

## Essential Peer-reviewed Reading in Kidney Cancer

The peer-reviewed articles in this section were selected by the editor, Robert A. Figlin, MD, for their timeliness, importance, and relevance to clinical practice or translational research.

### New data clarify guidelines on tissue microarrays

**Tissue microarrays: one size does not fit all.** Eckel-Passow JE, Lohse CM, Sheinin Y, Crispen PL, Krco CJ, Kwon ED. *Diagn Pathol.* 2010. 75:48. [Epub ahead of print.]

**Summary:** Although tissue microarrays (TMAs) are commonly employed in clinical and basic-science research, there are no guidelines for evaluating the appropriateness of a TMA for a given biomarker and tumor type. TMA performance across multiple biomarkers has not been systematically explored. A simulated TMA with between 1 and 10 cores was designed to study tumor expression of 6 biomarkers with varied expression patterns (B7-H1, B7-H3, survivin, Ki-67, CAIX, and IMP3) using 100 patients with clear cell renal cell carcinoma (RCC). The authors evaluated agreement between whole tissue section and TMA immunohistochemical biomarker quantification to assess how many TMA cores are necessary to adequately represent RCC whole tissue section expression. Additionally, it evaluated associations of whole tissue section and TMA expression with RCC-specific death. The number of simulated TMA cores necessary to adequately represent whole tissue section quantification is biomarker specific.

Although 2 to 3 cores appeared adequate for B7-H3, Ki-67, CAIX, and IMP3, even as many as 10 cores resulted in poor agreement for B7-H1 and survivin compared to RCC whole tissue sections.

**Conclusion:** While whole tissue section B7-H1 was significantly associated with RCC-specific death, no significant associations were detected using as many as 10 TMA cores, suggesting that TMAs can result in false-negative findings if the TMA is not optimally designed. Prior to TMA analysis, the number of TMA cores necessary to accurately represent biomarker expression on whole tissue sections should be established as there is not a one-size-fits-all TMA. The use of a simulated TMA is a cost-effective tool for this purpose.

### New dual inhibitor shows promise in RCC

**The efficacy of the novel dual PI3-kinase/mTOR inhibitor NVP-BEZ235 compared with rapamycin in renal cell carcinoma.** Cho DC, Cohen MB, Panka DJ, et al. *Clin Cancer Res.* 2010;16:3628-3638. Published online ahead of print July 6, 2010.

**Summary:** Inhibitors of TORC1 have been shown to be active in patients with metastatic renal cell carcinoma (RCC). As the phosphatidylinositol 3-kinase (PI3K) pathway activates numerous other kinases, transcription factors, and proteins associated with cell growth and survival besides mammalian target of rapamycin (mTOR), disruption of this pathway upstream of mTOR may be more effective than inhibition of TORC1 alone. To investigate this possibility, the dual PI3K/mTOR inhibitor NVP-BEZ235 was compared with rapamycin in RCC cell lines

and xenografts generated from 786-O and A498 cells. Treatment of RCC cell lines with NVP-BEZ235 in vitro resulted in the nuclear translocation of p27, greater reduction in tumor cell proliferation, and more complete suppression of Akt, Mnk-1, eIF4E, and 4EBP-1 phosphorylation and cyclin D1 and hypoxia-inducible factor 2alpha (HIF-2alpha) expression than that achieved with rapamycin. The reduction of HIF-2alpha levels correlated with reduced HIF activity as determined by luciferase assay. NVP-BEZ235 induced growth arrest in both the 786-O and A498 xenografts that was associated with inhibition of Akt and S6 phosphorylation as well as the induction of apoptosis and reduction in markers of tumor cell proliferation. In contrast, rapamycin induced only minimal growth retardation.

**Conclusion:** Dual inhibition of PI3K/mTOR with NVP-BEZ235 induced growth arrest in RCC cell lines both in vitro and in vivo more effectively than inhibition of TORC1 alone. These results provide the rationale for the clinical assessment of agents such as NVP-BEZ235 in patients with advanced RCC.

### New perspectives emerge on poor prognostic factors

**Concomitant CXCR4 and CXCR7 Expression Predicts Poor Prognosis in Renal Cancer.** D'Alterio C, Consales C, Polimeno MN, et al. *Curr Cancer Drug Targets.* 2010. [Published online June 25, 2010 ahead of print].

**Summary:** CXCR4 is a chemokine receptor implicated in the metastatic process. The CXCR4 ligand, CXCL12, was shown to bind also the CXCR7 receptor, a recently deorphanized chemokine receptor whose signaling pathway and function are still controversial. This study was conducted to determine clinic-pathological factors and outcome according to the expressions of CXCR4 and CXCR7 in renal cell carcinoma (RCC). CXCR4 and CXCR7 expression was evaluated in 223 RCC patients through immunohistochemistry; CXCR4 and CXCR7 was detected in 49 other consecutive RCC patients through RT-PCR. CXCR4 expression was low in 42/223 RCC (18.8%), intermediate in 71/223 (31.9%) and high in 110/223 (49.3%). CXCR7 expression was low in 44/223 RCC patients (19.8%), intermediate in 65/223 (29.1%) and high in 114/223 (51.1%). High CXCR4 and high CXCR7 expression predicted shorter disease free survival. In multivariate analysis, high CXCR4 expression ( $P = .0061$ ), high CXCR7 ( $P = .0194$ ) expression and the concomitant high expression of CXCR4 and CXCR7 ( $P = 0.0235$ ) are independent prognosis factors. Through RT-PCR, CXCR4 was overexpressed in 36/49 and CXCR7 in 33/49 samples correlating with symptoms at diagnosis and lymph nodes status.

**Conclusion:** CXCR4 and CXCR7, singularly evaluated and in combination, are valuable prognostic factors in RCC patients. KCJ