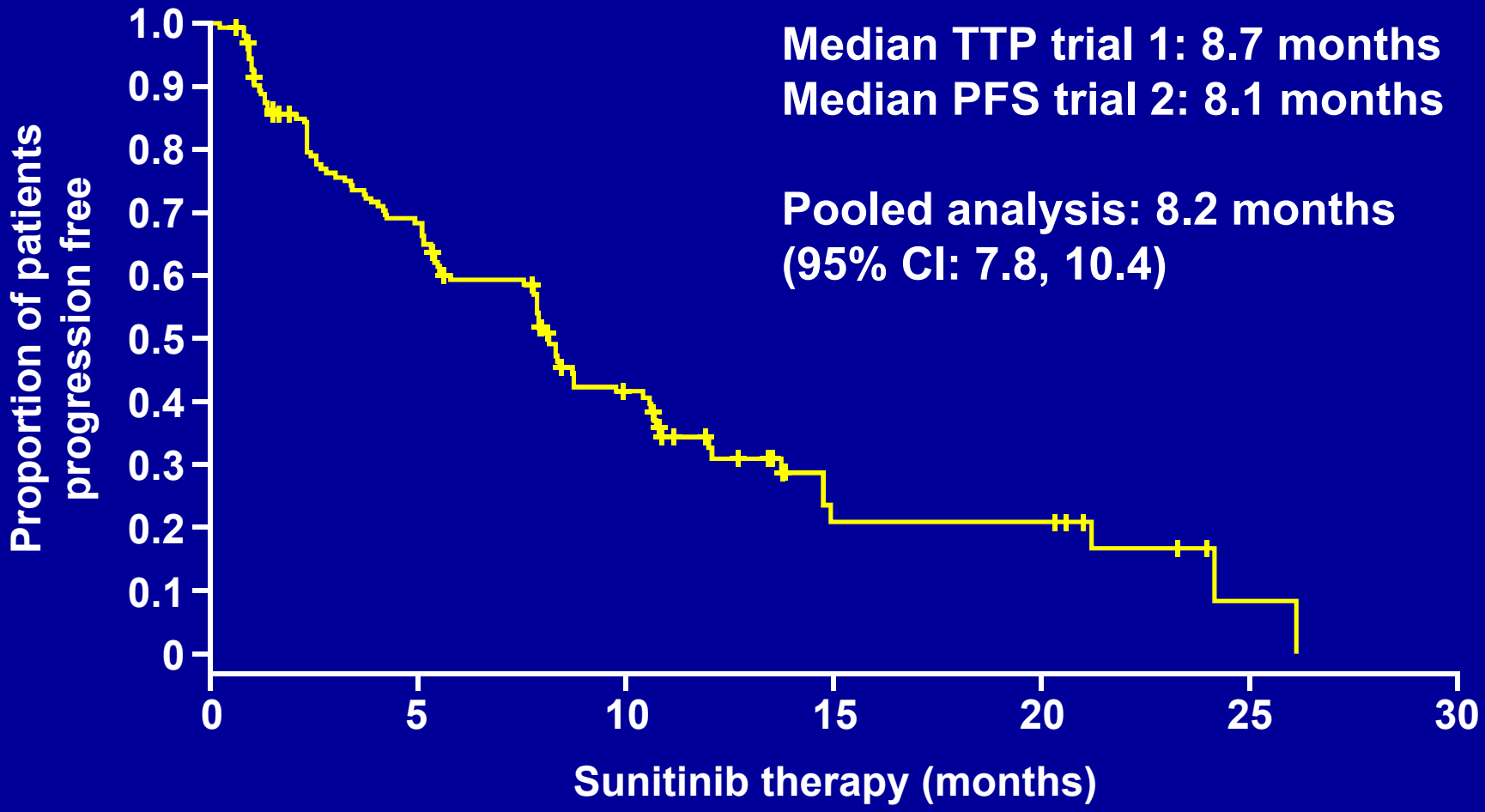
Slide Courtesy of Dr. Motzer, New York

Progression-free Survival chez les répondeurs et non-répondeurs (combinaison 2 études)

	Progression-free survival (months)
Responders (n = 71)	14.8 (95% CI: 10.9 - 24.2)
Stable disease ≥ 3 months (n = 41)	7.9 (95% CI: 5.5 - 8.2)
Stable disease < 3 months or progressive disease (n = 56)	2.1 (95% CI: 1.2 - 2.3)

Motzer JCO 2006
Motzer JAMA 2006

Temps ad progression (2 Phase II)



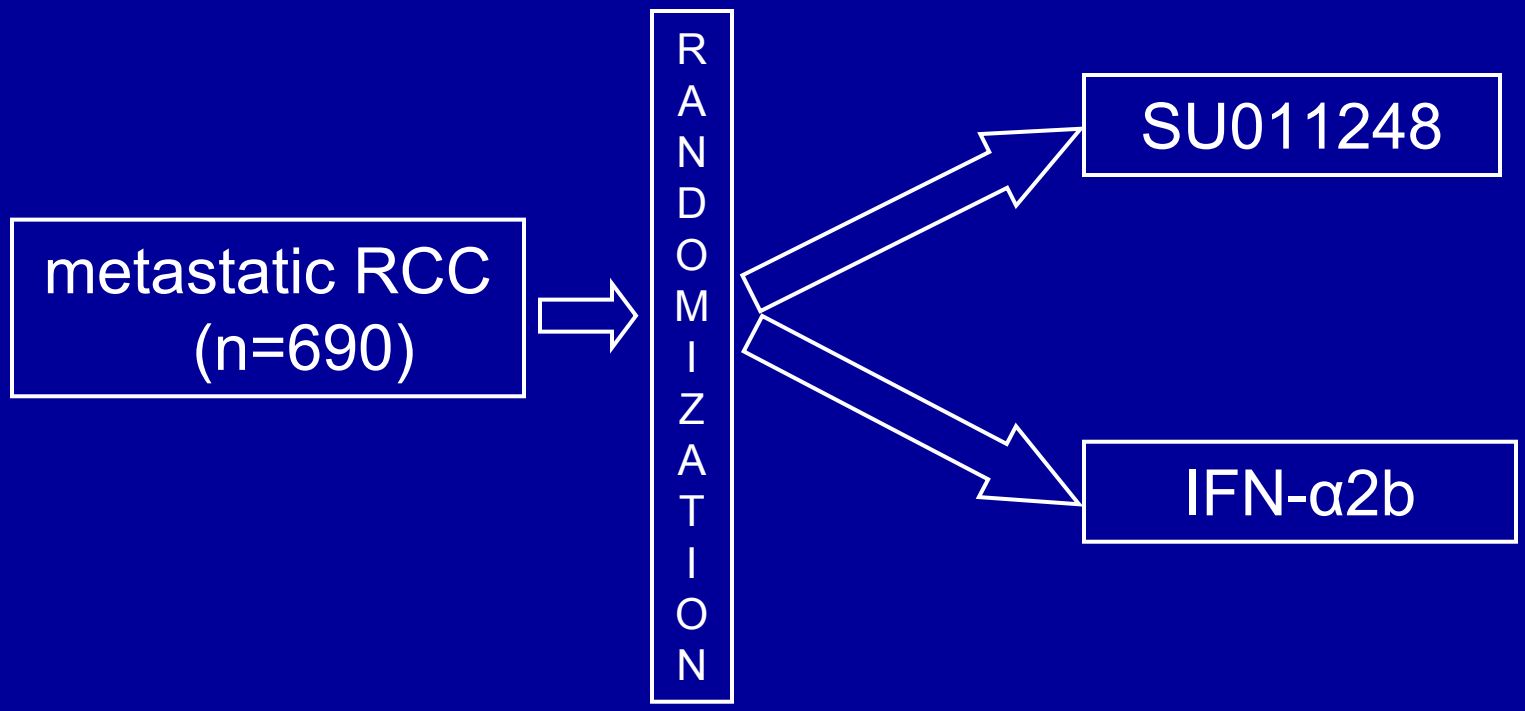
Median TTP trial 1: 8.7 months
Median PFS trial 2: 8.1 months

Pooled analysis: 8.2 months
(95% CI: 7.8, 10.4)

Motzer JCO 2006
Motzer JAMA 2006

SU011248 - Phase III

- **international, multi-centre, randomized study of SU011248 vs. IFN-α first-line**



Objectifs:

Objectif premier

- **Progression-free survival**
  - **Puissance 90% pour détecter une différence de 35%**
    (4.6 months* → 6.2 months)
  - **Évaluation indépendante**

Objectifs secondaires

- **Taux de réponse, OS, innocuité et patient reported outcomes**

**Motzer et al. JCO 2002;20:289-296*

Traitements à l'étude

Arm A: Sunitinib
50 mg po/jr (4 sem on/2 sem off)

vs

Arm B: IFN-α
3 MU 3X/sem1^{ère} sem$\rightarrow$
6 MU 3X/sem 2ème sem $\rightarrow$
9 MU 3X/sem 3ème sem et + SC Injection

- **Évaluation innocuité et efficacité aux 6 sem**
- **Réductions de doses pour toxicité**
- **Traitement continué ad progression ou intolérance**

Best Response selon RECIST

(Revue indépendante)

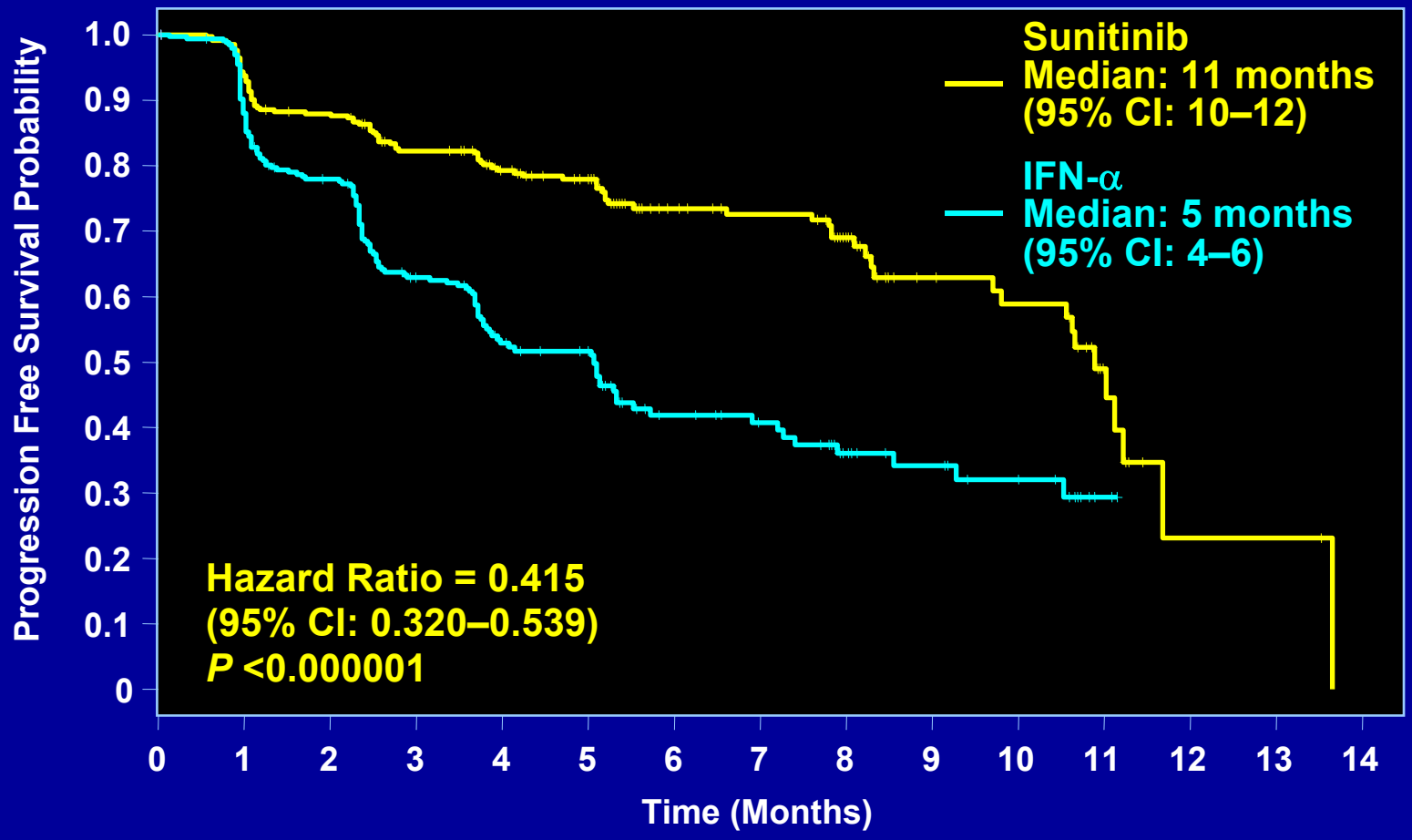
Response	*Sunitinib*	*IFN-α*
Pts with measurable disease at baseline (n)*	335	327
*Objective response***	103 (31%)	20 (6%)
Complete response	0	0
Partial response	103	20
Stable disease	160 (48%)	160 (49%)
Progressive disease/Not evaluable	72 (21%)	147 (45%)

**88 patients not yet assessed by central review*

*****Sunitinib vs IFN-α: P <0.000001***

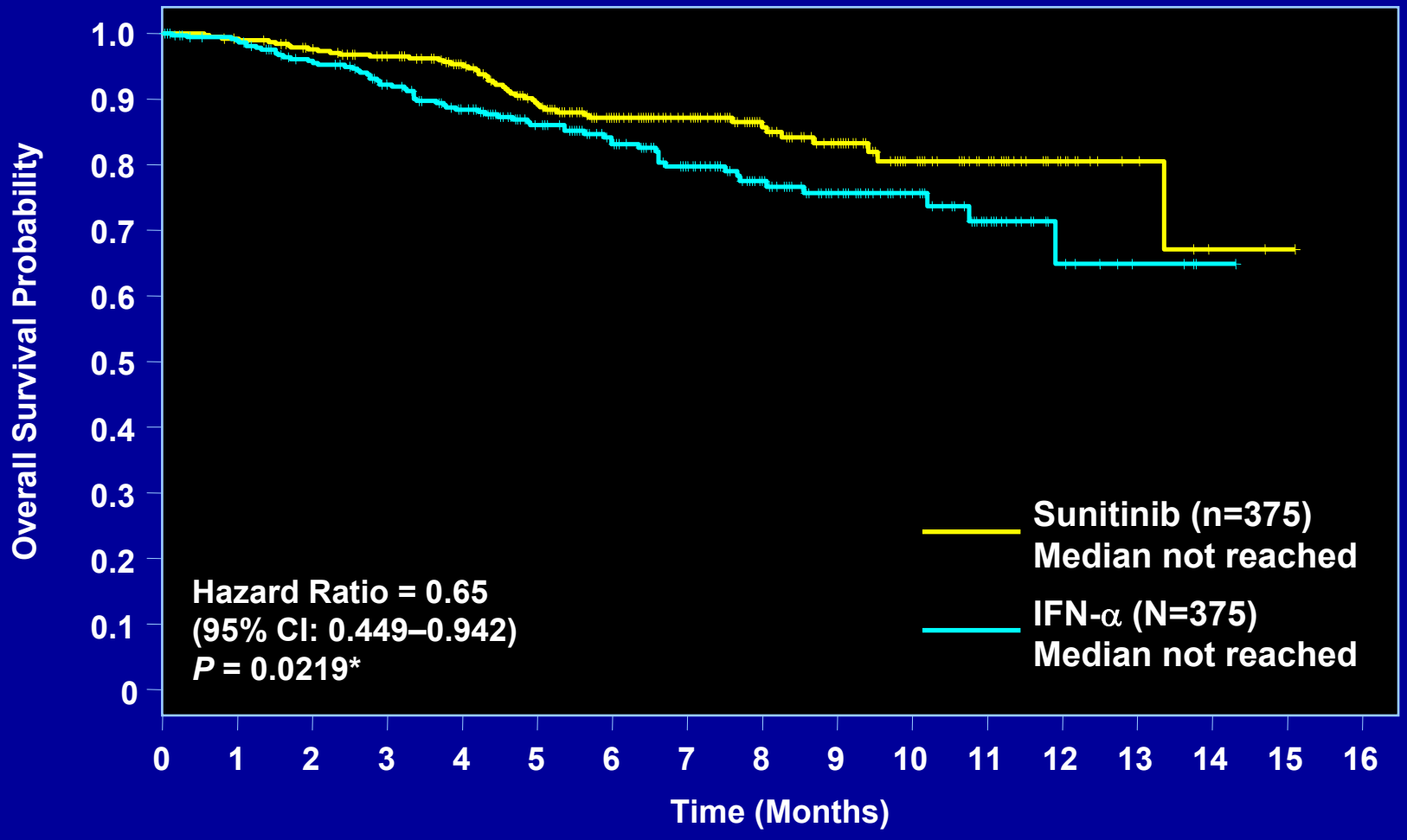
Progression-Free Survival

(Revue centrale)



No. at Risk Sunitinib:	235	90	32	2
No. at Risk IFN-α:	152	42	18	0

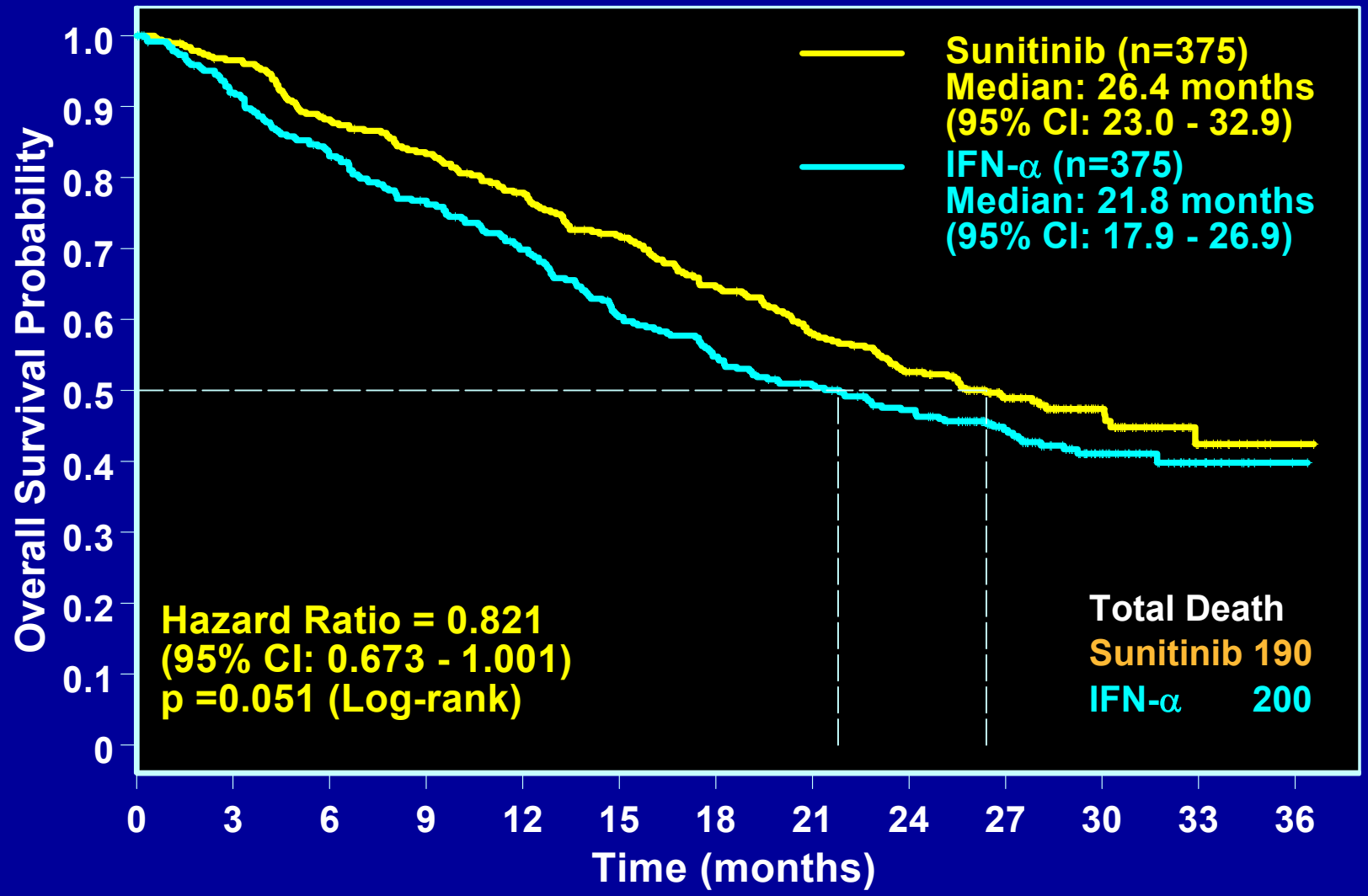
Survie globale



No. at Risk Sunitinib:	341	190	84	15	1
No. at Risk IFN-α:	296	162	66	10	0

**The observed p-value did not meet the pre-specified level of significance for this interim analysis*

Final Overall Survival



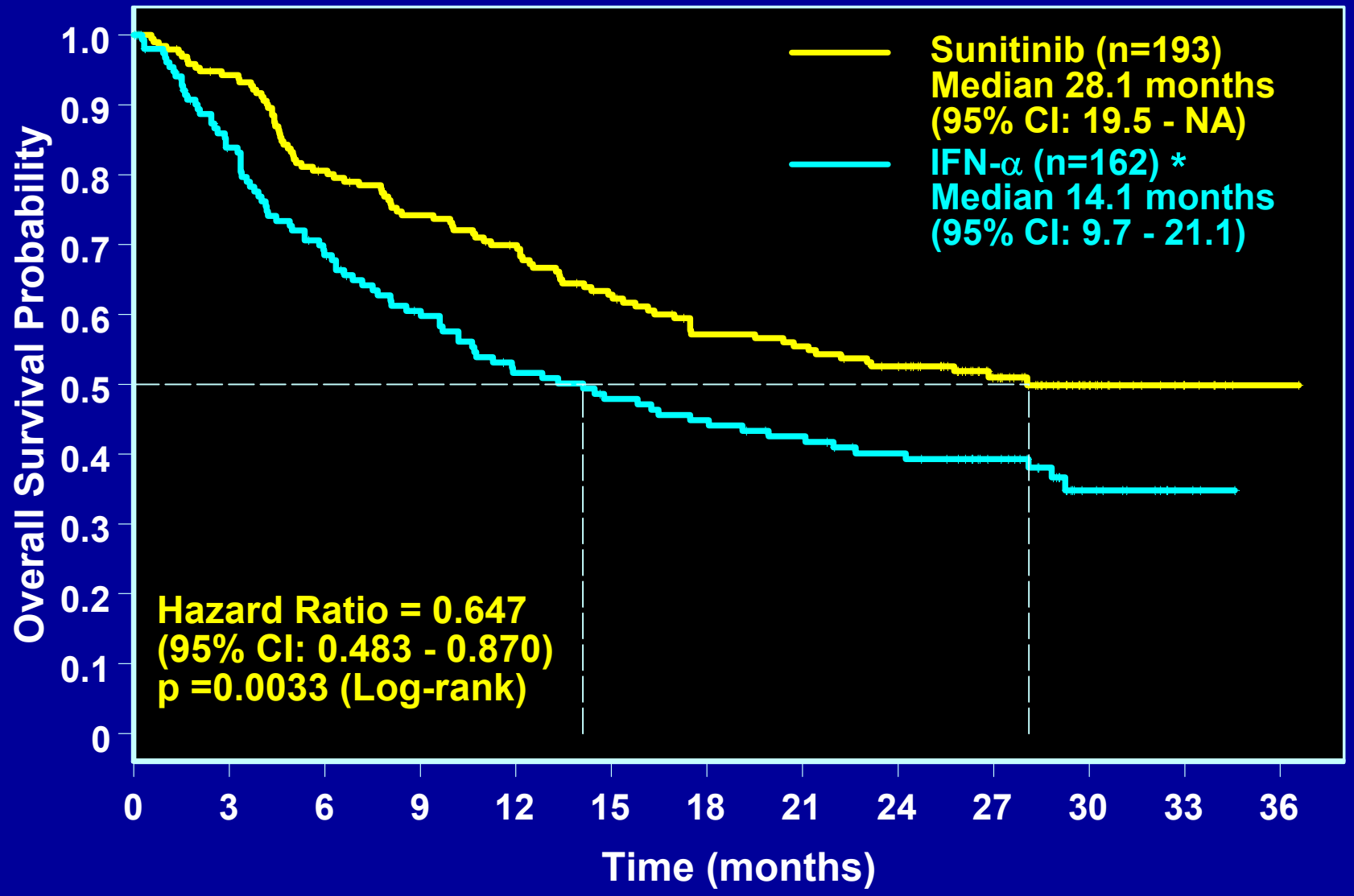
nDeath/nRisk Sunit	375	44 / 326	38 / 283	48 / 229	42 / 180	14 / 61	4 / 2
nDeath/nRisk IFN-α	375	61 / 295	46 / 242	52 / 187	25 / 149	15 / 53	1 / 1

Overall Survival Analyses

	Pre-specified Analyses		Exploratory Analyses
	Unstratified	Stratified	Crossover pts censored
Median OS (mos)	26.4 vs. 21.8	26.4 vs. 21.8	26.4 vs. 20.0
HR (95% CI)	0.821 (0.673, 1.001)	0.818 (0.669, 0.999)	0.808 (0.661, 0.987)
P-value (Log-rank)	0.0510	0.0491	0.0362
P-value (Wilcoxon)	0.0128	0.0132	0.0081

**Stratification factors: ECOG PS, LDH, and nephrectomy*

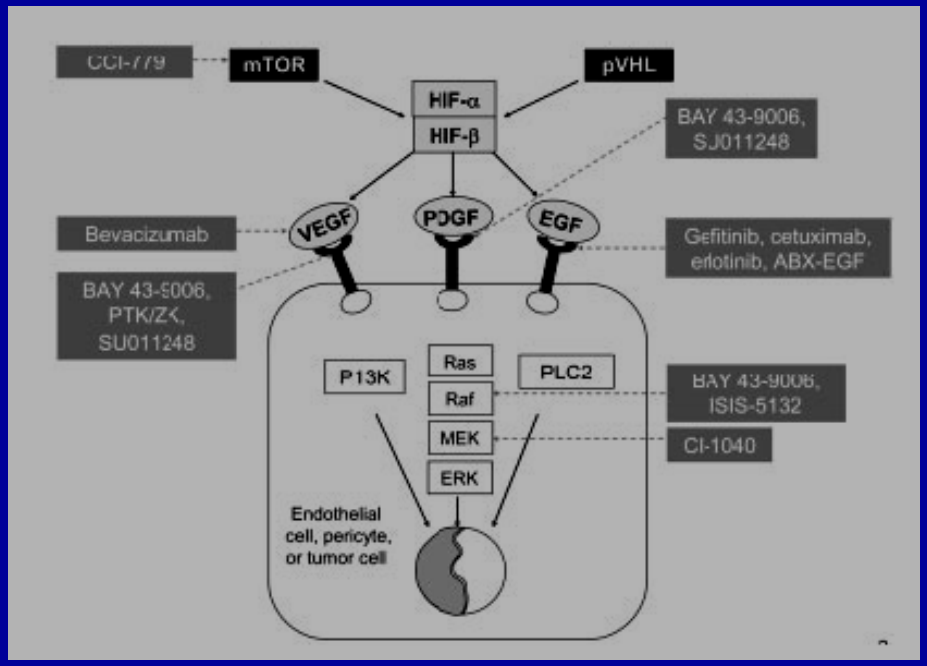
OS in patients who did not receive any post-study treatment



**Includes 20 patients who crossed over to sunitinib on study*

Autres approches: inhibition m-TOR

- **mTOR: Target of rapamycine**
- Régulation du cycle cellulaire
- Agit sur PI3k et Akt/PTEN
- Stimule traduction protéique et stabilisation HIF

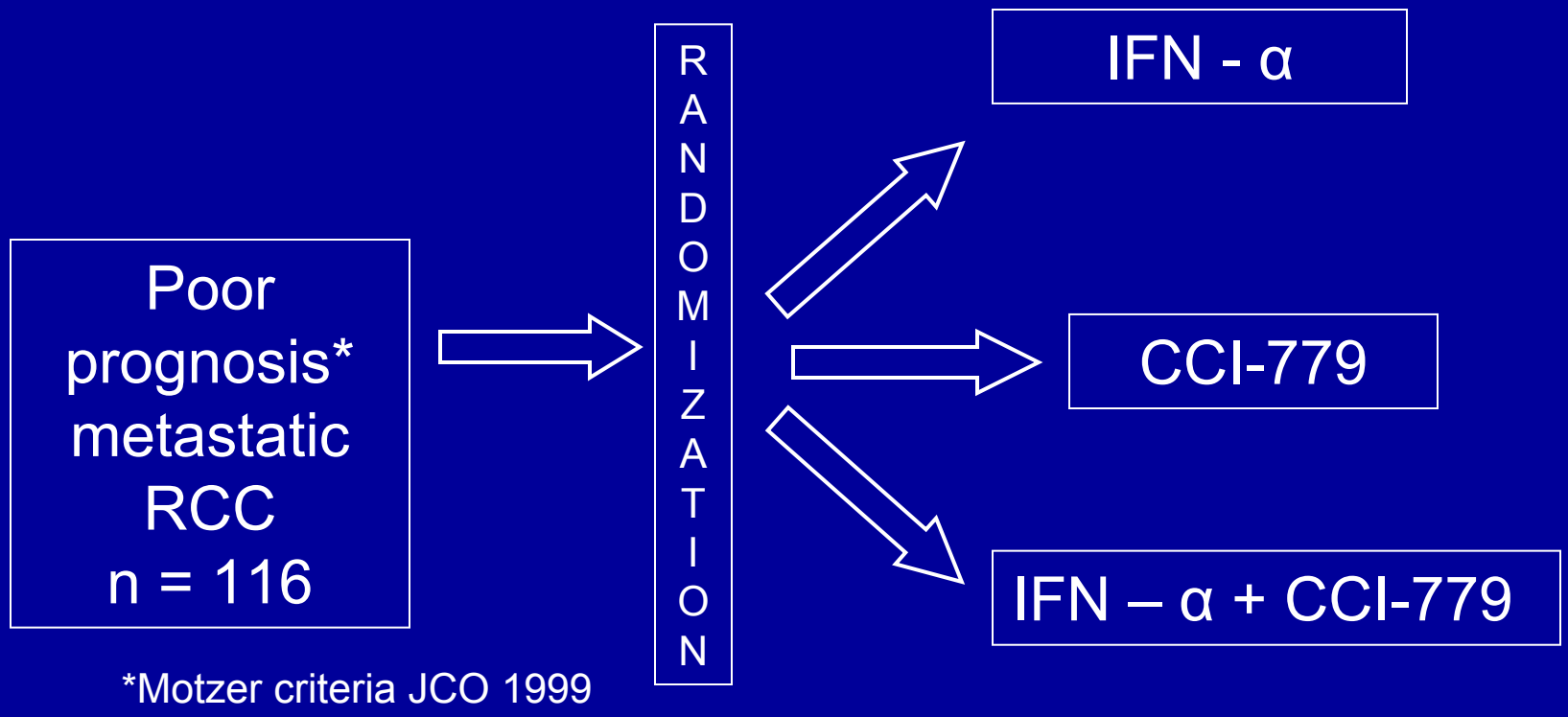


CCI-779

- TR 7% chez CR réfractaire aux cytokines
- TR 26% chez Répondeurs/SD aux cytokines

Atkins JCO 2004

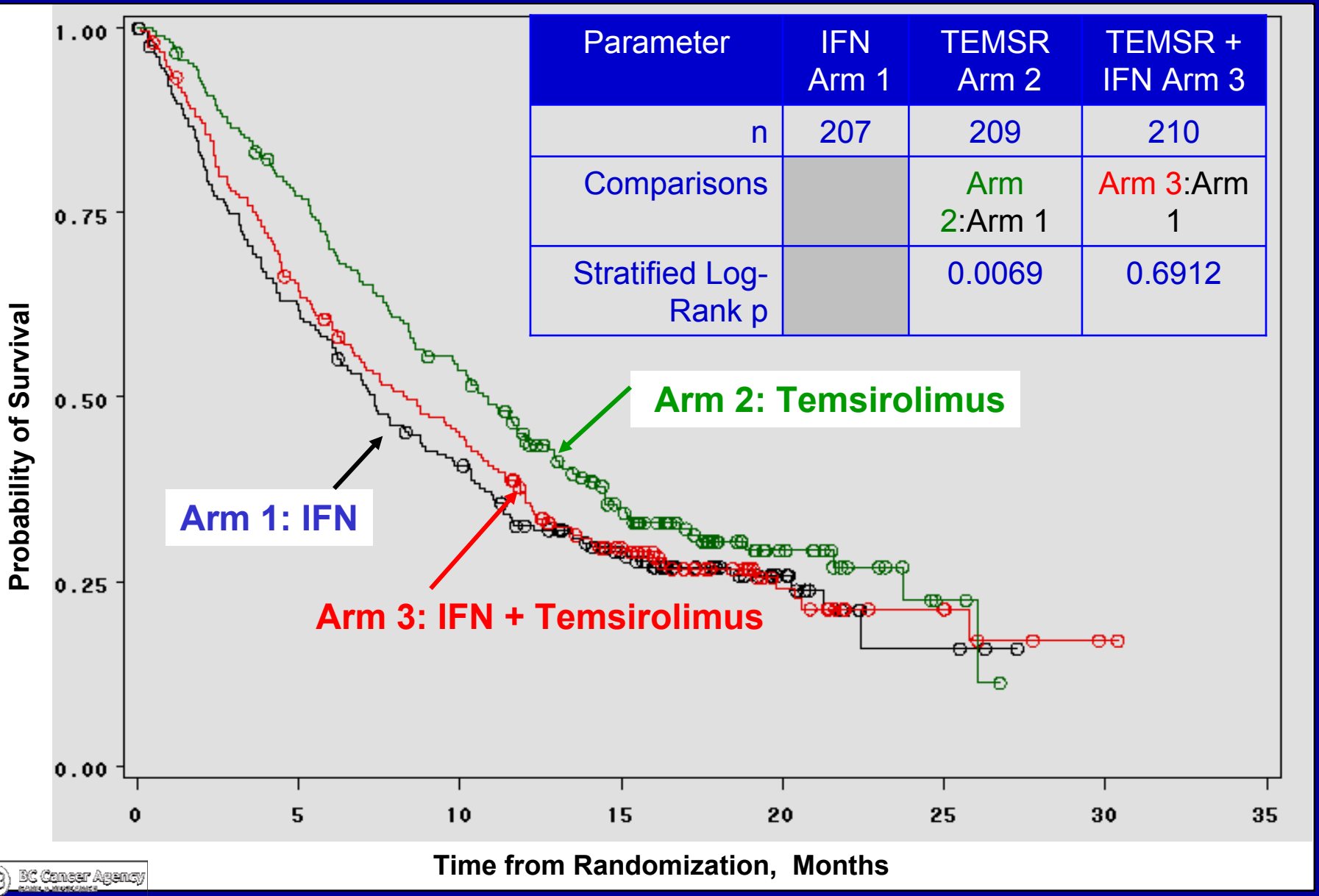
Autres approches: inhibition m-TOR



*Motzer criteria JCO 1999

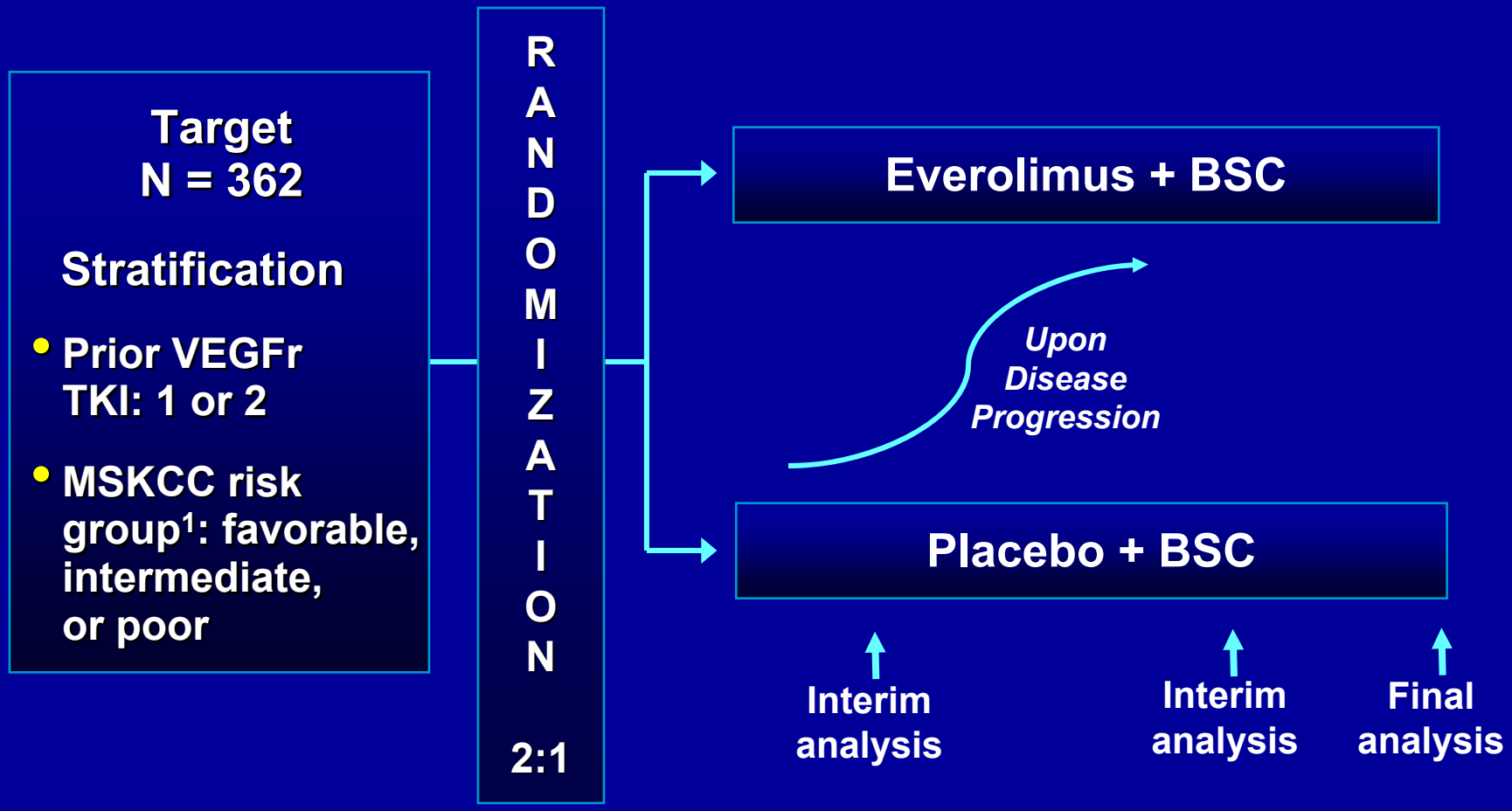
Survie globale

Parameter	IFN Arm 1	TEMSR Arm 2	TEMSR + IFN Arm 3
n	207	209	210
Comparisons		Arm 2:Arm 1	Arm 3:Arm 1
Stratified Log-Rank p		0.0069	0.6912



BC Cancer Agency

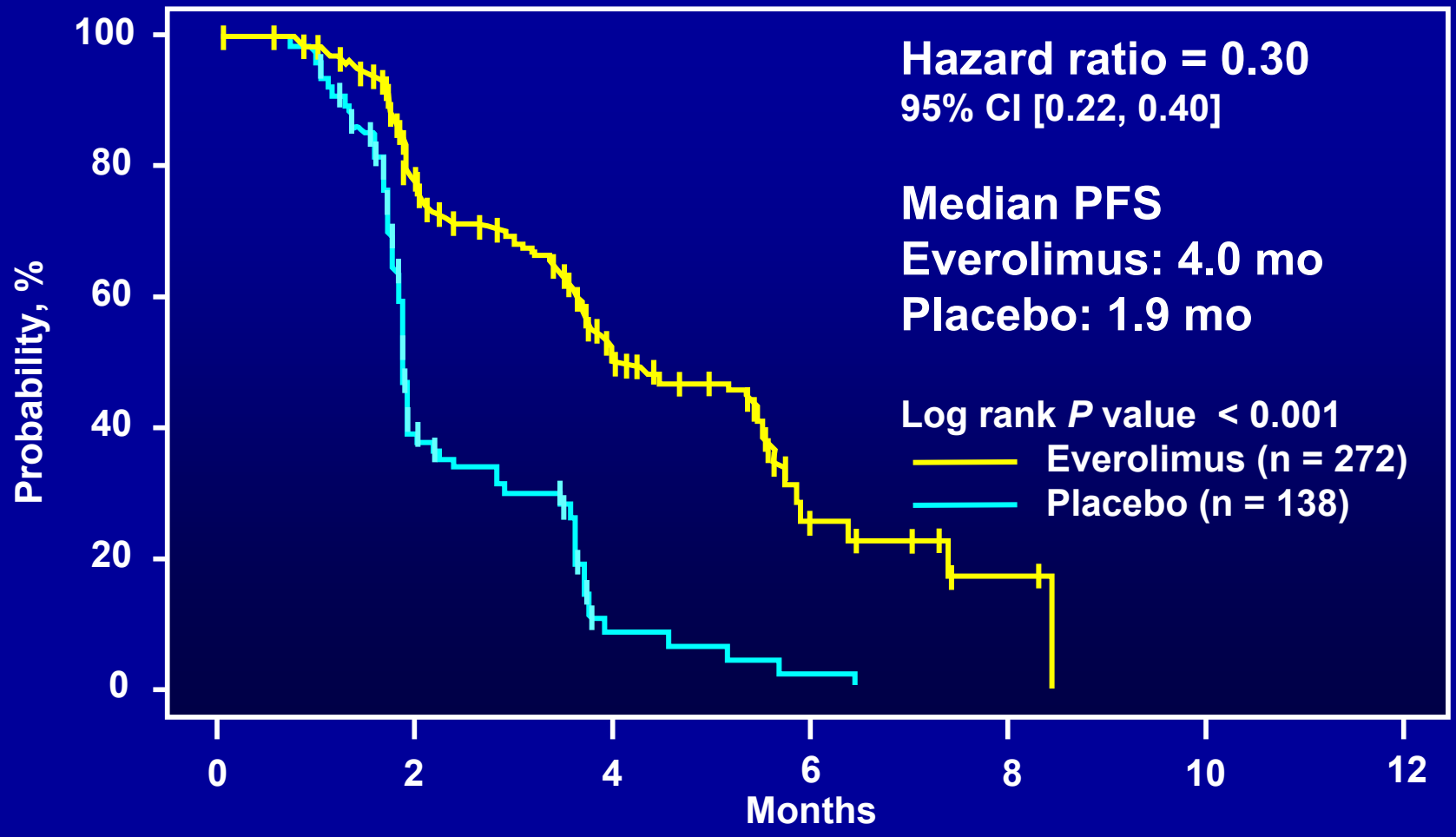
Study Design



- Interim analyses planned after ≈ 30% and 60% of targeted 290 events

1. Motzer et al. *J Clin Oncol.* 2004;22:454-463.

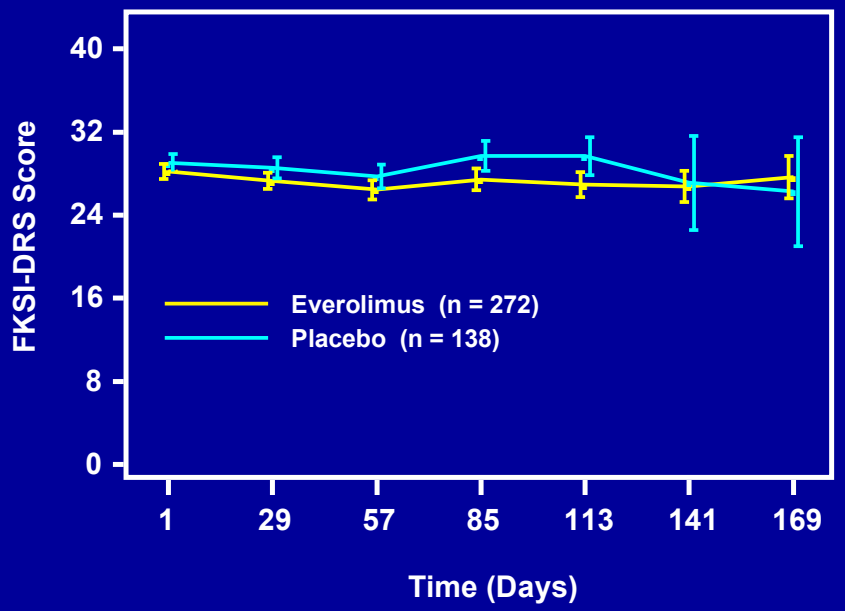
Progression-Free Survival by Treatment
Central Radiology Review



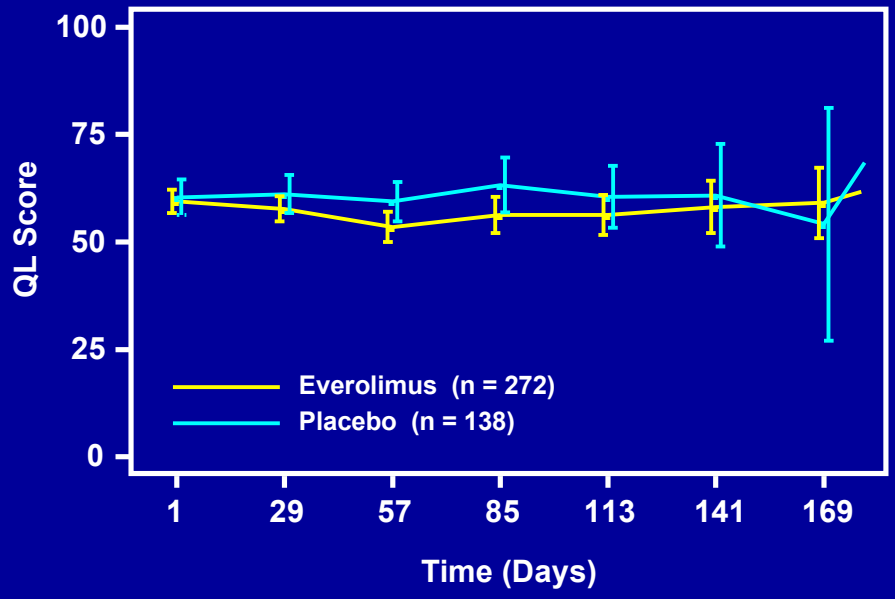
Patients at Risk							
Everolimus	272	132	47	8	2	0	0
Placebo	138	32	4	1	0	0	0

Health-Related Quality of Life

Mean FKS-DRS Scores



Mean Global Health Status/QoL*



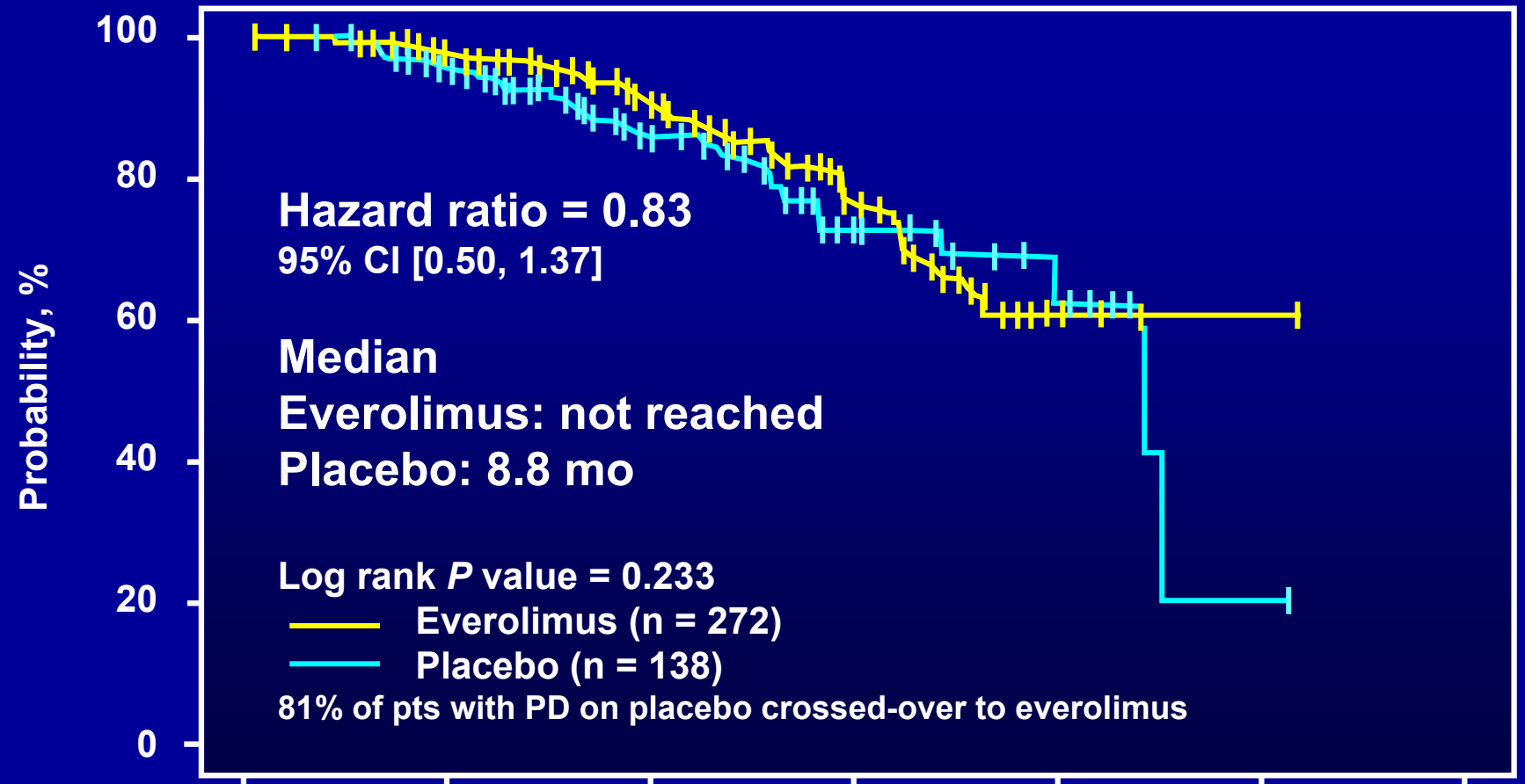
Patients at risk

Everolimus	234	202	179	116	83	53	33
Placebo	126	106	86	36	27	9	4

	237	206	175	116	82	53	33
	125	105	87	38	27	10	4

* EORTC QLQ-C30

Overall Survival by Treatment



Patients at Risk							
Everolimus	272	229	126	61	9	1	0
Placebo	138	111	62	25	9	1	0

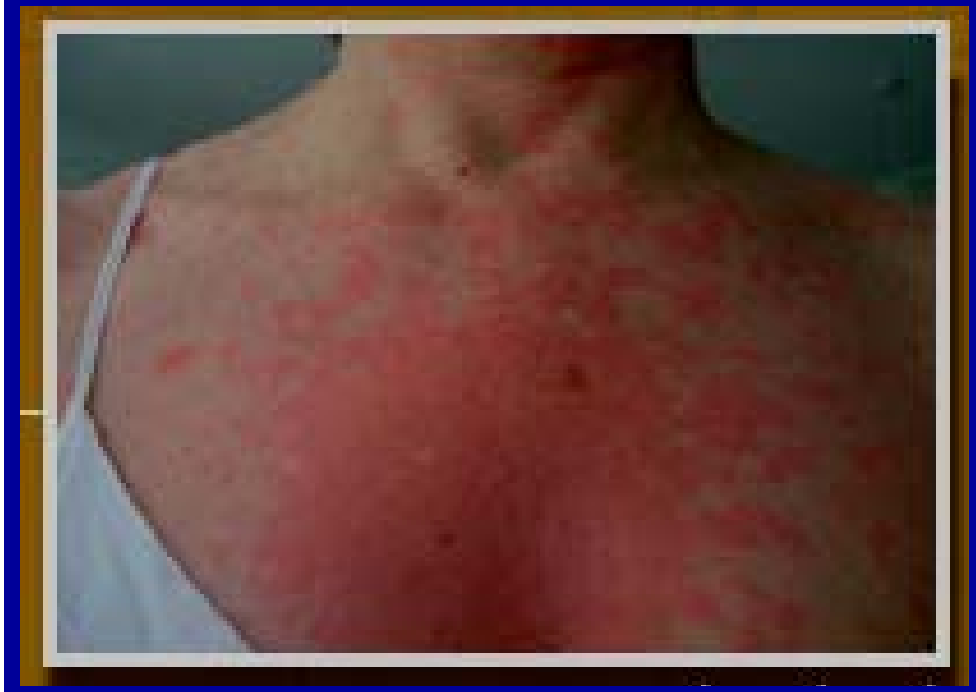
Sorafenib (BAY 43-9006) – Phase III
Autres toxicités non-hématologiques

- Nausea
- Anorexia
- Vomiting
- Constipation
- Mucositis
- Rash
- Alopecia
- Pruritus
- Neuropathy

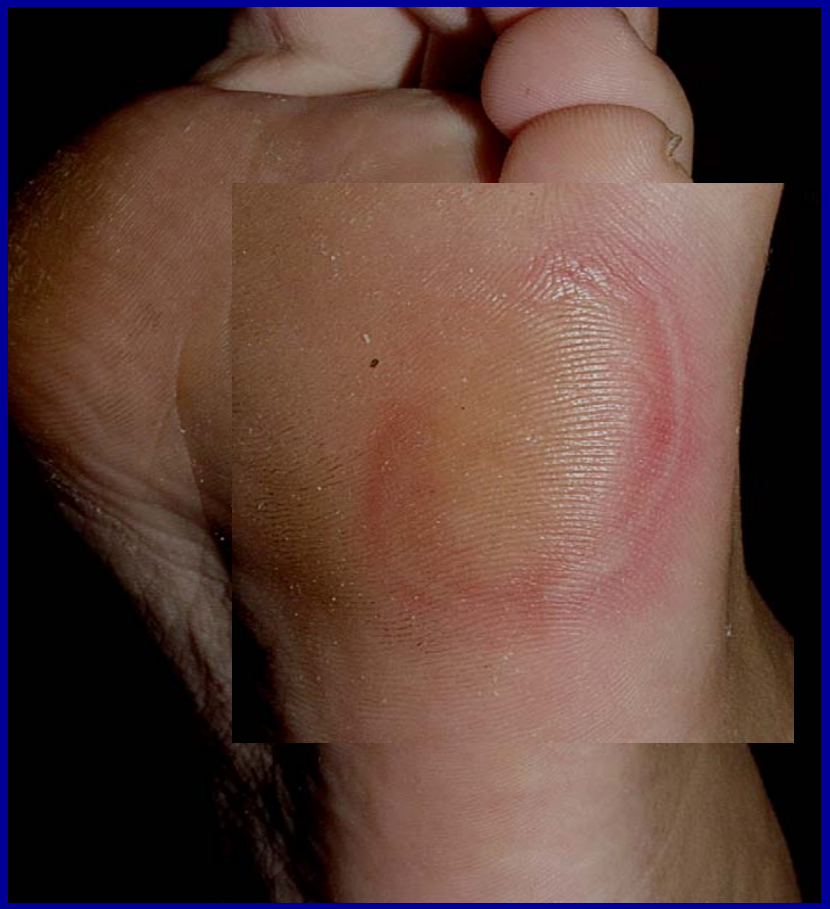
<5% grade 3 et 4

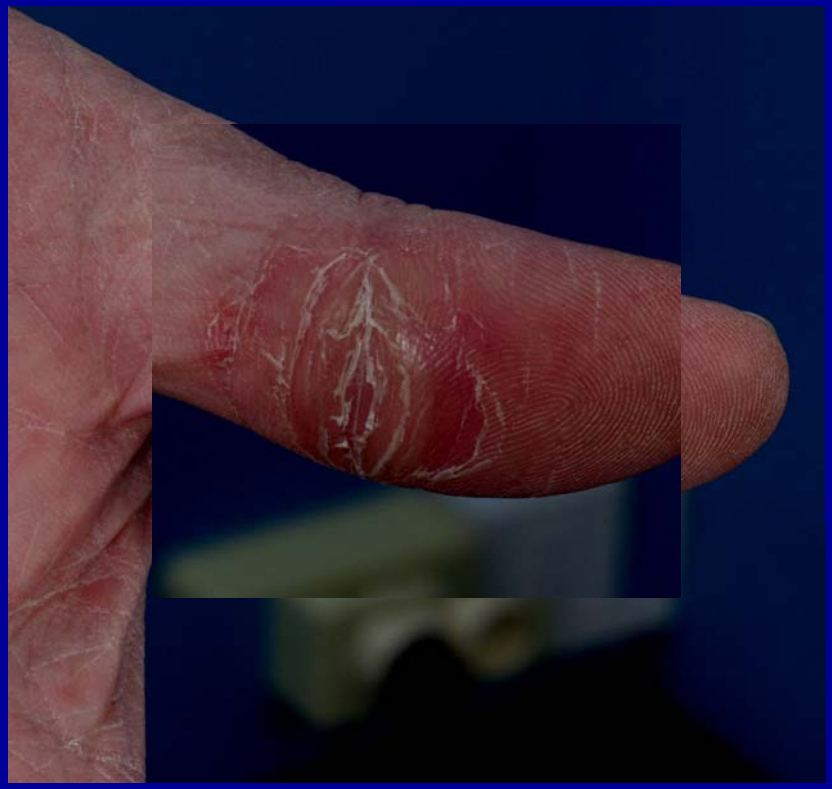
Escudier ECCO 2005

Sorafenib (BAY 43-9006)



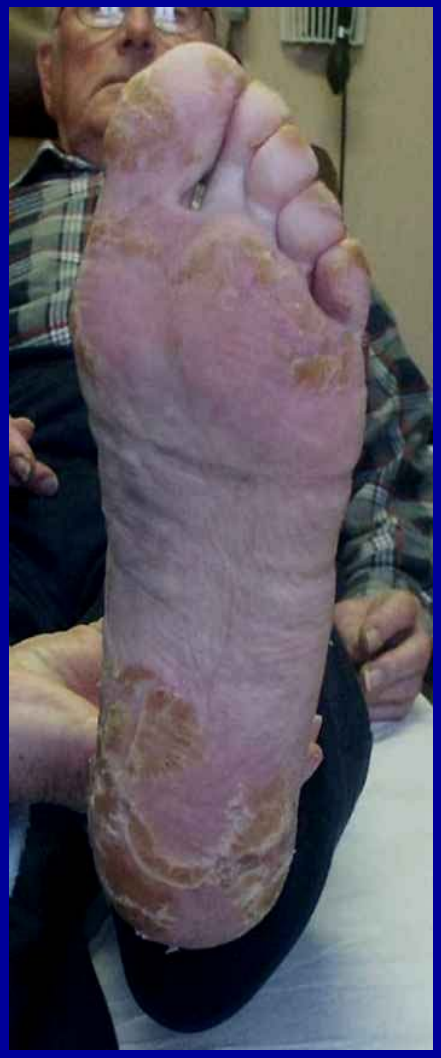
Sorafenib (BAY 43-9006) – Phase III
Toxicité cutanée





Escudier ECCO 2005

Sorafenib (BAY 43-9006) – Phase III
Toxicité cutanée



Courtesy of Dr. Escudier

Sorafenib (BAY 43-9006)
Hypertension via effet anti-angiogénique

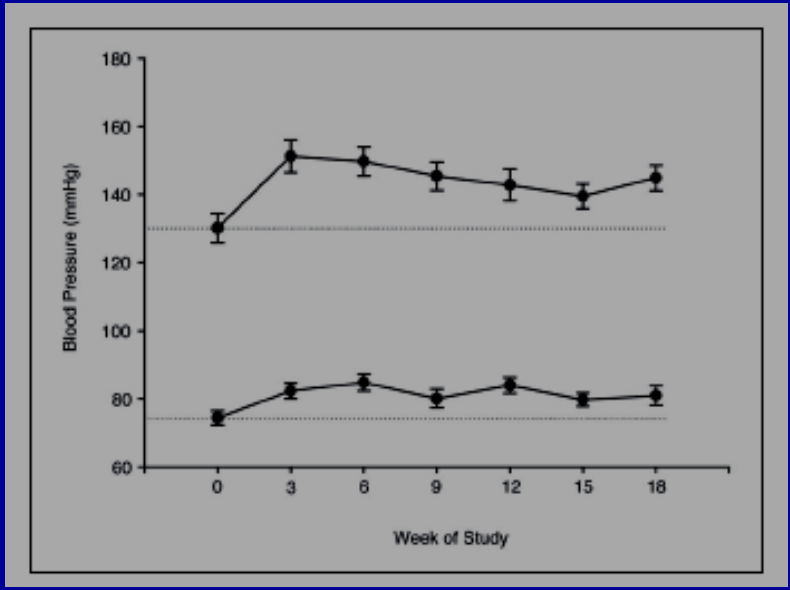


Table 2. Mean Values of SBP, DBP, and HR at Baseline, Week 3, and Week 18

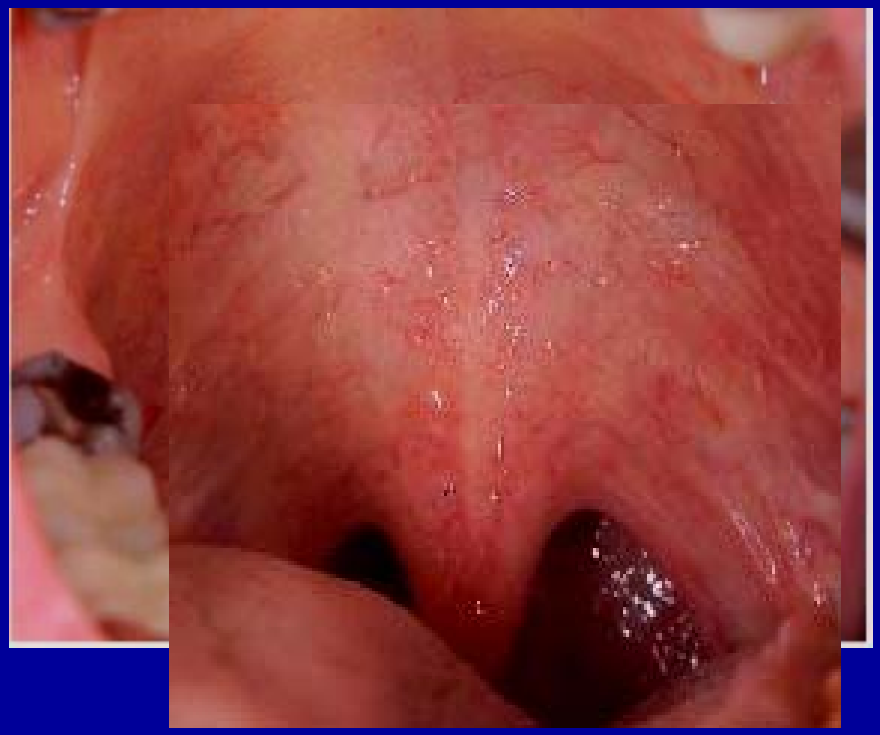
	Week 0 (mmHg)		Week 3 (mmHg)		Week 18 (mmHg)	
Measure	Mean	SEM	Mean	SEM	Mean	SEM
SBP*	130.6*	4.3	151.2*	4.8	144.4*	3.7
DBP*	74.4*	2.1	82.3*	2.3	80.9*	2.9
HR*	81.1†	3.7	80.8†	4.1	81.2†	3.9

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.
*$P < .001$.
†P = not significant.

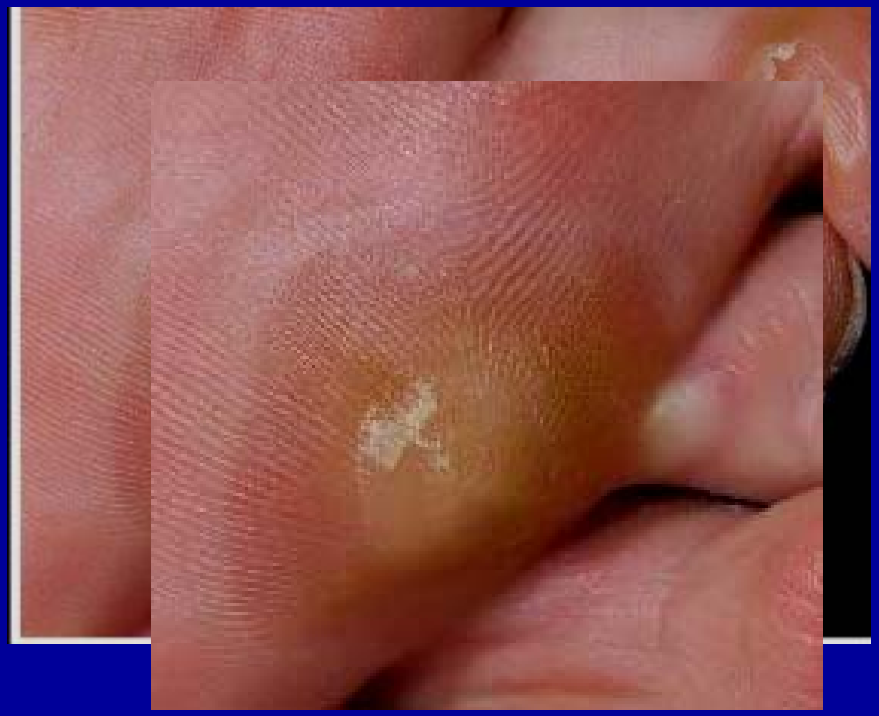
- **> 60% des patients avec augmentation de systolique de ≥ 20 mmHG**
- **ACE-I, bloqueurs récepteur AT ou bloqueurs calciques suggérés**
- **Éviter verapamil / diltiazem (inhibiteurs CYP 3A4)**

Veronese JCO 2006
Sica JCO 2006

SU011248 – 2 Phase II
Toxicité



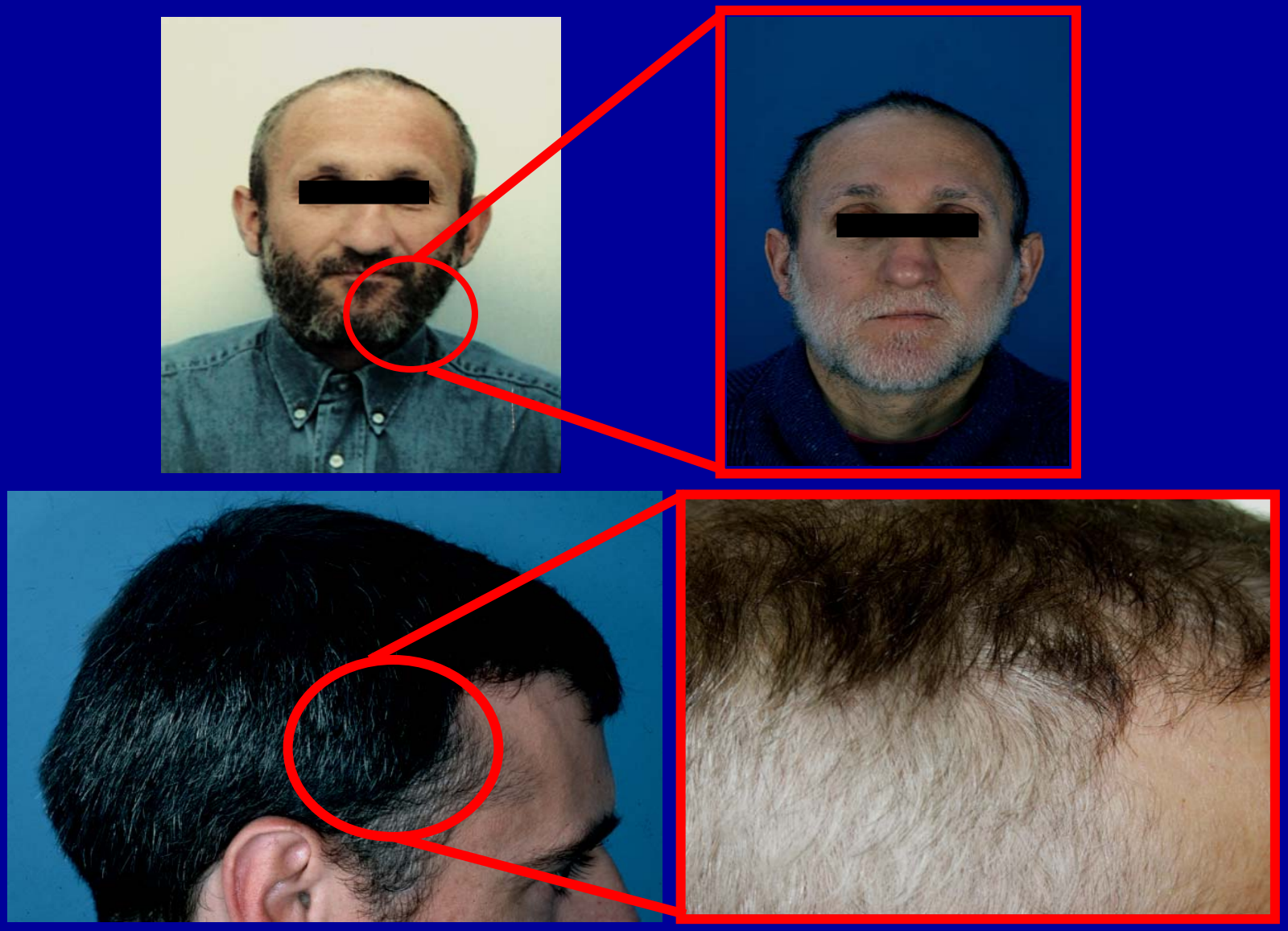
Stomatite fantôme



Toxicité cutanée

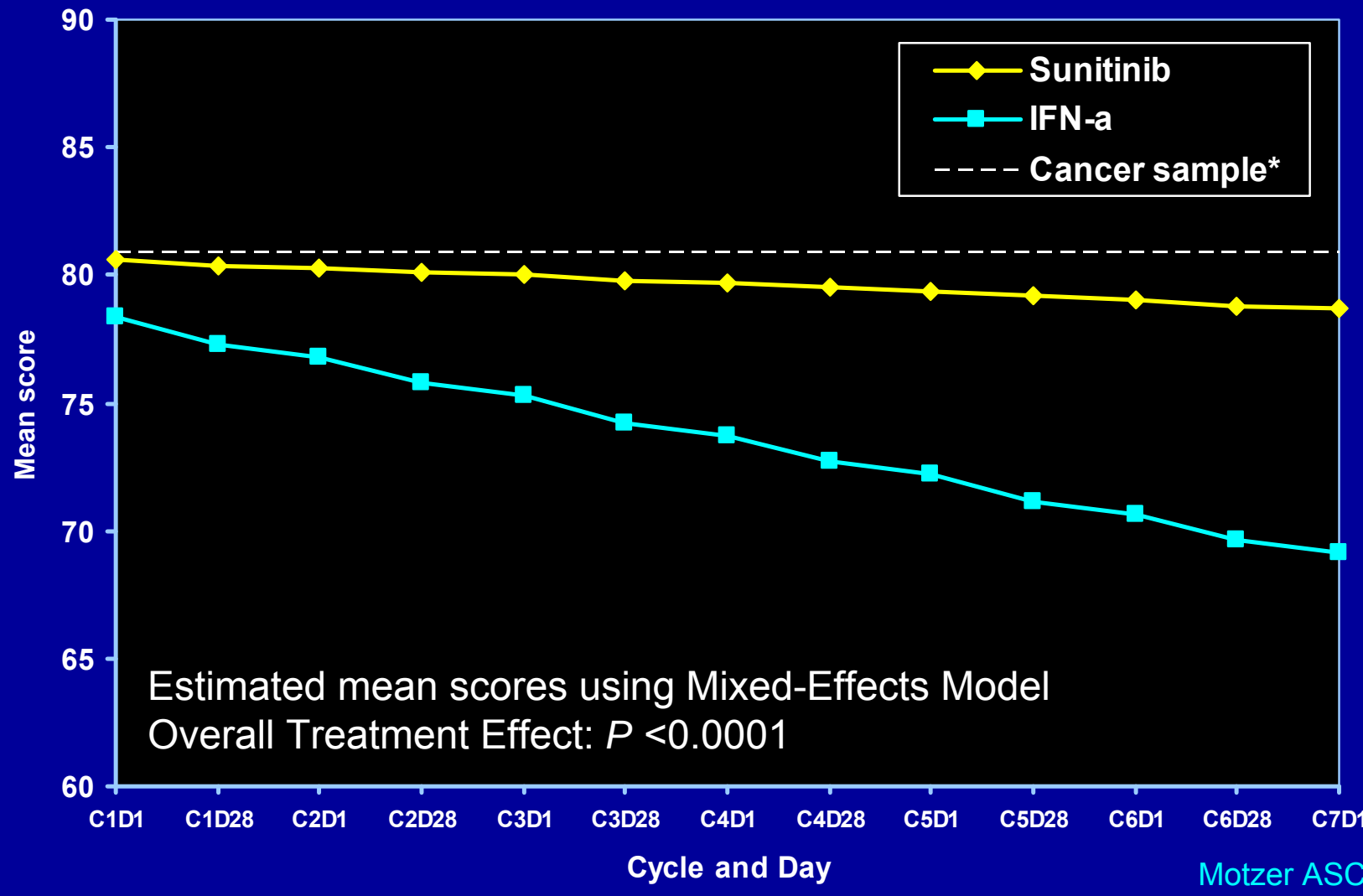
Motzer Jama 2006
Motzer JCO 2006

Décoloration de la pilosité avec Sutent



Slide Courtesy of Dr. Escudier

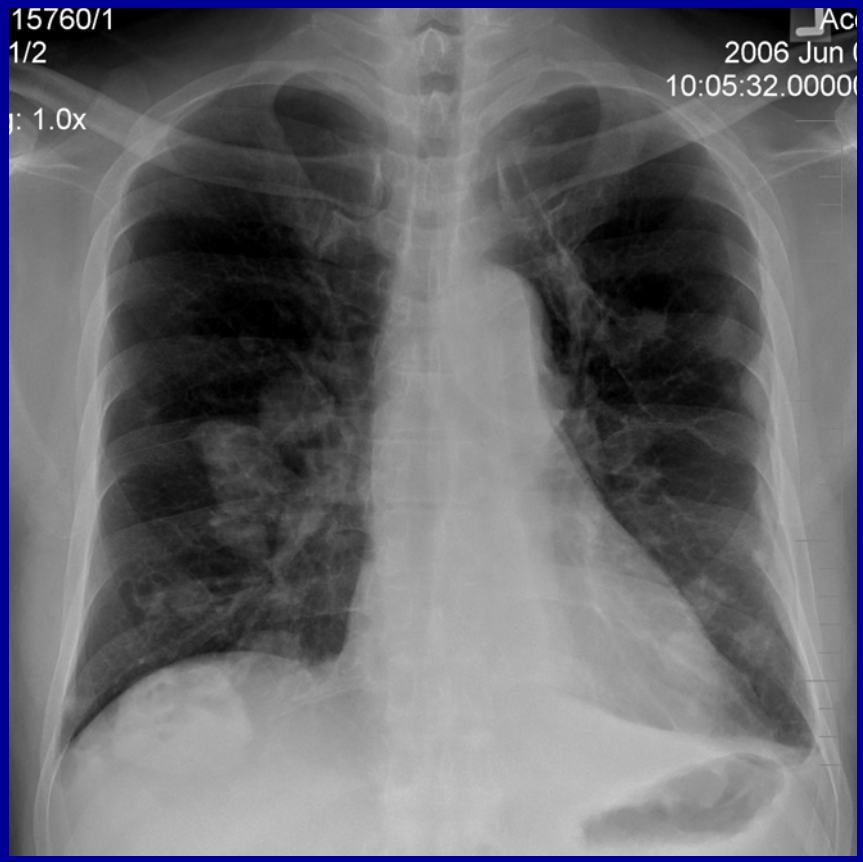
Functional Assessment of Cancer Therapy-General (FACT-G): Total Score

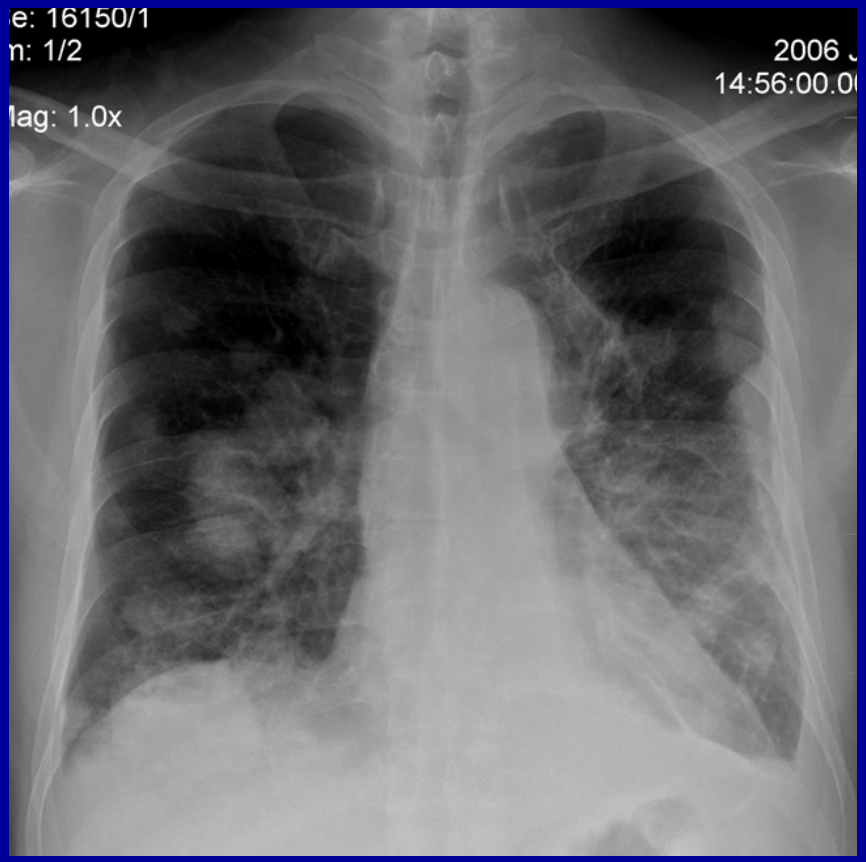


Motzer ASCO 2006

**Brucker et al. Evaluation & The Health Professions 2005*

Cas I : Pat. E.C.

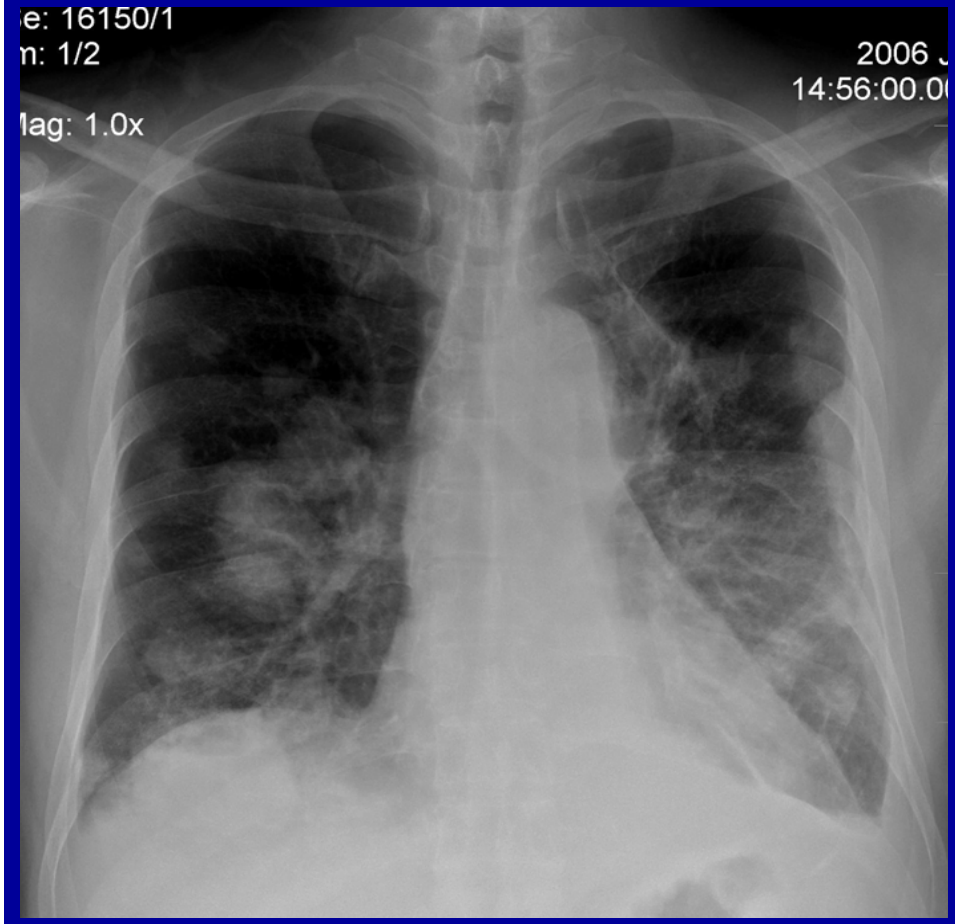


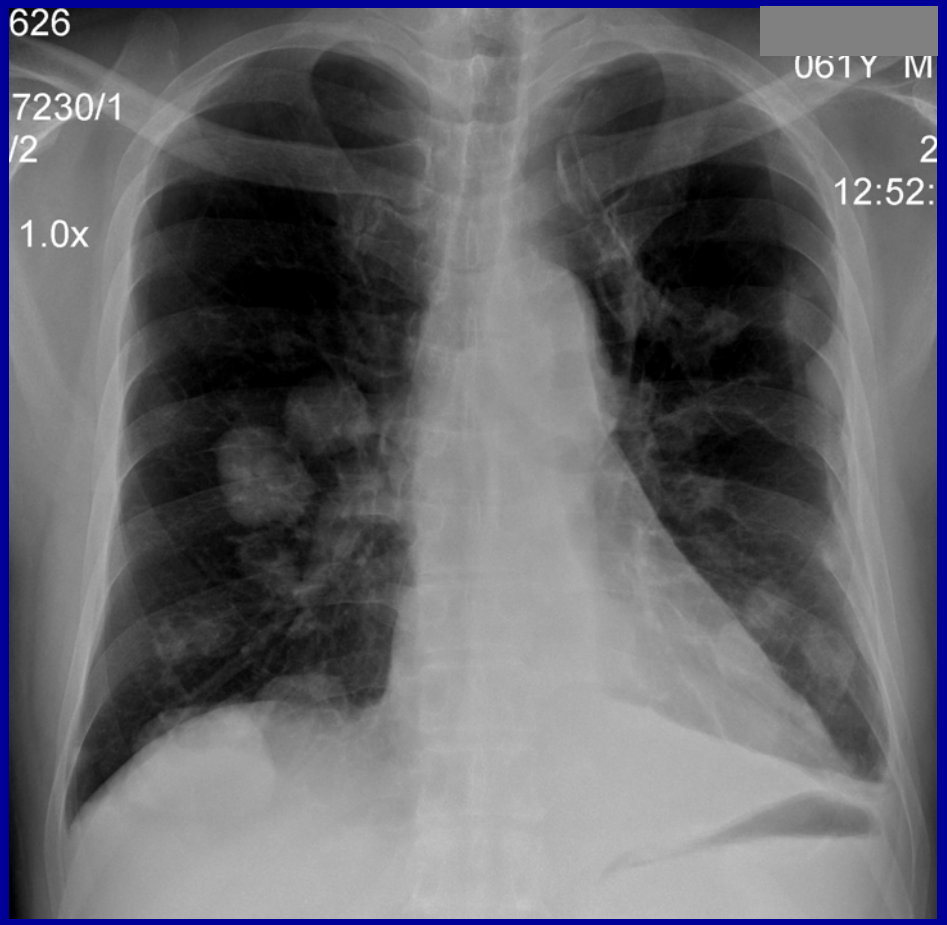


7 Juin 2006 **14 juin 2006**

Arrêt une semaine pour toxicité

Case I : Pat. E.C.





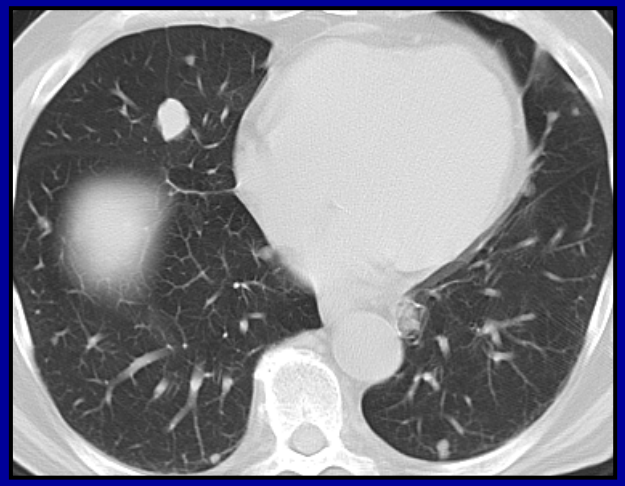
14 juin 2006

12 juillet 2006

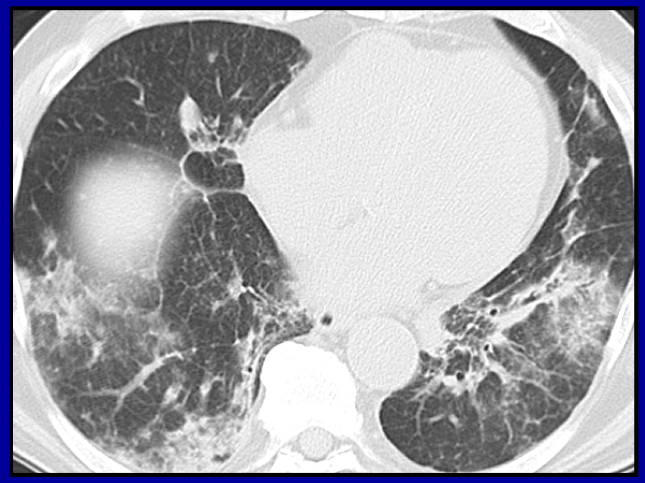
Reprise thérapie 14 juin 2006

Pneumonitis with Everolimus Therapy

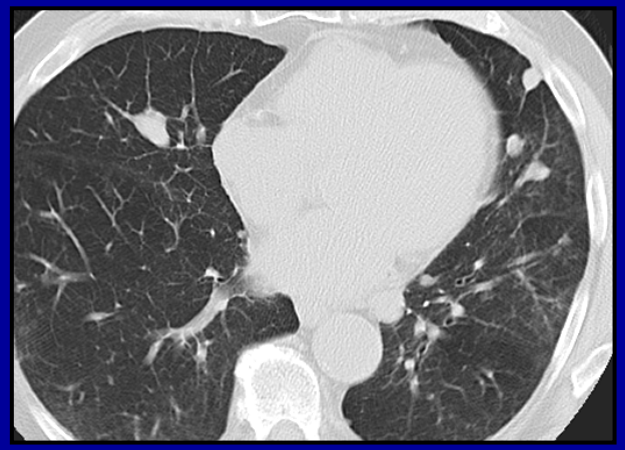
Baseline



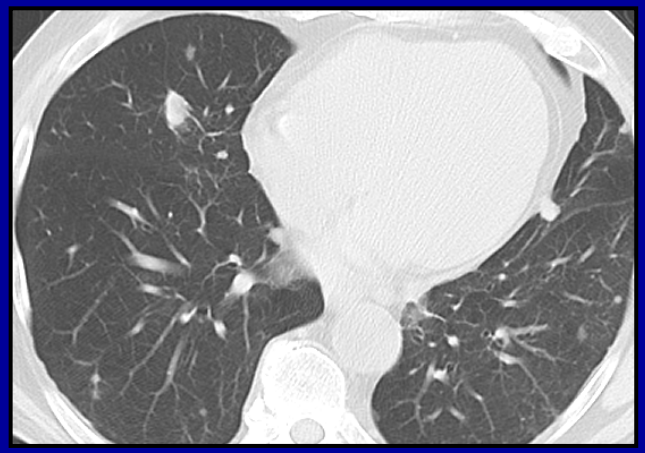
Month 5



Month 11



Month 12



Possible Algorithm for RCC Therapy Based on Phase III data: 2007

<table>
<tr><th colspan="2">Setting</th><th colspan="2">Therapy</th></tr>
<tr><td rowspan="2">First -line therapy</td><td>Good + interm risk</td><td rowspan="3">Sunitinib</td><td>HD-IL-2</td></tr>
<tr><td>Poor Risk</td><td>Temsirolimus</td></tr>
<tr><td rowspan="2">Second-
Line Therapy</td><td>Cytokine failures</td><td rowspan="2">Sorafenib</td></tr>
<tr><td>VEGFR or TOR inhibitor failures</td><td colspan="2">?????</td></tr>
</table>

Lack of phase III data with a particular agent in a particular setting, doesn't equal lack of efficacy

From Atkins, ASCO 2006

Standards for RCC Therapy by Phase III Trial
ASCO 2008

	Setting	Phase III
Treatment-naive	Good or intermediate risk*	Sunitinib
		Bevacizumab + IFN-α
	Poor risk*	Temsirolimus Sunitinib
Previously treated	Prior cytokine	Sorafenib
	Prior VEGFr-TKI	Everolimus
	Prior mTOR inhibitor	

*MSKCC risk status.