Understanding the new agents for treatment of Renal Cell Carcinoma

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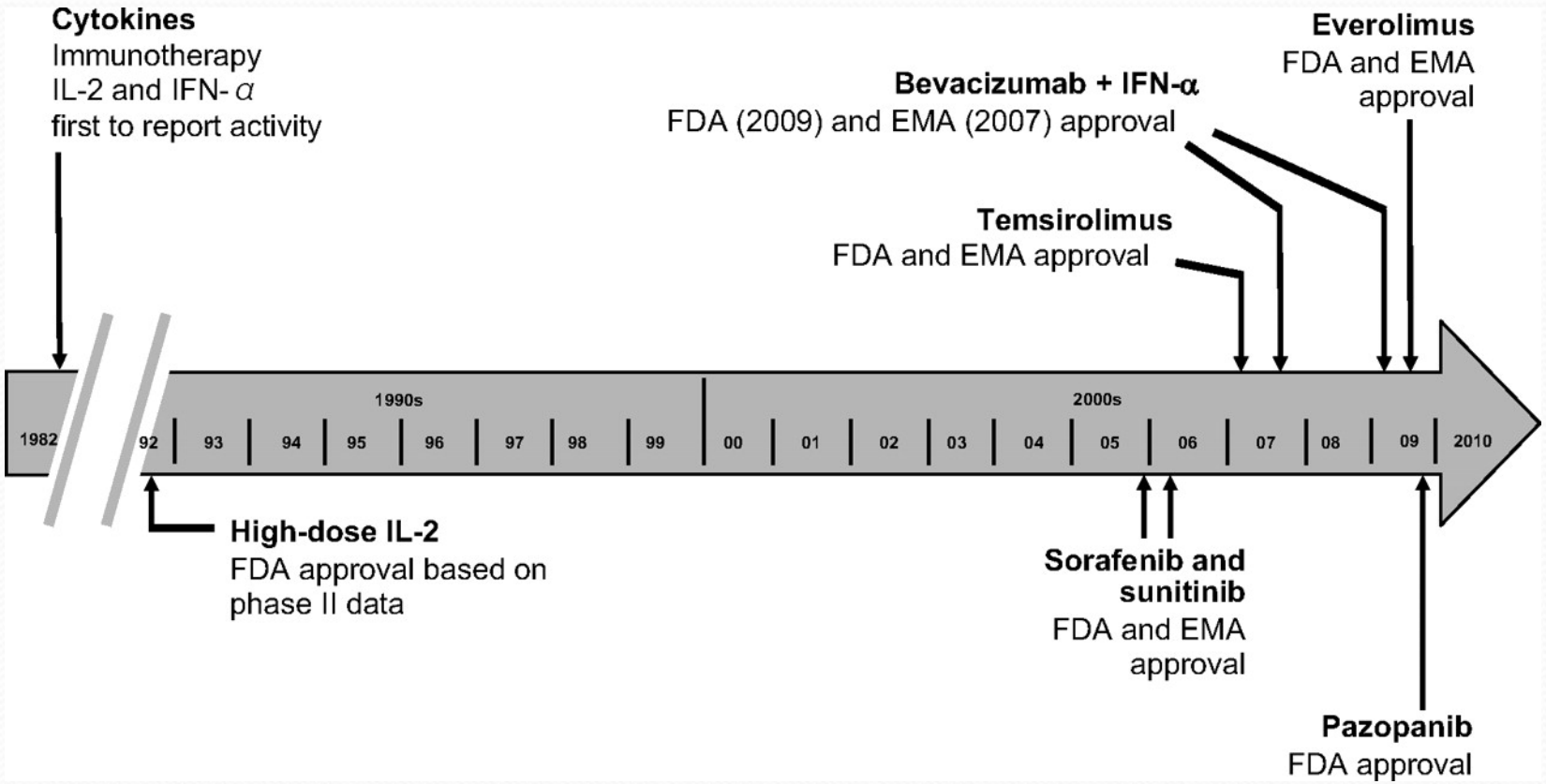
Background and Treatment of mRCC

Background	▪ ~ 64,770 new cases of kidney/renal pelvis cancers will be diagnosed in the US in 2012 with an estimated 13,570 deaths[1] • ~ 75% are clear-cell RCC[2] • ~ 25% to 30% of pts with RCC are diagnosed with metastatic disease[2]
Before the Era of Targeted Agents	▪ Cytokine-based therapy was associated with a median PFS of 3-5 mos[3-5] and median OS of 13 mos[6]
Current Situation	▪ Targeted agents have resulted in substantial improvements in treatment outcomes for patients with mRCC[5,7,8]

1. Siegel R, et al. CA Cancer J Clin. 2012;62:10-29. 2. Motzer RJ, et al. N Engl J Med. 1996;335:865-875.
3. Rini BI, et al. J Clin Oncol. 2008;26:5422-5428. 4. Escudier B, et al. Lancet. 2007;370:2103-2111.
5. Motzer RJ, et al. N Engl J Med. 2007;356:115-124. 6. Coppin C, et al. Cochrane Database Syst Rev. 2005;1:CD001425. 7. Mulders P. Eur Urol Suppl. 2008;7:577-578. 8. Ljungberg B, et al. Eur Urol. 2010;58:398-406.

Timeline of Treatments for Renal Cell Carcinoma

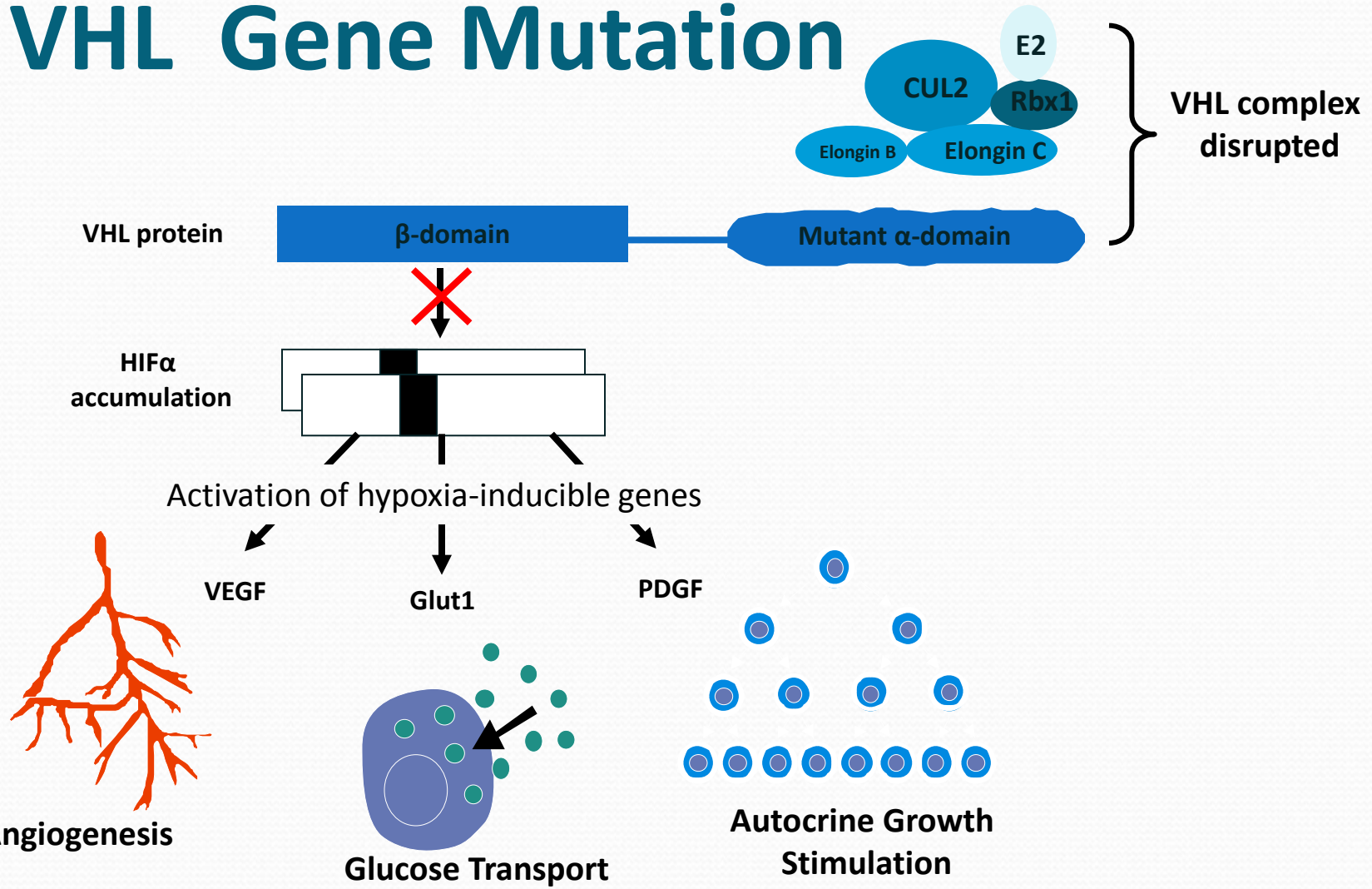


Motzer R J The Oncologist 2011;16:1-3

The Oncologist

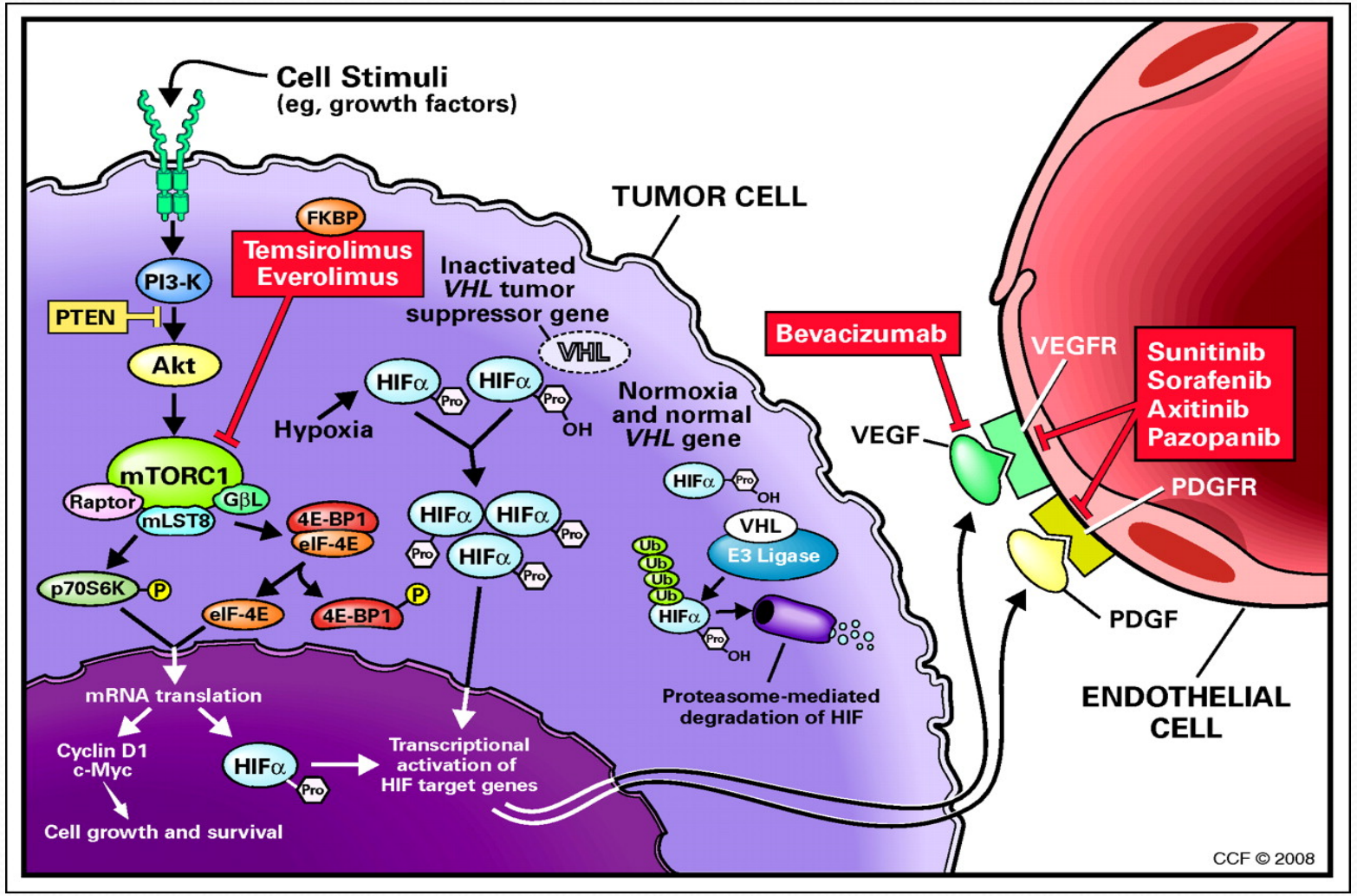
BIOLOGICAL PATHWAYS IN RENAL CELL CARCINOMA

The Biology of Clear-Cell RCC: VHL Gene Mutation



Bratslavsky G, et al. Clin Cancer Res. 2007;13:4667-4671.

Therapeutically Relevant Biologic Pathways in Renal Cell Carcinoma



Rini B I JCO 2009;27:3225-3234

THERAPEUTIC OPTIONS

High-Dose IL-2 vs Subcutaneous IL-2 + IFN for Patients With mRCC: Phase III Trial

Tumor Response	IL-2 + IFN (n = 91)		HD IL-2 (n = 95)		*P* Value
	Patients	%	Patients	%	
Overall response	9	9.9	22	23.2	.018
CR	3	3.3	8	8.4	.214
PR	6	6.6	14	14.7	
Durable 3-yr CR	0	0	7	7.4	.014
Response by stratification criteria					
Liver or bone metastases	1/39	2.6	10/44	22.7	.008
Primary tumor in place	0/27	0	6/29	20.7	.024

- **Grade 3, 4 toxicities more common in HD IL-2 arm vs IL-2 + IFN**
  - ***Hypotension: 56.8% vs 1.1%***
  - ***Neurologic AEs: 14.7% vs 3.3%***
  - ***Hematologic, pulmonary, renal/electrolytes: 13.7% vs 0%, 1.1%, 3.3%, respectively***

McDermott DF, et al. J Clin Oncol. 2005;23:133-141.

First-line Treatment of RCC Overview

Study	N	ORR vs IFN-α, %	Median PFS vs IFN-α, Mos	Final Median OS vs IFN-α, Mos
Sunitinib vs IFN-α[1]	750	47.0 vs 12.0	11 vs 5* *P* < .001	26.4 vs 21.8 *P* = .051
Bevacizumab + IFN-α vs IFN-α[2]	649	31.0 vs 12.0	10.4 vs 5.5* *P* < .0001	23.3 vs 21.3 *P* = .1291
Bevacizumab + IFN-α vs IFN-α[3]	732	25.5 vs 13.1	8.4 vs 4.9 *P* < .0001	18.3 vs 17.4 *P* = .069
Sorafenib vs IFN-α[4] (phase II)	189	5.2 vs 8.7	5.7 vs. 5.6* *P* = .504	NA
Pazopanib vs placebo[5]	233	32.0 vs 4.0	11.1 vs 2.8 *P* < .0001	NA
Temsirolimus vs IFN-α[6] (poor risk)	626	8.6 vs 4.8	5.5 vs 3.1* *P* < .001	10.9 vs 7.3 *P* = .008

Independent assessment.

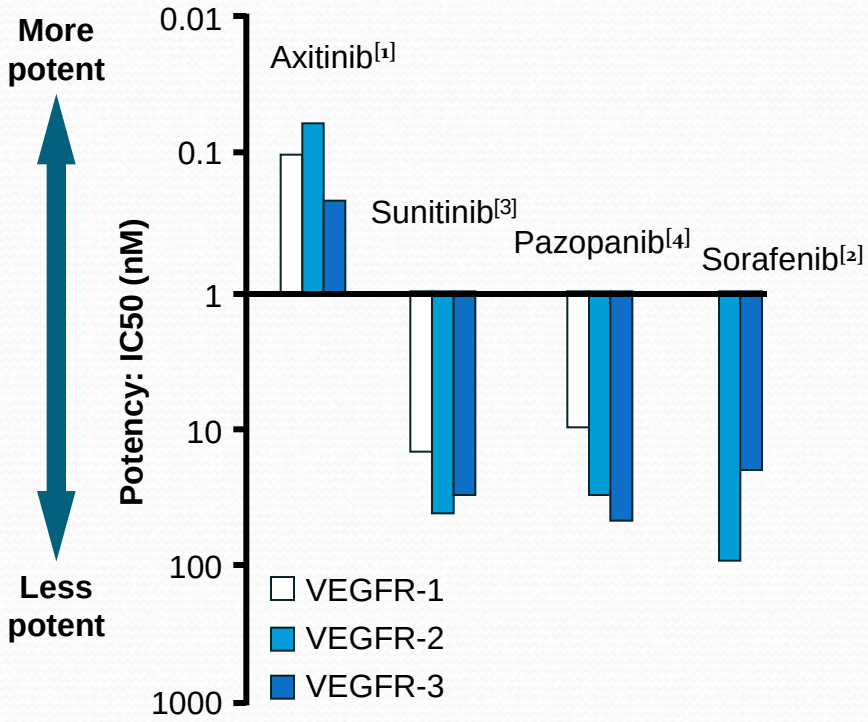
1. Motzer RJ, et al. J Clin Oncol. 2009;27:3584-3590. 2. Escudier BJ, et al. ASCO 2009. Abstract 5020. 3. Rini BI, et al. J Clin Oncol. 2009. Abstract LBA5019. 4. Escudier BJ, et al. J Clin Oncol. 2009;27:1280-1289. 5. Sternberg CN, et al. J Clin Oncol. 2010;28:1061-1068. 6. Hudes G, et al. N Engl J Med. 2007;356:2271-2281.

Targeted Agents: Common Adverse Events

Adverse Event	Bevacizumab	Sunitinib	Sorafenib	Pazopanib	Temsirolimus	Everolimus
Fatigue	+	++	+	+	+	+
Rash	-	-	+	-	+	+
Hand-foot syndrome	-	+	++	+	-	-
Hypertension	+	+	+	+	-	-
Diarrhea	-	+	+	+	+	+
Stomatitis	-	+	-	-	+	+
Myelosuppression	-	+	-	-	+	+
Metabolic syndrome	-	-	-	-	+	+
Epistaxis/bleeding	+	-	-	-	-	-
Proteinuria	++	-	-	-	-	-

Axitinib: Recently Approved Potent and Selective VEGFR TKI

Most Potent for VEGFR-1, -2, and -3



Most Selective for VEGFR -1, -2, and -3

	Target Selectivity			
	Axitinib [1]	Sorafenb[2]	Sunitinib [3]	Pazopanb [4]
VEGFR-2	+	+	+	+
PDGFR b		+	+	+
c-kit		+	+	+
FLT-3		+	+	
CSF-1R		ND	+	+
Raf-1	ND	+	ND	ND

+: inhibition of receptor kinase comparable (≤ 5 times) to potency for VEGFR-2
ND: not determined

1. Hu-Lowe DD, et al. Clin Cancer Res. 2008;14:7272-7283. 2. Wilhelm SM, et al. Cancer Res. 2004;64:7099-7109. 3. Roskoski R. Biochem Biophys Res Commun. 2007;356:323-328. 4. Kumar R, et al. Mol Cancer Ther. 2007;6:2012-2021.

THERAPY SELECTION

Patient Management and Therapy Selection in Advanced RCC: Considerations

- **Previous nephrectomy**
  - ***Patients with intact primary tumor may benefit from surgical resection***
- **Tumor histology**
  - ***Evidence supporting the current therapeutic paradigm is largely limited to clear-cell RCC***
- **Extent of metastases**
  - ***Patients with 1-3 metastatic sites or those with metastases affecting QoL may benefit from additional treatment interventions including surgery, radiation, and/or bone-modifying agents***
- **Previous systemic therapy**
- **Preexisting comorbidities**
- **Patient considerations**
  - ***Cost***
  - ***Convenience vs. Compliance***

Risk Factors in Advanced Untreated RCC: MSKCC Criteria

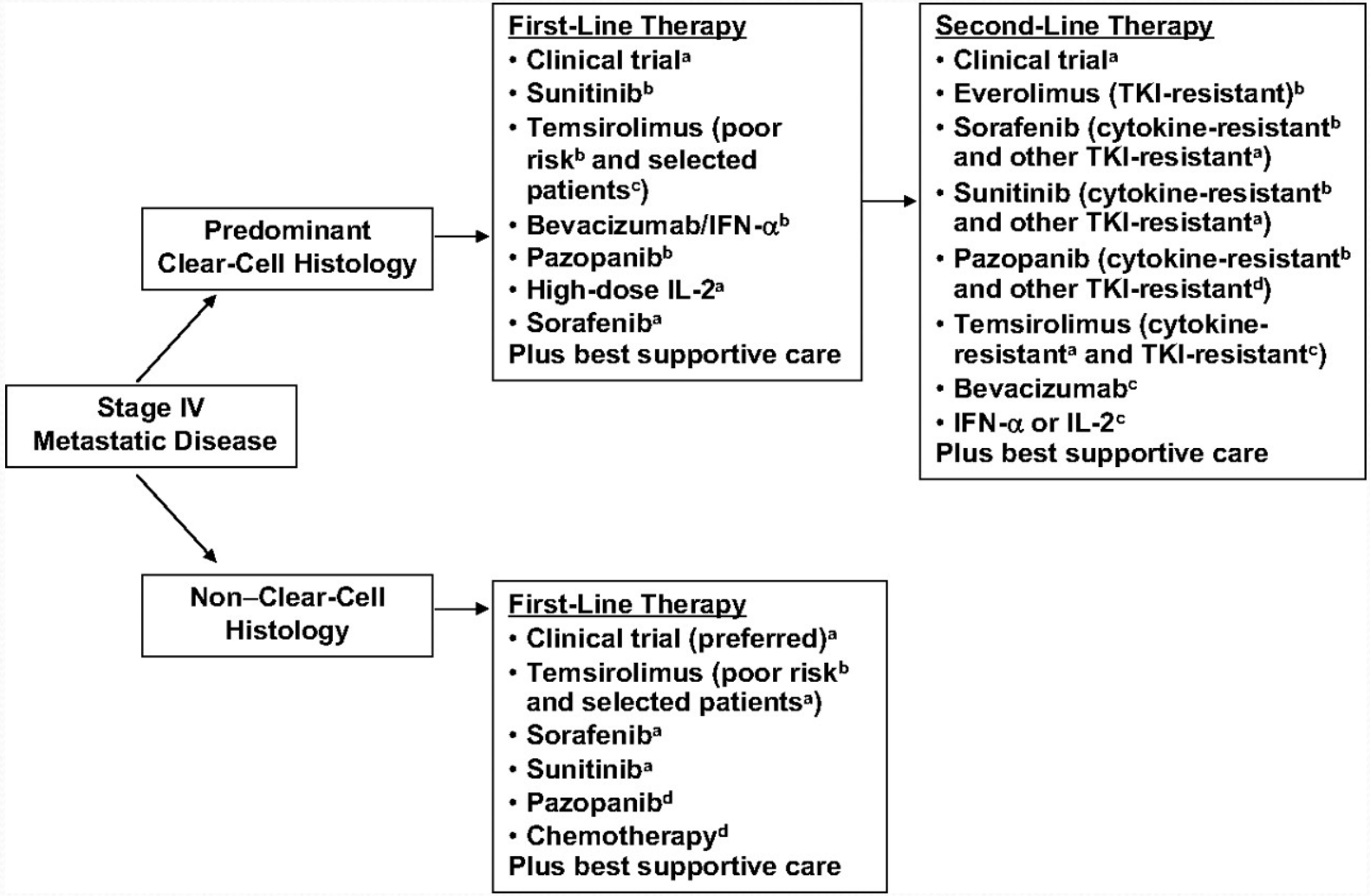
MSKCC Criteria 2002[1]	
KPS	< 80%
Time from diagnosis to treatment with IFN-α	< 12 mos
Hemoglobin	< LLN
LDH	> 1.5 x ULN
Corrected serum calcium	> 10.0 mg/dL

Risk Group by No. of Risk Factors	
Favorable	0
Intermediate	1 or 2
Poor	3-5

- **Independent validation at the Cleveland Clinic identified 2 additional prognostic factors[2]**
  - ***Previous radiotherapy***
  - ***Presence of lung, hepatic, retroperitoneal nodal metastasis***
- **Platelet and neutrophil counts > ULN identified as adverse prognostic factors for patients treated with VEGF-targeted therapies[3]**

1. Motzer RJ, et al. J Clin Oncol. 2002;20:289-296. 2. Mekhail TM, et al. J Clin Oncol. 2005;23:832 841.
3. Heng DY, et al. J Clin Oncol. 2009;27:5794-5799.

Summary of the National Comprehensive Cancer Network Guidelines



Molina A M , Motzer R J The Oncologist 2011;16:45-50

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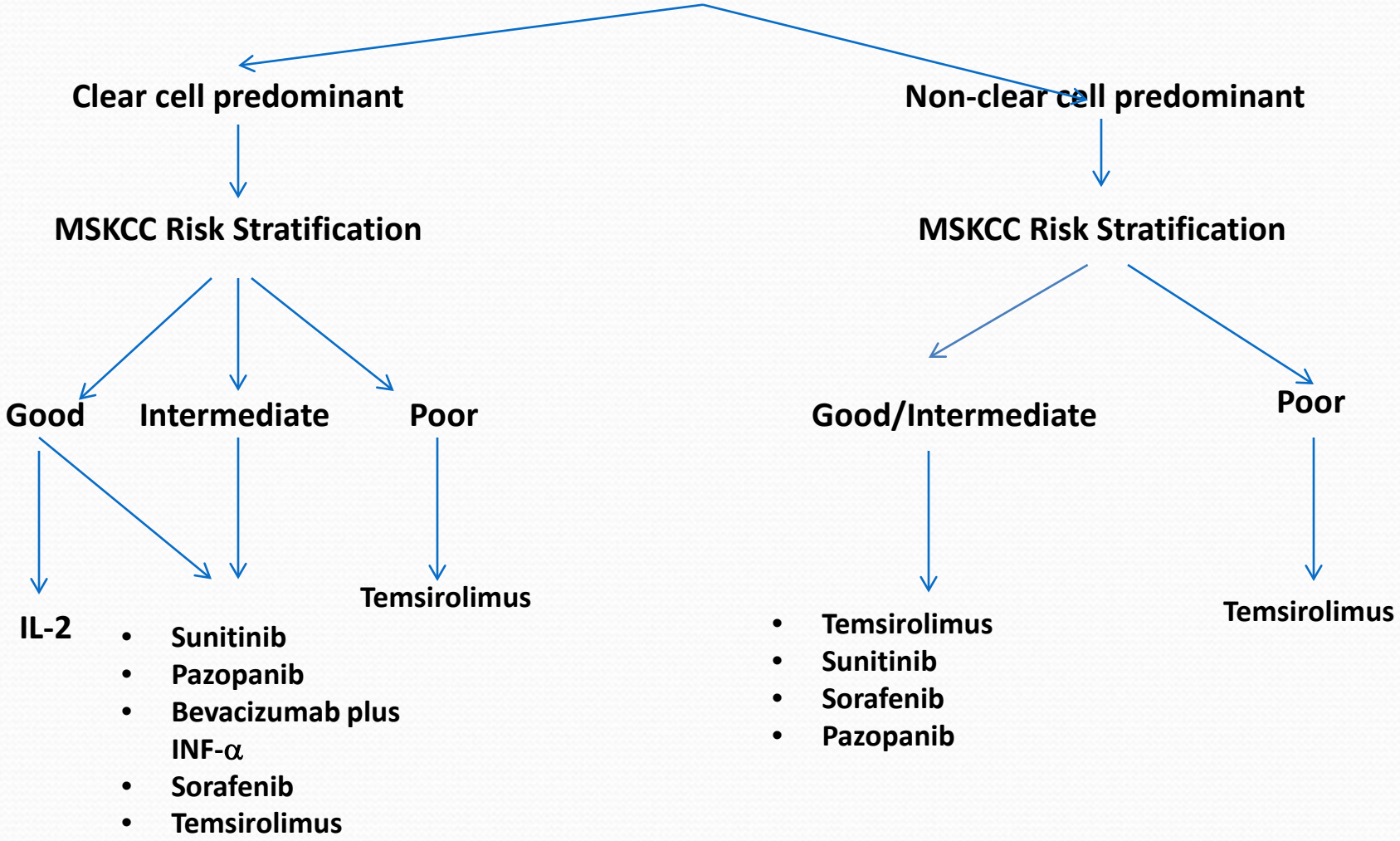
1st line Therapy for Metastatic Renal Cell Carcinoma



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2nd Line Therapy for Metastatic Renal Cell Carcinoma

Prior Immunotherapy →	**•Sunitinib* •Sorafenib* •Pazopanib* •Temsirolimus •Bevacizumab**
Prior VEGF-agent →	**•Everolimus* •Axtinib* •Temsirolimus •Bevacizumab •IL-2/IFN**
Prior mTOR agent →	**•Axitinib •Sorafenib**

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Investigational Agents in Trials

Agent	Class	Target(s)	Trial Phase
Tivozanib[1,2]	TKI	VEGFR	III
Dovitinib[2]	TKI	FGFR, VEGFR, PDGFR	III (ongoing)
Lenvatinib[3]	TKI	FGFR, VEGFR, PDGFR	II (ongoing)
GDC-0980[4]	Kinase inhibitor	mTOR, PI3 kinase	II (planned)
MDX-1106[1]	MoAb	PD-1	II, III (planned)
AGS-003[5]	Dendritic cell	Tumor antigens	II, III (planned)
IMA901[6]	Vaccine	Multipeptide	III (ongoing)

1. Gross-Goupil M, et al. Curr Urol Rep. 2012;13:16-23. 2. Motzer RJ, et al. ASCO 2012. Abstract 4501. 3. Boss DS, et al. Br J Cancer. 2012;106:1598-1604. 4. Wallin JJ, et al. Mol Cancer Ther. 2011;10:2426-2436. 5. Amin A, et al. ASCO 2010. Abstract 4588. 6. Rini BI, et al. ASCO 2011. Abstract TPS183.

VEGF-R Inhibitors in VEGF-targeted Therapy-Naïve RCC Patients

Treatment	Objective Response	% Pts with Tumor Burden Reduction	PFS
Sunitinib	**30 - 45%**	**~ 70-75%**	**11 months (treatment-naïve)** **8.4 months (cytokine-refractory)**
Sorafenib	**2% - 10%**	**~ 70-75%**	**5.5 - 5.7 months**
Pazopanib	**30%**	**~ 70-75%**	**9.2 months**
Axitinib	**47%**	**~ 70-75%**	**15.7 months (cytokine-refractory)**
Tivozanib	**24%**	**83%**	**8.9 – 11.8 months** **15 mos for ccRCC**

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