

Objectives and Outcomes With Cytokine Therapy

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Cytokine Treatment for RCC

- Only systemic therapy for metastatic RCC before anti-angiogenic and targeted agents
- Interferon (IFN)- α
 - 26% reduction in risk of death vs control¹
 - Median improvement in survival, 3.8 months
- Interleukin (IL)-2
 - ORR, 15-23%; CR, 7-10%^{2,3}
 - Median response ranges from 3 to >131 months

1. Coppin C et al. *Cochrane Database Syst Rev.* 2005;(1):CD001425.

2. Fisher RJ et al. *J Sci Am.* 2000;6 Suppl 1:S55.

3. McDemott J *Clin Oncol* 2005

Developments in Cytokine Therapy

- Aim to reduce toxicity, enhance efficacy
 - Constant-infusion IL-2¹
 - Subcutaneous IL-2²
 - Combining IL-2 and IFN- α ³
 - Selection of patients most likely to respond⁴
 - Combining cytokines with targeted and anti-angiogenic agents

1. West WH et al. *N Engl J Med.* 1987;316:889.

2. Arzpodien J et al. *Lancet.* 1990;335:1509.

3. Negrier S et al. *N Engl J Med.* 1998;338:1272.

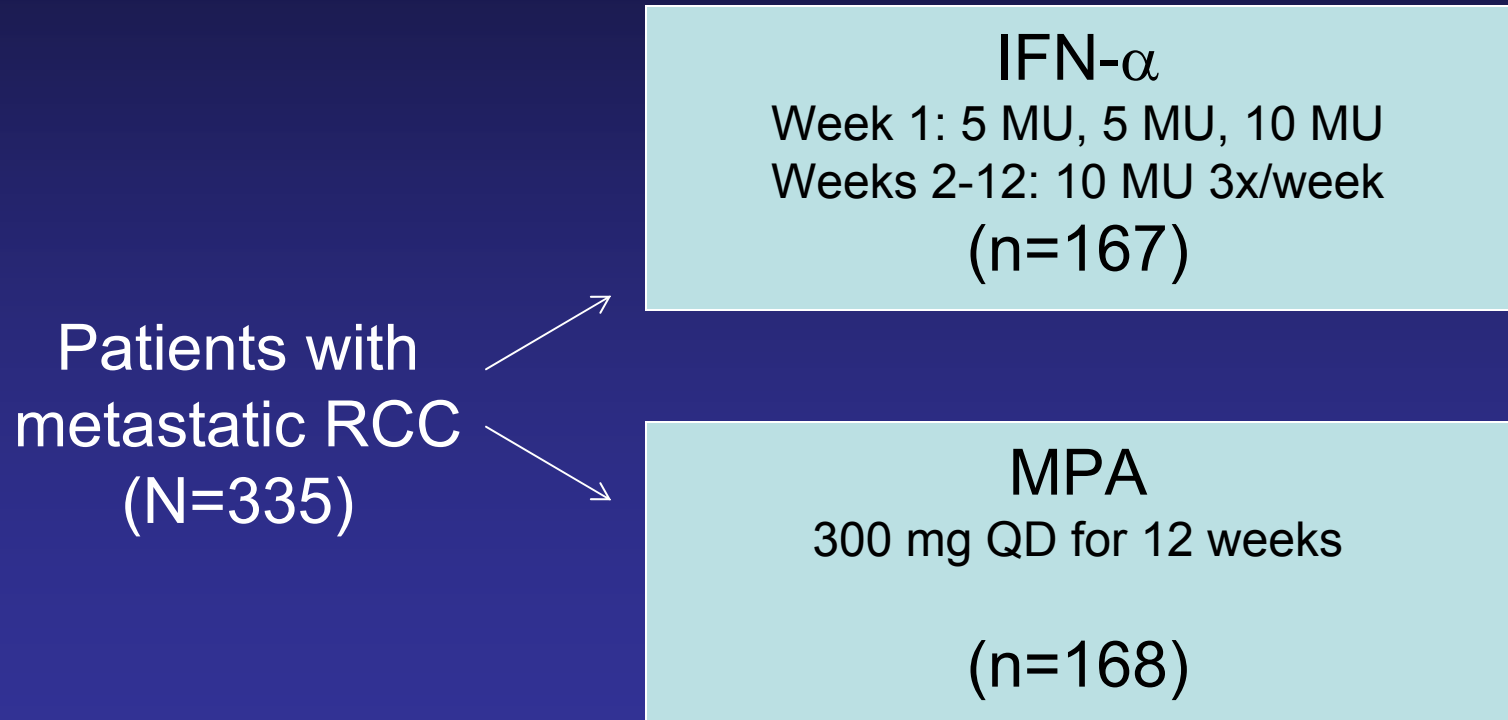
4. Atkins M et al. *Clin Cancer Res.* 2005;11:3714.

Considerations in Using Cytokine Therapy

- Efficacy
- Toxicity
- Experience
- Patient selection

Interferon- α vs MPA for Metastatic RCC

Patients with
metastatic RCC
(N=335)



IFN- α

Week 1: 5 MU, 5 MU, 10 MU

Weeks 2-12: 10 MU 3x/week

(n=167)

MPA

300 mg QD for 12 weeks

(n=168)

MPA = medroxyprogesterone
acetate

Medical Research Council Renal Cancer Collaborators. *Lancet*. 1999;353:14.

Minimal Response Rate, Survival Improvement With IFN- α

Efficacy benefits of IFN- α vs MPA

- 28% reduction in risk of death
 - HR, 0.72 (95% CI, 0.55-0.94; $P = .017$)
- 12% improvement in 1-year survival
 - 43% vs 31%
- 2.5-month improvement in median OS
 - 8.5 vs 6 months

IL-2 Highly Effective in Subset of Patients

- Review of 7 phase II studies (N=255)
- ORR, 15%
- CR, 7%
- Median response duration, 54 mos (3 to >131)
 - Duration among patients with CR, >80 mos
- Median OS, 16.3 mos
 - 5-10-year survival rate, 10-20%

Comparison of IL-2 Dosing Strategies

Patients with
metastatic RCC

(N=400)

High-dose IL-2

720,000 U/kg IV bolus q8 hrs up to 15
doses/cycle
(n=156)

Low-dose IL-2

72,000 U/kg IV bolus q8 hrs up to 15
doses/cycle
(n=150)

Low-dose SC IL-2

Week 1: 250,000 U/kg/dose QD for 5 days
Weeks 2-6: 125,000 U/kg/dose for 5 days/week
(n=94)

Efficacy of High-Dose vs Low-Dose IL-2

Outcome	High-Dose IL-2	Low-Dose IL-2	SC IL-2
2-arm study	-	-	-
ORR	21%	13%*	
CR	7%	4%	-
3-arm study	-	-	-
ORR	21%	11%	10%†
CR	6%	1%	2%
Response duration in patients with CR	19 to 130+ months	3 to 128+ months	13 to 78+ months

* $P = .048$ by χ^2 test

† $P = .033$ by χ^2 test; $P = .043$ by Fisher's exact test vs high-dose IL-2

Safety of High-Dose vs Low-Dose IL-2

Grade 3/4 Adverse Event	High-Dose IL-2 (285 courses)	Low-Dose IL-2 (272 courses)	SC IL-2 (181 courses)
Hypotension	36.4%	29.0%	0%
Malaise	20.5%	9.9%	9.4%
Nausea/vomiting	13.4%	8.5%	3.3%
Oliguria (≤ 80 mL/8 h)	12.0%	7.7%	1.1%
CNS orientation	10.2%	3.7%	1.7%
Thrombocytopenia	9.2%	1.5%	0%

Combining Cytokines: IL-2 + IFN- α -2a

Patients with
metastatic RCC
ECOG PS 0-1

(N=425)

IL-2 + IFN α -2a
(n=140)

IFN α -2a
(n=147)

IL-2
(n=138)

PS = performance status
ECOG = Eastern Cooperative
Oncology Group

Negrier S et al. *N Engl J Med.* 1998;338:1272.

IL-2 + IFN α -2a More Effective Than IL-2 or IFN Alone

Outcome	IL-2 + IFN α -2a	IL-2	IFN α -2a
1-year EFS	20%*	15%	12%
Week 10 ORR	18.6% [†]	6.5%	7.5%
Week 25 ORR	13.6% [‡]	2.9%	6.1%
Median OS	17 months	12 months	13 months

* $P = .01$ vs single-agent arms

[†] $P < .01$ vs single-agent arms

[‡] $P = .001$ vs single-agent arms

Safety of IL-2 + IFN α -2a Combination Therapy

- More adverse events with IL-2 vs IFN- α
- Few extra toxicities with combination vs IL-2
 - Only grade 3/4 fever more common with IL-2 + IFN- α vs IL-2 alone (79% vs 59%; $P = .02$)
- Factors predictive of response to treatment
 - Number of organs with metastases
 - 1 vs ≥ 2 ($P < .001$)
 - Treatment group
 - IL-2+IFN- α vs IL-2 or IFN- α alone ($P < .001$)

High-dose IL-2 vs Subcutaneous IL-2 Plus IFN- α

Patients with
metastatic RCC
PS 0-1

(N=192)

High-dose IL-2
600,000 U/kg/dose IV q 8h d1-15 and 15-19 q 12
weeks (max 28 doses)

(n =95)

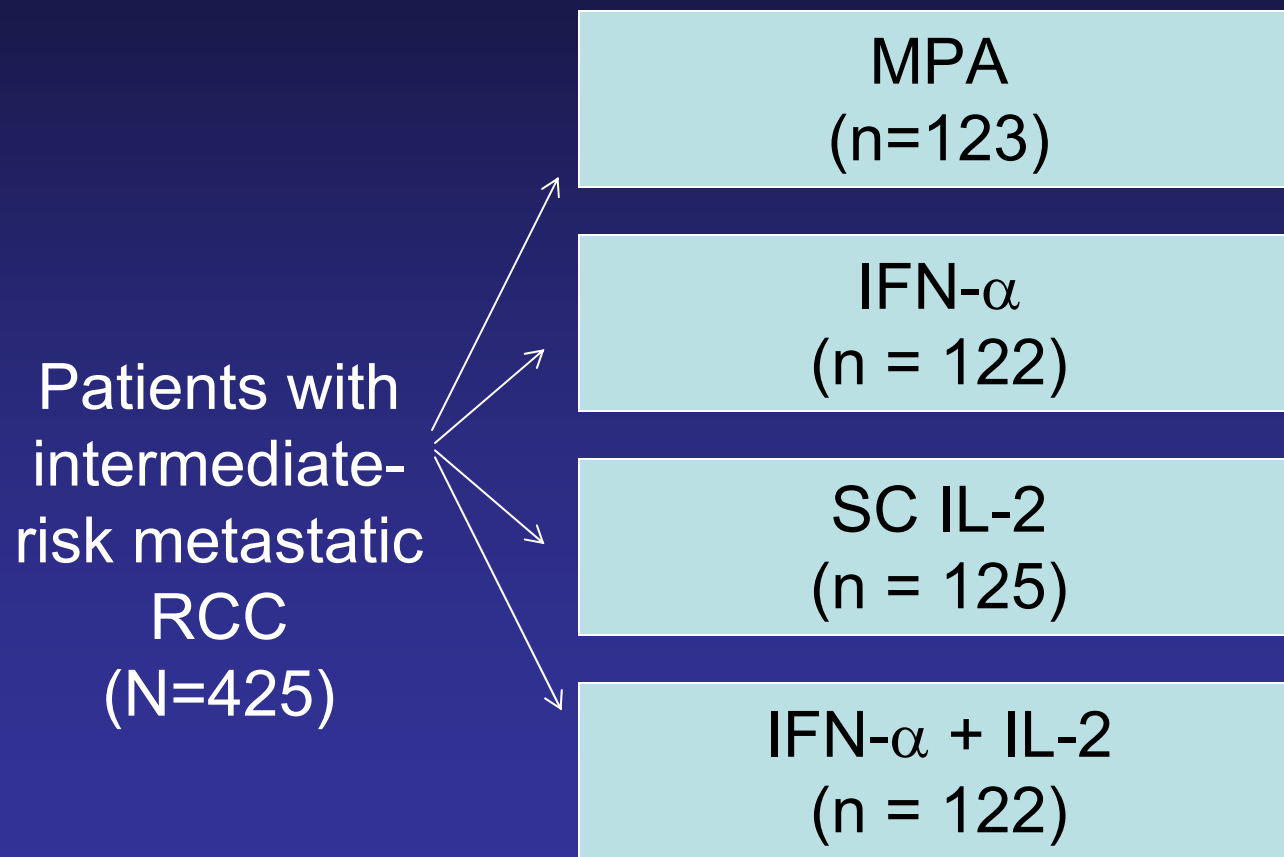
SC IL-2 + IFN- α
IL-2 5 MIU/m² SC q 8h for 3 doses on d1 then daily
5 days/week for 4 weeks q 6 weeks
IFN- α 5 MIU/m² SC 3x/week for 4 weeks q 6 weeks

(n=91)

High-dose IL-2 More Effective Than SC IL-2 Plus IFN- α

Outcome	High-Dose IL-2 (N=95)	SC IL-2 + IFN- α (N=91)	P Value
ORR	23.2%	9.9%	.018
Median response duration	24 months	15 months	.18
Durable 3-year CR	7.4%	0%	.014
Median OS	-	-	-
All patients	17.1 months	13.0 months	.211
Patients with bone/ liver metastases	14.7	8.0	.002
Patients with primary tumor in place	12.4	8.2	.034

Quattro: Cytokine Therapy in Intermediate-Risk Metastatic RCC



No Clear-Cut Benefit of Cytokines in Intermediate-Risk mRCC

Outcome	MPA (N=123)	IFN- α (N=122)	IL-2 (N=125)	IFN- α + IL-2 (N=122)
Median OS (95% CI)	14.9 months (11.7-19.2)	15.2 months (12.8-19.9)	15.3 months (13.3-20.0)	16.8 months (14.0-18.9)
Median PFS (95% CI)	3.0 months (2.9-3.6)	3.4 months (3.0-5.6)	3.4 months (2.9-5.8)	3.8 months (3.0-5.9)

- Greater toxicity in cytokine arms
 - Grade 3/4 adverse event rate with MPA vs cytokines: 9.9% vs 58.9%; $P = .0001$

Effect of Nephrectomy on Survival in Metastatic RCC

Patients with
metastatic RCC
with PS 0-1
(SWOG, N=241)
(EORTC, N=83)

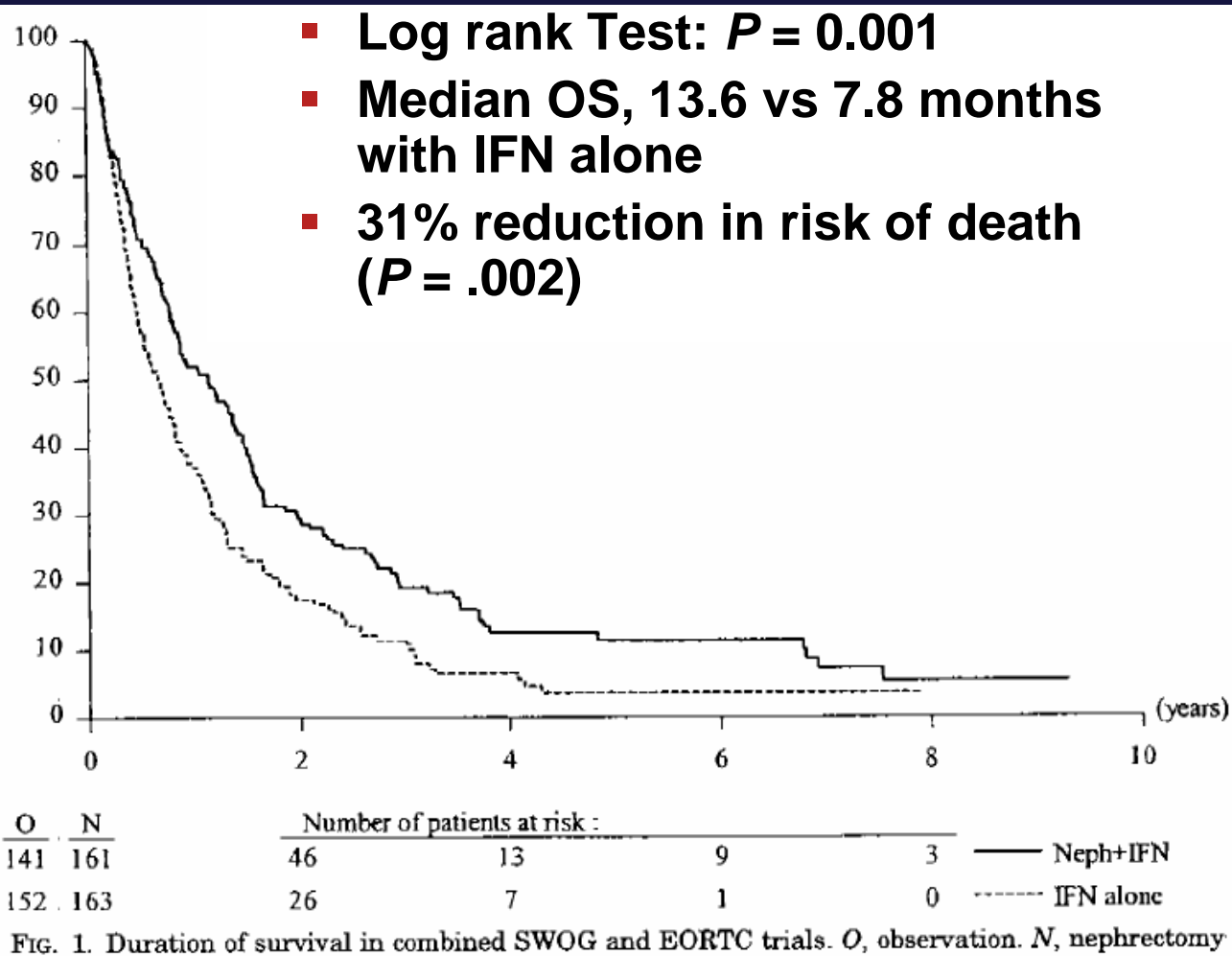
Radical Nephrectomy + IFN- α

**(SWOG, n=120)
(EORTC, n=42)**

IFN- α

**(SWOG, n=121)
(EORTC, n=43)**

Small Survival Advantage With Cytoreductive Nephrectomy



Cytoreductive Nephrectomy + IL-2 in Metastatic RCC

- Fallick et al¹
 - Nephrectomy → IL-2 in 28 highly selected patients
 - ORR, 39%; 18% CR
 - Median OS 20.5 months (range, 1-66 months)
- Pantuck et al²
 - Nephrectomy → IL-2 in 89 patients meeting SWOG criteria
 - Median OS 16.7 months
 - 5-year OS, 19.6%

Combining Cytokines With Targeted Therapy: Bevacizumab

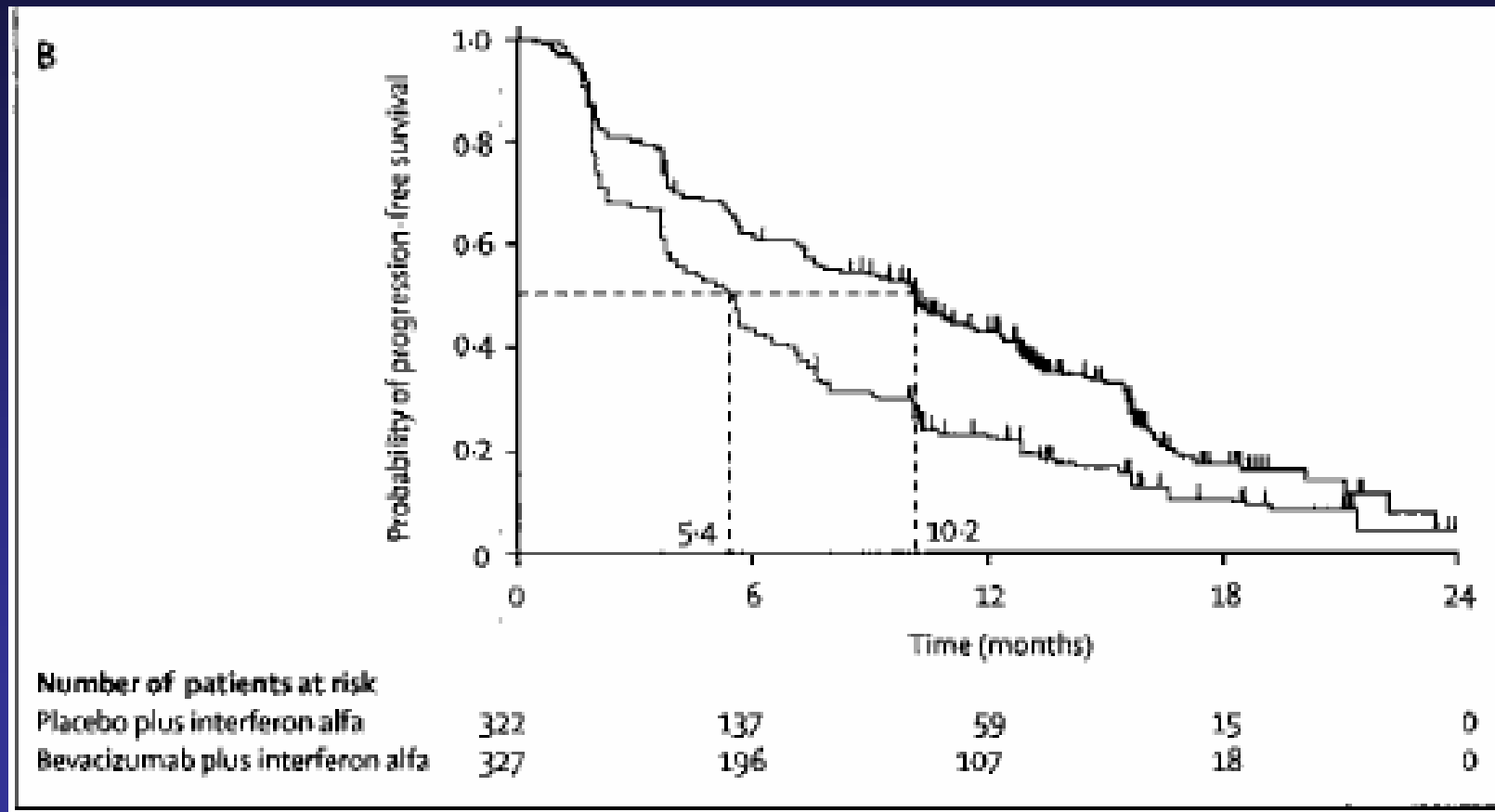
Patients with
untreated
metastatic RCC
(N=649)

The diagram shows a central text block on the left, 'Patients with untreated metastatic RCC (N=649)', with two arrows pointing to the right. The top arrow points to a light blue box containing the details for the 'IFN-α + Bevacizumab' arm, and the bottom arrow points to a light blue box containing the details for the 'IFN-α + Placebo' arm.

IFN- α + Bevacizumab
IFN α -2a 9 MIU SC 3x/week
Bevacizumab 10 mg/kg q 2 weeks
(n=327)¹

IFN- α + Placebo
9 MIU SC 3x/week
Placebo²
(n=322)

Bevacizumab + IFN- α Improves PFS Over IFN- α Alone



Bevacizumab + IFN- α Efficacy¹

Outcome	Bevacizumab + IFN (N=306)	Placebo + IFN (N=289)	P Value
ORR	31*	13	.0001
CR	1	2	-
Median TTP	10.2 months	5.5 months	.0001
Median OS	Not reached	19.8	.0670

* Single-agent bevacizumab associated with 13% ORR in another trial²

TTP = time-to-progression

1. Escudier B et al. *Lancet*. 2007;370:2103.
2. Bukowski RM et al. *J Clin Oncol*. 2007;25:4536.

Safety Outcomes With Bevacizumab + IFN- α

Adverse Event	Bevacizumab + IFN (N=306)	Placebo + IFN (N=289)
Any serious adverse event	29%	16%
Grade 3/4 fatigue	12%	8%
Grade 3/4 asthenia	10%	7%
Grade 3/4 proteinuria	7%	0%
Grade 3/4 neutropenia	4%	2%
Patients discontinuing any study drug	28%	12%

Combining Cytokines With Targeted Agents: Sorafenib

Phase II Trial	Regimen	N	ORR (CR)	PFS
Jonasch, 2007 ¹	Sorafenib	25	32% (4%)	9.3 months
	Sorafenib + IFN- α	25	8% (0%)	9.3 months
Gollob, 2007 ²	Sorafenib + IFN- α	40	33% (5%)	10 months
SWOG 0412 ³	Sorafenib + IFN- α	62	19% (1%)	7 months
Bracarda, 2007 ⁴	Sorafenib + IFN- α	63	25.4%	NR

1. Jonasch E et al. ASCO 2007. Abstract 5104.
2. Gollob JA et al. *J Clin Oncol.* 2007;25:3288.
3. Ryan CW et al. *J Clin Oncol.* 2007;25:3296.
4. Bracarda S et al. ASCO 2007. Abstract 5100.

NR = not rated

Combining Cytokines With Targeted Agents: Temsirolimus

Patients with
untreated, poor-
prognosis
metastatic RCC
(N=626)

The diagram shows a central text block on the left describing the patient population: 'Patients with untreated, poor-prognosis metastatic RCC (N=626)'. Three arrows originate from this text and point to three separate light blue boxes on the right, each representing a different treatment arm. The top box is for Temsirolimus (n=209), the middle box is for IFN-α (n=207), and the bottom box is for the combination of Temsirolimus + IFN-α (n=210).

Temsirolimus
25 mg IV weekly

(n=209)

IFN- α

3 million U (up to 18 million U) SC
3x/week

(n=207)

Temsirolimus + IFN- α

Temsirolimus 15 mg weekly
IFN 6 million U 3x/week

(n=210)

Combining Cytokines With Targeted Agents: Temsirolimus

Efficacy Outcome	Temsirolimus (n=209)	IFN- α (n=207)	Temsirolimus + IFN- α (n=210)
Median OS	10.9 months*	7.3 months	8.4 months
Median PFS (independent assessment)	5.5 months	3.1 months	4.7 months
Median TTF	3.8 months	1.9 months	2.5 months
ORR	8.6%	4.8%	8.1%
Stable disease \geq 6 months	32.1%	15.5% [†]	28.1%

* Hazard ratio for death with temsirolimus vs IFN = 0.73 (95% CI, 0.58-0.92; $P = .0008$)

[†] $P < .001$ vs temsirolimus; $P = .002$ vs temsirolimus + IFN- α

Combining Cytokines With Targeted Agents: Temsirolimus

Grade 3/4 Adverse Event	Temsirolimus (N=209)	IFN- α (N=207)	Temsirolimus + IFN- α (N=210)
Any	67%*	78%	87%
Asthenia	11% [†]	26%	28%
Anemia	20%	22%	38% [‡]
Neutropenia	3%	7%	15% [§]
Thrombocytopenia	1%	0%	9% [§]
Hyperglycemia	11%	2%	6%
Hypercholesterolemia	1%	0%	2%
Hyperlipidemia	3%	1%	8%

* $P = .02$ for temsirolimus vs IFN or combination

[†] $P < .001$ for temsirolimus vs IFN or combination

[‡] $P < .001$ for combination vs IFN; $P = .002$ for combination vs temsirolimus

[§] $P < .001$ for temsirolimus + IFN vs IFN or temsirolimus

Hudes G et al. *N Engl J Med.* 2007;356:2271.

Selecting Patients for IL-2-Based Therapy

- Pathology as a selection factor
 - Higher response rate in clear-cell vs non-clear-cell RCC (21% vs 6%; $P = .20$)
- Response associated with pathological features

Risk Group	Pathological Features	ORR to IL-2 in Primary	Response to IL-2 metastases
Good	Alveolar >50% <ul style="list-style-type: none">▪ No granular▪ No papillary	39%	25%
Intermediate	Alveolar <50% Granular <50% <ul style="list-style-type: none">▪ No papillary	19%	9%
Poor	Others	4%	0%

Selecting Patients for IL-2-Based Therapy (1)

- Carbonic anhydrase IX (CAIX) expression predicts responses to IL-2
 - Responders 3.3 times more likely than nonresponders to have high CAIX expression (78% vs 51% of patients; $P = .04$)¹
- All long term responders have high CAIX expression
- Patients with good histology or intermediate histology and high CAIX expression comprise 50-60% of patients with Stage IV RCC and contain > 90% of the responders to IL-2
- This model requires prospective validation, which is ongoing (IL-2 Select trial)

Selecting Patients for IL-2-Based Therapy (2)

- von Hippel-Lindau (VHL) typing
 - CAIX expression correlates with VHL mutation status
 - Low CAIX → absence of VHL mutation → poor prognosis in clear-cell RCC¹

Selecting Patients for Cytokine vs Targeted Therapy for RCC

- High tumor pS6 or pAKT expression needed for response to temsirolimus¹
 - Pattern different than for IL-2
- VHL status predictive in VEGF-targeted therapy²
 - Pattern may be similar to cytokine therapy, supporting combination in such patients

pAKT = phosphorylated Akt
VEGF = vascular endothelial growth factor

1. Cho D et al. *Clin Genitourin Cancer*. 2007;5:379.
2. Choueriri K et al. ASCO 2007. Abstract 5012.

NCCN Recommendations

- High-dose IL-2 feasible in certain patients
 - Karnofsky performance status >80, especially low-volume or lung-predominant disease
- Bevacizumab + IFN- α recommended as first-line therapy in patients with relapsed or unresectable stage IV disease (predominant clear-cell histology)

Summary

- Response rate to IFN- α is low with modest survival advantage
- High-dose IL-2 is associated with responses in 15-25% of patients, with 7-10% achieving durable complete responses
- Subsets of pathological and molecular features help identify patients who would respond to cytokine therapy vs targeted therapy
- Cytokines may enhance the efficacy of some targeted/anti-angiogenic agents