

## RENAL CELL CARCINOMA

### RENAL CELL CARCINOMA- BIOLOGIA MOLECULAR

DJ George & WG Kaelin (NEJM 2003;349:419-21)

VHL (mutated/hypermethylated in >60% RCC) inhibits HIF1 $\alpha$ . When it is mutated or hyperexpressed overaccumulation of HIF1 $\alpha$  causes increase in hypoxia induced genes, including VEGF, PDGF-Beta, TGF $\alpha$  & EPO. VEGF inhibitors prolong TTP in RCC, perhaps inhibition of PGE (pericytes) is required for response...

Pantuck et al UCLA. (Clin Ca Res 2003;9:4641-52). HRE (Hypoxia responsive element) responds to HIF-1 $\alpha$  (Hypoxia inducible factor 1). HIF-1 $\alpha$  is induced by PI3K-AKT-mTOR (AKT is blocked by PTEN) (mTOR is blocked by Rapamycin & CI779). When this is not blocked HIF1 $\alpha$  induces several genes (Glut1 –glucose transport-, VEGF, TGF $\alpha$ , IGF, CA –carbonic anhydrase a potent prognostic factor in RCC- all responsible of tumor growth). HIF1 $\alpha$  has a very short life in presence of VHL and undergoes degradation (proteasome ubiquitination); VHL is frequently absent due to mutation or LOH/hypermethylation in family or sporadic RCC. This pathway opens up a lot of targeted therapies...

S Negrier. Group Francais d Immunotherapie (JCO 2004; 22:2371-8) IL6 serum level prognostic factor in RCC. IL6 is a growth factor for RCC, induce fever, wt loss, and inflammatory cytokines and inhibit dendritic cell differentiation. IL6 < 3 pg/mL MST 3 y; IL6 3-35 pg/mL MST 14 mo; & IL6 >35 pg/mL MST 6 mo.

R Laonser (NIH). NEJM 2004;350:2481-6) VHL disease includes: RCC, Pheochromocytoma, Pancreatic cyst and neuroendocrine tumors, cystadenomas of ovary, Hemangioblastoma of cerebellum, spinal cord brain stem and retina. Also described in this publication tumors of endolymphatic sac (hearing loss). Resection for cure.

W Marston Linehan (Clin Ca Res 2005;10:6282-9). Disease specific genetics of RCC:

1.- Renal clear cell ca. VHL gene, 3p25, associated to hemangioblastoma of CNS.

Target HIF-1 $\alpha$ , EGFR, VEGF, TGF $\alpha$ , PDGF downstream genes.

2.-Hereditary papillary ca type 1 (HPRC) gene c-Met, 7q31. TK activation.

3.- Hereditary leiomyomatosis, renal cell carcinoma type 2. Gen responsible FH (Fumarate hydratase, a Krebs cycle enzyme gene) 1q42

4.-Chromophobe carcinoma and oncocytoma, Birt-Hogg-Dubé syndrome (BHD gene 17p11, overexpress c-kit. Associated to cutaneous tumors, lung cysts, colon polyps and cancer.

HSP90 is genetic target for all these as a multitargeted approach...

### RENAL CELL CARCINOMA PRONOSTICO

Motzer (MSKCC) prognostic score (JCO 1999;20:289-96) is based in KPS<80, interval from dx to IFN<12 mo, Hb<low normal limits; LDH >1.5 normal limits; & Ca>10.

Good =0factors, Intermediate 1-2 & Poor>2

Validation by CCF, R Bukowski in 353 adding metastases in >1 site and prior RT. Good OS 26 mo, Intermed MST 14.4 mo and Poor risk MST 7.3 mo. (JCO 2005;23:832-41). French group correlated with Bukowski results and joined another 10 centers with >4000 cases to validate it. It is a pity no pathological classification is included (clear cell, papillary and distal tubule are very distinct entities) and that genetics are not included... It will fail very soon...

Y Mizutani et al (JCO 2005;23:448-54). Smac-DIABLO gene (second mitochondria-derived activator of caspase/direct inhibition of apoptosis binding protein with low pI) is released by mitochondria in response to stimuli & promote apoptosis by antagonizing the inhibition of apoptosis proteins. Expression of smac-DIABLO in tumour as compared to normal kidney is correlated with better survival 1/12 deaths compared to lack of expression with 10/12 deaths... Impressive prognostic factor if it is validated...

## RENAL CELL CARCINOMA EARLY STAGE

D Jocham et al. Lubeck Med School Germany (Lancet 2004;363:594-99). After surgery 10 g of tumor are incubated with IFN $\alpha$  tocopherol and washed. Thaw (Freezing and heating) and inject intradermally q 4 wk x 6. Randomized vaccine n=113, 5yPFS 77.4% and TTP 63.2 mo, Control n=133, 5 yPFS 67.8% and TTP 42.1 mo no side effects. HR for tumor progression =1.58. Active...

R Flanigan (Clin Ca Res 2004; 10:6335-41) Nephrectomy value confirmed in SWOG trial with randomised 241 pts, being MST for IFN  $\alpha$  8.1 mo and surgery+IFN  $\alpha$  11.1 mo, no diff in OR. WEORTC with only 85 pts IFN  $\alpha$  MST 7 mo, and surgery+IFN  $\alpha$  17 mo. Confirm value of nephrectomy in OS, not in OR, probably immunological effect...

A Hines-Peralta & S Nahum Goldberg (Clin Ca Res 2004; 10:6328-34) Review RFA series with more than 200 pts and 9 publication series. Median size of tumors 1.7 to 3.5. Success by CT scan 85-100%. Not recommended in >3 cm. Interesting for elderly pts, mets pts, and multiple tumors of VHL syndrome to preserve function... Do not propose as an alternative conservative modality?

D Bottaro and M Linehan (Clin Ca Res 2005;11:7206-8). Review multifocal RCC. 1) VHL-Rec: Clear cell type (75%). Recommend waiting until it is >3 cm. Prognosis is excellent for 3 cm tumors without metastases. Multifocality is a genetically related spreading of a clonal tumor. 2) Papillary type-1/Met (1%): Multifocal cases are genetically discordant (95%) for 6 microsatellite markers. It is not recommended to wait and see or to perform a nephron sparing surgery because they are independent tumors. 3) Papillary type-2 (10%). 4) Other tumors related to Birt-Hogg-Dubé syndr are chromophobe adenoma and oncocytoma, both benign...

## RENAL CELL CARCINOMA ADVANCED DISEASE- CYTOKINE THERAPY

S Fossà et al EORTC (Cancer 2004;101:533-40) Randomized study comparing IFN  $\alpha$  9 MU qd and IFN  $\alpha$  same dose + Cisretinoic acid 1 mg/kg. Found 9% OR (2 CR and

1 PR) in single drug versus 19% OR in combination arm (2 CR + 8 PR) strict criteria RECIST.

J Atzpodien et al (JCO 2004; 22:1188-94) Randomized 341 pts to IFN alfa sq+ IL2 sq+5FU (OR 31%, CR 5%, and MST 25 mo) versus similar combination + Cisretinoic acid (OR 26%, CR 8%, MST 26 mo) and IFN alfa+ VBL (OR 20%, CR 6%, MST 16 mo).

G Alatrash et al (R Bukowski) (JCO 2004;22:2891-900). Phase I sc IL2 + IFNa2b. IL2 RTD 500 ng/kg biwk + IFNa2b RTD 1 MU/m<sup>2</sup> tiwk. RCC 2/19 OR, Melanoma 1/7 OR. Feasible. Low activity...

B Rini et al. (Clin Ca Res 2004;10:2584-6). Based on data showing BV > placebo. Randomized study of IFNa 9 MU tiwk vs IFNa same dose + BV, 10 mg/kg iv d 1 & 15. Wait results...

\*D Mc Dermott et al. (JCO 2005;23:133-141). Important randomized trial of high dose IL2 and low dose IL2+IFN alfa. N192 pts. HD IL2 600 u/kg bolus iv q 8 h x 5 days (max 14 doses) d 1-5 and repeat d 15-19 q 12 wks, up to a maximum of 3 cycles, OR 22/95 (23.2%), with 10 PFS at 3 y, MDR 14 mo and MST 17.5 mo. Low dose arm with IL2 5 MIU/m<sup>2</sup> sq q 8 h x 3 and then qd x5/wk x 4 + IFN alfa 5 MIU sq tiw x 4 q 6 wk. OR 9/91 (9.9%), PFS 3 pts, MDR 7 mo and MST 13 mo. Very clear results favoring HDIL2 in selected expert units, strict OR criteria. The median number of IL2 doses was 68% (10/14 of planned doses) with stop in case of serious toxicity, monitor carefully and use preventive atbs and antacids...

Renal cell ca: N=51 pts. Inhaled IL2: OR 13.7%, MPFS 8.6 mo, MOS 23 mo (Abst 4756 Proc ASCO, 2005; 23)

\*RJ Amato (Cancer 2006;106:1498-506). Phase I-II trial of escalated Thalidomide (MTD 400 mg po qd ) starting one week before IL2 and continued for 2 y + IL2 fixed sc dose 7 MIU/m<sup>2</sup> x 5 q wk x 4 every 6 wks. N=52 (combined Phases I & II). Results: CR 8% + PR 29% + SD 15%. Response durable > 4 y in some CR and PR. Unexpected synergism because both agents have a OR rate <15% as single agents. Good tolerance. Need confirmation!

B Rini et al (Cancer 2006;106:566-75). Phase II IFNa, 3 MU qd + Celecoxib 400 mg po bid. N=25, untreated RCC. PR 3/ (12%), MDR 3.3 mo. Fail...

## RENAL CELL CARCINOMA- TARGETED THERAPY

G Varmi Kondagunta et al MSKCC (JCO 2004;22:3720-5). Bortezomib 1.3 mg/m<sup>2</sup> bi wkx 2 q 3, in 37 pts. PR 4 (11%) and NC 14 (38%). MDR 8, 8+, 15+,20+ mo. Reasonable...

M Atkins et al (JCO 2004;22:909-18) Phase II in 111 patients with RCC with CCI-779 (inhibitor of mTOR TK) 25-250 mg wkly iv in 30 min infusion. OR 7%+ NC 26%, MTTP 5.8 mo, MST 15 mo. Toxicity rash, mucositis(70%), nausea, hyperglycemia, increase in phosphates and triglycerides. All doses equal side effects. Very interesting...

J Yang (Clin Ca Res 2004;10:6367-70) (Prior publication NEJM 2003;349:427-34). Randomized study in metastatic renal cell carcinoma comparing placebo, Bevacizumab (BV) 3 mg/kg q 2 w and BV 10 mg/kg q 2w. N=116 pts. Crossover allowed. Placebo patients in progression entered a combination of BV and Thalidomide. BV side effect proteinuria only. OR only in high dose BV 10% and NC the majority at this dose. Low dose only stable disease in 30%. Long term responses, with 4 pts on going in NC for > 3.5 y.

T Ahmad and T Eisen, Royal Marsden Hosp (Clin Ca Res 2004;10:6388-92). Phase II of BAY 43-9006. 400 mg bid po in 41 pts obtained 40% reponse (defined as >25% size reduction) ad 30% NC. Mild hypertension, edema, diarrhea, hand foot syndrome. Since Raf is not mutated in RCC other mechanism of action must be involved in response. Very interesting to follow...

M Ratain. Sorafenib (BAY 43-9006) PR + mR 30%, MPFS 10 mo and MST was prolonged in patients not exhibiting a response from 6 wks to 24 wks. (JCO, ASCO 2004; 22:44 Abstract 4501; ASCO 2005; 23:388 Abstract 4514).

Hainsworth et al. BV + Tarceva: PR 21% + SD 66% (N=62), PFS at 1 y 50%. ASCO 2005;23:382 Abstract 4542). Final report (JCO 2005;23:7889-96) BV 10 mg/kg iv q 2 wk + Erlotinib 150 mg po qd in N=63 patients. OR 25% (15/59) and SD 61% (36/59) at 8 wk. MOS and PFS at 1 y: 11 mo and 15 mo.

Spigel et al: BV+ Tarceva + Imatinib do not improve on the response or survival data. (ASCO 2005;23:287 Abstract 4540)

E Rowinsky et al (JCO 2004;22:3003-15) ABX-EGF (fully human Mo Ab antiEGFR) 1-2.5 mg/kg Phase II in 88 pts. EGFR staining positive in 88% tumors (n=76). Only 3 OR+2 mR+38 NC, with MPFS 3 mo. Deception...

BI Rini and E Small (JCO 2005;23:1028-43). Review antiVEGF therapy. The majority of RCC have VEGF overexpression. VEGF mRNA is detected in over 90% of the cases. VEGF is related to stage of the disease and prognosis. Trials have been done with Thalidomide (OR 56-15%); AE941 (shark cartilage derivative, Neovastat) OR9%; BV OR 10% and mainly a TTP delay 4.8 versus 2.5 months in a randomised trial indicative of effect on tumor growth; and VEGF-trap also showing a delay in TTP. More recently small molecule inhibitors: SU11248 (OR24%), PTK787/ZK222584 (OR 5%) and BAY43-9006 showing an OR 38%. No doubt small molecules are the leading drugs...

\*R Motzer et al. Renal cell ca: SU11248 (multitarget TKI for PDGFR/VEGFR) 50 mg po qd x 4 wk q 6 wk. OR 25/63 + NC 21. MDR 10+mo, MTTP 8.3 mo. A second trial showed 29/83 OR (1CR, 16PR, 7<PR). Substantial activity in second line therapy. (Abst 4508 Proc ASCO, 2005; 23)

R Motzer et al (JCO 2006;24:16-24). Phase II Sunitinib (Sutent), 50 mg po qd, in mets 2nd line RCC: Results 25/63 PR (40%) + 17/63 SD>3mo (27%), MTTP 8.7 mo. Demonstrated a decrease of VEGFR2 and an increase in Placental growth factor after treatment which might represent unmutated signalling pathways of RCC.

Sunitinib (SU11248) SUTENT approved by FDA in RCC and GIST in January 2006. 50 mg po qd (10% require dose reduction). Side effects: Hypertension 15%, discoloration of skin and hair, mucositis, asthenia, hypothyroidism. Metabolism involved P450-CYP3A4.

\*Rini et al. Renal cell ca: AG013736 (multitarget TKI). OR 40% 21/52 + 40% SD, MTTP > 1y (Abst 4509 Proc ASCO, 2005; 23)

\*\* Escudier et al. Renal cell ca: Sorafenib (BAY43-9006, dual inhibitor of Raf kinase and VEGFR) randomized study to placebo. N=884 pts. MPFS 24 wks vs 12 wk and 12 wk PFS 79% vs 50%. PR 2% + SD 78%. Very promising. Lacking data on OS... (Abst 4510 Proc ASCO, 2005; 23).

BC Kuenen et al (H Pinedo) (Clin Ca Res 2005;11:6240-6). SU6668 (TKI targeting PDGFRB, FGFR1, VEGFR2 and KIT). Phase I MTD 100 mg/m<sup>2</sup>. Acute phase response observed (nmediated by IL6?). DLT abdominal pain, anorexia, N&V. No Ors.

S Faivre et al (JCO 2006;24:25-35). Phase I of Sunitinib 50-150 mg qd (15-59 mg/m<sup>2</sup> qd x 4 wk q 6 wk. MRD 50 mg/d. 3 PR in RCC + 1 PR in neuroendocrine tumor + 1 PR in GIST + 1 PR in adenocarcinoma (6/28 patients). DLT fatigue, hypertension, skin and hair discoloration.

#### RENAL CELL CARCINOMA- INMUNOTHERAPY

D Avigan et al DFCI (Clin Ca Res 2004;10:4699-708). Fusion dendritic-tumor cell vaccine in breast and renal cell ca, given intranodally q 3 wk 1-4x10<sup>6</sup> fusion cells non toxic, increase in T4, T8 and positive Elispot to IFN gamma secretion. N=23 pts. RCC 5 NC and breast ca 2PR & 1 NC. See follow up...

\*D Jocham et al (Lancet 2004;363:594). Autologous tumor incubated with dendritic cells vs placebo after RCC resection for T3. N= 174 randomized trial. 5 y PFS 67.5% in vaccine group and 49.7% in control group. Quite remarkable.

Y Takahashi & R Childs (NIH, USA) (Clin Ca Res 2004;10:6353-9). Miniallotransplantation. Their own series had 10/19 OR, delayed response quite common. Strategy was CPA 60 mg/kg x 2 d -7 & -6 followed by Fludara 25 mg/m<sup>2</sup> x 5 d -5 to -1. Need an identical HLA donor, T cell replete stem cell transplant and CsA full dose early for short period to avoid immunosuppression in case of full T cell chimerism take off CsA on day +60. When mixed T cell chimerism, usually no responses, then take off CsA on day +40 and infuse T cells from donor (DLI) x 3-4 times to convert to 100% T cell chimerism from donor. Mortality is about 15%. Prolonged OR 10-15%. Oldest CR is of >5 years... Wait till confirmation. FHCC (Seattle) has poorer response rate and results.

G Cesaan et al (JCO 2006; 24:1169-77). Studied T regulator cells (CD4+ CD25+) after IL2 600,000 iu/kg q 8 h in melanoma and RCC. CD4+CD25+ were elevated in cancer patients (7.75%) as compared to normal controls (2.24%). Main effect of IL2 was to increase T reg, but when there is a tumor response T reg decrease. T reg cells produce IL10.

Renal cell cancer: MoAb MDX-010 (against CTLA4), 3 mg/kg followed by 1 mg/kg or 3 mg/kg x 2. N= 41 pts. Autoimmune syndrome (enteritis, hypophysitis, meningitis, quite serious side effects) appeared in 12 patients, and 6 of them had a PR. (Abst 2501 Proc ASCO, 2005; 23)

H Uemura et al (Clin Ca Res 2006; 12:1768-75). Vaccination peptides of CA9 (antigenic peptide present in the surface of RCC) p 219-227, p288-296 & p323-331 given subcutaneously + Incomplete Freund's adjuvant q 2 wks. N=23 with HLA-A24. Most patients showed CTL reactive to peptides or IgG against it after 6-9 vaccines. OR: 3 PR (lung metastases) + 6 SD>6 mo, MST 21 mo. Active...!

#### RENAL CELL CARCINOMA- CHEMOTHERAPY

DM Namus et al Cornell Univ. (Cancer 2004;101:1545-51). Selected aggressive tumors: sarcomatoid, collecting duct and refractory rapidly progressive tumors. GEM 1500-2000 mg/m<sup>2</sup> + DOX 50 mg/m<sup>2</sup> q 3 wk + GCSF. 2CR+5PR+3mR+1NC. Quite good in these rare tumor types...

G Keller et al (Cancer 2005;104:2266-74). AN 215 consists in AN-201 (a doxorubicin derivative) linked to Bombesin-gastrin releasing peptide (GRP). Tested in RCC cell lines demonstrated growth inhibition and it was active in xenografts (50-65% growth inhibition)

\*Renal cell ca: Ixabepilone (BMS247550, tubule stabilising agent). OR 8/57. Active. (Abst 4541 Proc ASCO, 2005; 23)

\*\*Renal cell ca: Temozolomide 200 mg/m<sup>2</sup> d 1-5 q 4 wk OR 18% + 42% NC, MTTP 7.2 mo, MOS 11.9 mo. Active (Abstract 4600 Proc ASCO, 2005; 23)

