



2007 ASCO Meeting - Genitourinary Tumour Sites

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Genitourinary Tumour Sites

Renal Cell Carcinoma (RCC)

RCC continued its recent run of success with a plethora of studies being reported, including another plenary presentation.

Bevacizumab

Escudier et al. (abstract #3) presented results of a multinational, double-blinded study evaluating the combination of intravenous monoclonal antibody against vascular endothelial factor (VEGF) bevacizumab (BEV) with interferon alpha 2a (IFN-a2a) versus IFN-a2a alone as first-line treatment in nephrectomized patients with metastatic renal cancer (mRCC). Enrolled patients (649 randomized, 641 treated) were to receive subcutaneous IFN-a2a 3 times per week at a recommended dose of 9 million international units for up to 1 year plus either BEV 10 mg/kg or placebo every 2 weeks until disease progression. Primary endpoint was overall survival (OS) and results of a planned interim analysis were presented (see table 1). The study was halted due to a statistically significant improvement in the secondary endpoint of progression-free survival (PFS) and the remaining patients on interferon allowed to crossover.



Table 1 Escudier et al (abstract #3) - Results

	<i>IFN/Placebo</i>	<i>IFN/BEV</i>	<i>HR</i>	<i>p-value</i>
Response Rate: CR	2%	1%		<i>p</i> <0.0001
PR	11%	30%		
Duration of Response	11m	13m		
Tumor Shrinkage	39%	70%		
PFS	5.4m	10.2m	0.63	<i>p</i> <0.0001
PFS: Good Risk	7.6m	12.9m		<i>p</i> =0.004
Intermediate Risk	4.5m	10.2m		<i>p</i> <0.0001
Poor Risk	2.1m	2.2m		<i>p</i> =0.457
OS	19.8m	NR		

NR = not reached

Comment: The results for the combination arm are similar to that previously seen with sunitinib. The necessity of interferon in the combination and its added toxicity remains unclear. It is unlikely to replace sunitinib, which is the current standard first line therapy.

Sunitinib

Motzer et al. recently published the results of their study of oral VEGF inhibitor sunitinib versus interferon-alfa (IFN- α) as first-line treatment of mRCC (NEJM Jan 2007). At ASCO, they presented updated results and analysis of prognostic factors (abstract 5024). Predictive factors of longer survival in the sunitinib arm in a multivariate analysis are shown in Table 2. A nomogram to predict PFS at 12 months was also presented.

Table 2 Motzer et al. - Predictive factors

Predictive Factory	Hazard Ratio	95% Confidence Interval	P value
ECOG performance status score of 0	0.7	0.543-0.901	0.006
time from diagnosis to	0.618	0.482-0.792	0.001



treatment of ≥ 1 year			
corrected serum calcium ≤ 10 mg/dL	0.503	0.325-0.778	0.001

Sorafenib

Escudier et al. (NEJM Jan 2007) recently published the results of the randomized trial of cytokine failure second-line oral VEGF inhibitor sorafenib vs. placebo showing a PFS benefit of 2.7 months (0.44; 95% confidence interval [CI], 0.35 to 0.55; $P < 0.01$).

Bukowski et al. (abstract #5023) updated the primary endpoint result of OS showing a non-significant trend of 2.6 months ($p = 0.146$, HR 0.88, 95% CI 0.74-1.04).

Comment: Much like the previously mentioned bevacizumab study in mRCC, the survival outcome of this trial was confounded by cross-over of the placebo arm to sorafenib after the interim analysis showing a PFS survival benefit. If crossover patients were censored the overall survival benefit was borderline significant but this analysis remains controversial.

Szczylik et al. presented the results of an open-label randomized phase II trial of first-line treatment with sorafenib versus interferon in patients with advanced RCC (abstract 5025). Primary endpoint was PFS. Patients initially receive either sorafenib 400 mg twice per day or IFN- α 9 million units 3 times per week (period 1). Upon disease progression, patients on sorafenib had the option of increasing their dose to 600 mg twice per day or and those on IFN- α of crossing over to sorafenib 400 mg twice per day (period 2). PFS for period 1 for sorafenib vs. INF were 5.7 months and 5.6 months respectively (HR 1.14 95%CI 0.613-1.272 $p = 0.504$). Escalating the dose of sorafenib did not result in any further significant responses. However, the response rate for patients crossed over from INF to sorafenib was 22%.

Comment: This represents a major blow to sorafenib achieving first line therapy status and that dose escalation following progression does not improve activity. However, promising response rate of 22% in cytokine failure patients immediately switched to sorafenib is intriguing and worth further investigation.

Temsirolimus

Concurrently with ASCO, Hudes et al. (NEJM May 2007) published results of a multinational 3 arm trial of an intravenous mTOR inhibitor temsirolimus vs. temsirolimus + interferon vs. interferon in Motzer poor risk mRCC which demonstrated a 3.6 month OS advantage for temsirolimus alone compared to control interferon (HR 0.73; 95%CI 0.58-0.92). Dutcher et al. (abstract #5033) performed subgroup analyses of predictive



factors shown in Table 4. It should be noted that chromophil (papillary) histology represented 76% of the non-clear cell histologies.

Table 3 - Dutcher et al. - Subgroup analyses

Variable		INF	TEM	HR (95% CI)
Clear cell	n=339	8.2 mo	10.6 mo	0.85 (0.64,1.06)
Non-clear cell	n=73	4.3 mo	11.6 mo	0.55 (0.33, 0.90)
<65 yrs	n=287	6.9 mo	12.0 mo	0.82 (0.57, 0.87)
>65 yrs	n=129	8.3 mo	8.6 mo	1.15 (0.78, 1.68)
Intermediate	n=115	17.7 mo	13.0 mo	1.17 (0.74, 1.84)
Poor	n=301	6.0 mo	10.2 mo	0.70 (0.55, 0.89)

Comment: These results provide vital information for subgroups of patients such as chromophil (papillary) that are generally excluded from trials. It remains to be seen if survival benefits seen in poor prognosis patients are replicated in ongoing trials of mTOR agents in favourable and intermediate risk populations.

Canadian abstract

Sridhar et al. (abstract #5093) reported, on behalf of the Princess Margaret Hospital Phase II Consortium, the preliminary results of a phase II trial of an oral VEGF inhibitor AZD2171 for mRCC. The first 24 patients were reported having a 38% response rate and an overall clinical benefit (PR + CR + stable disease) of 75%.

Comment: This agent appears to have comparable activity to existing agents and will undoubtedly warrant further investigation.

Bladder Cancer

Bellmunt et al (abstract #5030) reported the results of the EORTC/ Intergroup trial that randomized phase III study comparing paclitaxel/cisplatin/gemcitabine (PCG) and gemcitabine/cisplatin (GC) in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy, which NCIC endorsed (BL7). Of the 627 patients, 82% were primary bladder. Primary endpoint was OS. Results are shown in table 4.

Comment: GC remains the standard of care for advanced urothelial cancer in Canada.



	PGC (n=312)	GC (n=315)	HR	p-value
RR: CR +PR CR PR SD	57% 15% 42% 23%	46% 10% 36% 30%		<i>p</i> =0.02
PFS	8.8m	7.7m	0.87 (0.74-1.03)	<i>p</i> =0.11
Overall Survival	15.7m	12.8m	0.86 (0.72-1.03)	<i>p</i> =0.10

Prostate

Bolla et al. (abstract #5014) presented the results of the EORTC long term versus short term androgen ablation for high risk prostate cancer post radical radiotherapy. The trial randomized 970 patients after 6 months of androgen ablation to 30 months further androgen ablation versus no further treatment. This was an equivalence trial and primary endpoint was OS with short term ablation having a HR less than 1.35. The results presented were from an ad hoc interim analysis. Five year OS for short term vs long term androgen ablation were 80.6% and 85.3% respectively (HR 1.43 95%CI 1.04-1.98 *p*=0.6543)

Comment: Despite criticism for an ad hoc analysis, discussant Dr Ian Tannock agreed non-inferiority could not be confirmed and 36 months of androgen ablation remains the standard of care.

Sternberg et al. (abstract #5019) presented the results of a phase III trial randomized trial of second-line oral satraplatin versus placebo in hormone refractory prostate cancer (HRPC) (SPARC trial). Interestingly the primary endpoint included both OS and PFS. The trial enrolled 950 patients. Results are shown in Table 4.



Table 4 Sternberg et al - Results

	Satraplatin (n=635)	Placebo (n=315)	HR	p-value
PFS* (Independent Review)	11.1m	9.7m	0.67 (0.57-0.77)	$p<0.000003$
PSA Response	25%	12%		$p<0.001$
RECIST Response	7%	1%		$p=0.001$
Pain Response	24%	14%		$p=0.005$
Time to Pain Progression	66.1 wks	22.3 wks	0.64 (0.51-0.79)	$p=0.0002$

* 1 Primary endpoint = Progression Free Survival defined as: RECIST or symptomatic progression, skeletal related event, or death but NOT PSA.

Comment: Satraplatin is active in second line therapy but OS results are still pending. In the interim it is unclear, without direct trial comparison, whether this drug is any better than the current de facto standard of care mitoxantrone.

Armstrong et al (abstract #5009) presented an analysis of the TAX 327 trial of docetaxel in HRPC looking at PSA decline as a surrogate for OS. They found a PSA decline of 30% at 3 months of therapy correlated to improvement in OS 8.6 months (21.6 months versus 13.0 months HR 0.50 95% CI 0.43-0.50 $p<0.001$).

Comment: Study confirms results seen in an analysis of SWOG 9916 (Petrylak JNCI 2006). Fact that delayed PSA responses at 3 months may be seen which still are predictive of improved survival are re-assuring when early PSA response is not seen. Finally, future definitions of PSA response (typically > 50%) may need to be re-evaluated.

Moreno et al. (abstract #5016) presented interesting data about circulating tumour cells (CTC) as a surrogate for OS in HRPC. At baseline, having >5 CTC/7.5ml blood is prognostic of improved OS (21.4 months vs. 10.7 months $p<0.0001$). For patients given chemotherapy, CTC levels provided better predictive value for benefit from chemotherapy than the tradition > 50% drop in PSA.



Comment: This result replicates similar findings in colon and breast cancer and provides another potentially useful tool to guide physicians and patients. However, further validation in prospective trials is underway.

Canadian abstract

Chi et al (abstract #5069) reported the NCIC CTG IND.165 randomized phase II trial in HRPC of docetaxel + prednisone with or without OGX-11, an antisense oligonucleotide inhibiting clusterin expression. The trial met its endpoint of 50% patients receiving OGX-11 obtaining a PSA response although this was no different than the control arm. Interestingly, the experimental arm had no patients had a best response of progression and trended towards improved PFS compared to the control arm.

Comment: With no increase in side effect profiles, this drug has satisfied criteria for ongoing clinical investigation.

Testes

Canadian abstract

Duran et al (abstract #5021) presented a retrospective review of the Princess Margaret Hospital non-risk adapted surveillance policy for stage I non-seminomatous testicular tumours. A total of 305 patients were divided into pre-1993 (n=141) and post-1993 (n=164) cohorts. There was both a reduction in relapse in both the low and high risk groups from 53.3% to 38.6% and from 17.3% to 11.7% respectively. Most common location of recurrence was retroperitoneum (74%) and most were picked up by more than one modality of surveillance (i.e. Physical exam, serum tumour markers, imaging). A significant proportion of those who relapse on survival require multimodality therapy. There was no difference in survival between the groups.

Comment: Surveillance, even in high risk patients, is an acceptable alternative to spare some patients unnecessary treatment without compromising cure rates. Although for those who do recur, they will likely require more intense treatment, which may be multimodality.