Trends-in-Medicine

February 2008
by Lynne Peterson

SUMMARY

Prostate cancer: Cougar Bioscience's abiraterone looks very promising in prostate cancer. There are competitors, including Medivation's MDV-3100, in this new class of drugs, but they are further behind. ♦ Oncologists have little interest in Nanosphere's supersensitive PSA test, insisting that there is no real need to measure PSA at super low levels, even in men who have recently undergone a prostatectomy. ♦ **Renal cell carcinoma:** Genentech's Avastin does not appear to be any more effective than Pfizer's Sutent in RCC, and doctors are divided on how they would choose between the two if Avastin gains FDA approval in RCC. But new data suggest that the two agents will ***not*** be combined because of excessive toxicity, though sequential therapy may work. ♦ Heart failure with Sutent occurs almost twice as much in the real world as in clinical trials, so doctors should monitor for this, but experts did not recommend avoiding Sutent because of this. ♦ **Testing:** Nanosphere's Verigene assay can detect super low levels of PSA, but oncologists don't see the utility of this test.

Trends-in-Medicine
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ASCO 2008 GENITOURINARY CANCERS SYMPOSIUM

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There were no dramatic announcements or big issues at this year's ASCO-GU meeting, making it relatively uneventful. Most interesting, perhaps, were positive data on Cougar Bioscience's abiraterone in prostate cancer and Genentech's Avastin (bevacizumab) in renal cell carcinoma (RCC) as well as new cardiac toxicity data on Pfizer's Sutent.

PROSTATE CANCER

A terminology change is occurring in prostate cancer. Oncologists said the term castration-resistant prostate cancer (CRPC) is now preferred to hormone-resistant prostate cancer (HRPC), though some doctors still use HRPC when talking to patients in order to avoid the emotionally-charged word "castration."

There were several interesting findings in prostate cancer, including:

- Body mass index (BMI) is not an independent predictor of the outcome in men with metastatic CRPC.
- Testosterone levels <50 ng/dL (the castrate range) are not prognostic for prostate cancer outcomes, and a lower level should not be used as it would keep a larger proportion of men with CRPC from participating in clinical trials.

However, much of the attention in prostate cancer at ASCO-GU was focused on a new class of agents – oral androgen synthesis inhibitors (also called CYP17 inhibitors, steroid enzyme inhibitors, or lyase inhibitors) – that irreversibly inhibit C17/20-lyase, a key enzyme in androgen synthesis. Furthest along in development is Cougar's abiraterone, but there are also other agents in this class, including Bristol-Myers Squibb's BMS-641988 and Medivation's MDV-3100. Dr. Bruce Roth of Vanderbilt said, "It is fascinating…If you asked most of us four years ago if anything was left to exploit in androgen suppression, we would have said no…but now we see that we had a simplistic approach anti-androgen. Assuming there was complete androgen blockade showed a lack of understanding of the biology of these tumors…It is exciting to revive a system we had put to rest thinking we had done all we could do with that system."

All of these agents are being designed to replace ketoconozole, the current standard of care for these patients.

➢ **Advantages** of ketoconozole therapy: oral, inexpensive, most effective, occasional long duration response.

➢ **Disadvantages**: significant treatment, majority do not respond, a lot of drug interactions (CYP3A4).

Other hormone therapy options include:

- Estrogens – a speaker said this is understudied.
- Diethylstilbestrol (DES) – probably ~25% of patients will respond to this.
- Wyeth's Premarin – about 25% of patients respond at higher doses (1.25 mg TID), but there also is a "moderate" PE/DVT rate that is not ablated by warfarin. This reportedly is a very popular therapy in Europe.

Key issues with secondary hormone therapies include:

1. *Are these therapies effective?* Dr. William Oh of Dana-Farber Cancer Institute said, "For some patients, yes, but this is anecdotal only."
2. *Is PSA a valid endpoint in a clinical trial of CRPC?* Dr. Oh said, "For screening new drugs, maybe. For improving survival or quality of life, no."
3. *Are there subsets of patients for whom secondary hormone therapy may be of particular value?* Dr. Oh said, "That is likely, but we need to identify them."

COUGAR BIOSCIENCE's abiraterone acetate (CB-7630)

The data on abiraterone came from four posters, one of which was also presented orally, and three of these updated data from previously reported clinical trials.

1. Impact of prior ketoconozole therapy

Researchers led by Dr. Charles Ryan of the University of California, San Francisco, studied the impact of prior ketoconozole therapy on abiraterone response in 30 evaluable Phase I CRPC patients at UCSF and Dana-Farber Cancer Institute. Researchers found that patients responded to abiraterone whether or not they had previously taken ketoconozole, and they recommended that trials be conducted in patients with ketoconozole-refractory disease.

Abiraterone Response Based on Prior Ketoconozole Use

Measurement	Prior ketoconozole n=19	No prior ketoconozole n=11
Response to abiraterone	53%	55%
PSA decline ≥50%	47%	33%

2. COU-AA-004

Dr. Daniel Danila, a medical oncologist from Memorial Sloan Kettering Cancer Center, presented updated preliminary data from this multicenter trial in the U.S. and U.K. testing abiraterone in men with metastatic CRPC who failed both androgen deprivation therapy and treatment with Sanofi-Aventis's Taxotere (docetaxel), the current standard of care and the only FDA-approved agent with a survival benefit in this group of men.

The trial was powered to be positive if it showed at least 30% of men had a ≥50% decrease in PSA, and it found that 45% met that criteria. Of the 54 enrolled patients, Dr. Danila reported on 38 from his center. As of the meeting, 13 of these 38 patients (34%) continued on treatment, with more than 3 cycles of therapy. Dr. Danila concluded: "Non-progression at 6 months was noted in 9 patients, including 3 patients with visceral (pulmonary and hepatic) metastases (mets)." He added that it may be that some patients fail quickly and some go a long time without failing.

Phase II Results with Abiraterone

Measurement	Abiraterone 13-24 weeks	Abiraterone >25 weeks
Primary endpoint: ≥50% decrease in PSA	44.7%	
≥50% decrease in PSA in patients with no prior ketoconozole (n=21)	57%	
≥50% decrease in PSA in patients with prior ketoconozole (n=17)	29%	
Bone scan unchanged	7 patients	9 patients
Patients with lymph node metastases		
Decreased	1 patient	0
Unchanged	4 patients	5 patients
Increased	5 patients	1 patient
Patients with visceral disease		
Decreased	0	0
Unchanged	0	3 patients
Increased	3 patients	0
Safety		
Hypokalemia	10% (vs. 40% with monotherapy)	
Fatigue	Mostly Grade 1-2	

In earlier monotherapy trials, the main issue with abiraterone has been hypertension, but experts insisted that this is resolved with the addition of a corticosteroid (prednisone or dexamethasone). Dr. Danila said, "The addition of prednisone reduced the frequency of adverse events seen with monotherapy. There was no Grade 3 hypertension in this trial." The prednisone also reduced the hypokalemia and edema with abiraterone.

Could some of the benefit from abiraterone be due to a secondary response to prednisone? That is impossible to determine from the 004 trial. Dr. Roth said, "That is a good question. The response with prednisone alone is ~12%...You want to at least stratify the data by whether or not the patient is getting simultaneous prednisone…I would bet the FDA will ask that question. The trial was designed in good faith, but it is a potential confounding variable."

COU-AA-004 Trial: CTCs as a Predictor of Abiraterone Response

Measurement		Number of patients	≤12 weeks		>12 weeks	
			Progressed	On study	Progressed	On study
Baseline	No change	10	10%	0	40%	50%
<5 CTCs	Rise in CTC	2	50%	0	50%	0
Baseline	CTC ≥5	16	56%	0	31%	13%
≥ 5 CTCs	Decrease to <5	10	10%	0	30%	60%

Phase I U.K. Results with Abiraterone

Measurement	Abiraterone n=21
≥50% decrease in PSA	57%
≥90% decrease in PSA	29%
PR by RECIST (n=8)	63%
Regression of bone disease on scan	63%
Improvement in symptomatic pain, including reductions in opioid use	73%

Updated COU-AA-001 Phase II Results with Abiraterone

Measurement	Abiraterone n=44
≥50% decrease in PSA	61%
≥75% decrease in PSA	50%
≥90% decrease in PSA	25%
PR	12 of 21 patients
SD >3 months	7 of 21 patients
Median TTP	252 days

Updated COU-AA-003 Phase II U.K. Results with Abiraterone

Measurement	Abiraterone n=31
≥50% decrease in PSA	48%
≥75% decrease in PSA	32%
≥90% decrease in PSA	19%
PR	26%
SD >3 months	10 of 19 patients

COU-AA-003 Trial: CTCs as a Predictor of Abiraterone Response

CTCs	Abiraterone
Pre-chemotherapy change from baseline	
Increased to ≥5 CTCs	39%
Decreased to <5 CTCs	58%
≥50% decrease in CTCs	63%
Post-chemotherapy	
Increased to ≥5 CTCs	75%
Decreased to <5 CTCs	33%
≥50% decrease in CTCs	62%

The 004 trial also looked at circulating tumor cells as a predictor of abiraterone therapy. Dr. Danila said, "The CTC numbers have tracked well with post-therapy PSA and radiographic change and may provide additional prognostic value."

A ~1,200-patient Phase III trial is expected to begin within a few months; details reportedly are still being finalized with the FDA. In that trial all patients will get prednisone as well as abiraterone. In that trial, patients will be randomized 2:1 to 1000 mg abiraterone daily + 10 mg prednisone daily vs. 10 mg prednisone daily alone. The primary endpoint will be overall survival, so final data are not expected until 2011, and there are no planned interim analyses. The goal is to enroll patients in 6-8 months, and experts said people are interested in participating in the trial so they considered that a reasonable timeframe. Dr. Danila said, "If the DSMB doesn't stop the trial, it will be a good sign."

3. COU-AA-001 and COU-AA-003

Dr. Gerhardt Attard from the Institute of Cancer Research and the Royal Marsden NHS Foundation Trust in the U.K. presented a poster on the 21 chemotherapy-naïve CRPC patients treated in the COU-AA-001 Phase I dose-finding study looking at predictors of response and pharmacodynamic endpoints. He reported that abiraterone was well tolerated at doses as high as 2000 mg/day with minimal toxicity, and no dose limiting toxicity has been observed so far.

4. Dr. Alison Reid, also from Royal Marsden in the U.K., presented another poster on these two ongoing Phase II trials of abiraterone – COU-AA-001 and COU-AA-003 in advanced prostate cancer patients who failed androgen deprivation and docetaxel therapy. She said that theoretically abiraterone could be potentiated by adding a steroid, and that is what she saw in the 001 trial, "We are seeing stability of PSA in some patients and further responses."

- **001 trial update.** Among the 44 evaluable patients, she said symptoms decreased, bone disease regressed on imaging, and the median time to progression was 8.4 months. With prednisone (or dexamethasone which was used in the U.K.), there was no hypertension, fluid retention, or hypokalemia. She said Pfizer's Inspira (eplerenone) also has been used to prevent these side effects with abiraterone.

- **003 trial update.** Dr. Reid provided an update on the 31 patients (some with and some without prednisone) who have been treated in the U.K. and who have been in this study for more than 3 months. She said there was no relationship between progression after docetaxel and response to abiraterone.

Abiraterone usage outlook

Medical oncologists asked about the outlook for abiraterone were very optimistic, but they cautioned that many agents look good in Phase II only to fail in Phase III, so they are reserving judgment until they see the Phase III data. Among their comments were:

- "If abiraterone is approved, people will use it before docetaxel instead of ketoconozole."
- "The data on ketoconozole is very interesting, so the concept of inhibiting androgens through drugs such as abiraterone has intriguing possibilities."
- "It seems it may be an important second-line hormone therapy…It could be important in any patient who becomes hormone refractory…Hypertensions, by itself, can be treated. As long as the hypertension is not associated with MI or heart failure, it might not be a concern."
- "I think the data are exciting because it is a new class of drugs that targets our understanding of the biology of CRPC…Our current approach is to reduce serum testosterone with LHRH antagonists…but it only reduced testosterone ~60% in the prostate, and when that happens, the androgen receptor goes through some changes that make it more sensitive to small changes in testosterone… It is clear that simply reducing serum testosterone is not enough…The side effects of abiraterone may be solved with prednisone; they looked pretty mild to me. Without question, the Phase III trial will enroll quickly…This is a little like the Gleevec (Novartis, imatinib) story (in chronic myelogenous leukemia). This (abiraterone) is based on biology…Abiraterone will be used everywhere, in anyone with prostate cancer, not just CRPC. It would require clinical trials to prove utility, but you could make the argument to use it before surgery, in men who have high risk features on a prostatectomy specimen or on biopsy who get treated with radiation, in patients with rising PSA after initial therapy to help delay metastatic disease, and perhaps upfront in men not castrated yet to delay castration. Off-label use would be broad as long as it is tolerable."
- "My concern is that it will be an expensive ketoconozole …Ketoconozole in my hands is much less toxic than reported here, with a lot of responses and some durable responses, and it is a cheap drug. So, if something is going to replace it, then it has to show me that it is better than ketoconozole or has less drug/drug interactions…But more importantly, most of us who give hormonal therapy think it is probably time to stop after two lines, and if these studies show it is appropriate to go to three lines and have some durable third-line responses, I think that would be an advance."
- "I think it is worthwhile in chemotherapy-naïve patients, earlier on – even before we see metastatic disease. Those are patients with a longer life expectancy, and studies would be longer. We hope people will do that cautiously, but the safety profile will be more mature by that time."
- "It is very promising...It is a better ketoconozole, and that is the way I view it…This (abiraterone) looks better than ketoconozole. It appears to be less toxic and is, so far, very promising…Adding a steroid clearly improves the side effect problem."

AstraZeneca's ZD-4054

Dr. Nancy Dawson of the Lombardi Comprehensive Cancer Center presented the results of an international, placebo-controlled Phase II trial in 312 men with asymptomatic or mildly symptomatic mCRPC. The study found that oral ZD-4054 10-15mg QD "demonstrated a promising survival benefit" and was generally well tolerated, with Grade 1 edema, headache, and rhinitis the most common adverse events. The definition of progression in this trial was different from other U.S. trials. It was a composite of clinical progression, cancer pain requiring opiates, soft tissue metastases, and death in the absence of progression. An increase in PSA or new mets on bone scan did not count as progression events.

The protocol for this Phase II trial was amended in 2006 after the first interim analysis (at 165 events) to support collection of survival data for two years. At that time, TTP numerically favored ZD-4054, but the difference was not statistically significant. A Phase III trial is ongoing. Another review in early 2007 found a survival benefit but no statistically significant increase in PFS and no statistically significant decrease in bone mets.

Phase II Results with ZD-4054 in CRPC

Measurement	ZD-4054 15 mg n=98	ZD-4054 10 mg n=107	Placebo n=107
Primary endpoint: PFS	Nss	Nss	---
Overall survival	p=0.052	p=0.008	---
Median survival	23.5 months	24.5 months	17.3 months
Safety			
Peripheral edema	48%	39%	10%
Headache	44%	36%	12%
Nasal congestion	34%	28%	4%
Rhinitis	15%	15%	2%
Serious adverse events			
Anemia	2%	3%	1%
Cardiac failure	0	3%	0
Hematuria	0	1%	2%
MI	0	1%	2%

Bristol-Myers Squibb's BMS-641988

This is currently in Phase I dose escalation studies at three sites in U.S. patients with CRPC. It reportedly has a 40-fold increase in affinity for the androgen receptor. Dr. Edward Gelman of Columbia University said, "What we know about it, makes it look promising because it is a drug that has a high affinity for the androgen receptor and seems to block certain mutant receptors."

CELGENE

➢ **Revlimid (lenalidomide).** Dr. J.A. Garcia and colleagues from the Cleveland Clinic presented a poster on the preliminary results from a Phase II study – done independently of Celgene – of Revlimid (25 mg Days 1-21) + ketoconozole in castrate-progressive prostate carcinoma (CPPCA). The researchers reported on the first 20 of 34 planned patients, finding that the combination was relatively well tolerated, with "clear evidence of anti-tumor activity." Dr. Garcia said, "There is a dramatic response within a month." When compared to historical data, the addition of Revlimid to ketoconozole doubled the PSA response rate. As usual with Revlimid administration, patients all received aspirin for DVT prophylaxis.

Asked about the possibility of combining Revlimid with abiraterone, Dr. Garcia said, "If Revlimid proves out, Revlimid + abiraterone could be a possibility." Another expert said, "I don't think Revlimid will make it without more studies."

Phase II Study of Ketoconozole + Revlimid in CPPCA

Measurement	Revlimid + ketoconozole n=20
PSA decline ≥50%	60%
Any PSA decline	70%
PSA decline ≥90% in the 12 patients with a PSA response	67%
PR	1 patient
SD	2 patients
Discontinued therapy	12 patients: 6 for PD, 4 for adverse events, 2 for consent withdrawal

➢ **Thalmid (thalidomide).** An NCI poster reported on an open-label, single-center, Phase II trial of the combination of ketoconozole with both thalidomide and Avastin in 60 patients with metastatic androgen-independent prostate cancer (AIPC). The majority of these patients had unfavorable prognostic factors: high Gleason score and short PSA doubling time. The researchers found the combination very active: 90% of patients had a PSA decline ≥50%, which lasted a median of 11 cycles, and 72% had PSA declines ≥80%. The estimated PFS was 18.2 months, and the estimated overall survival was 26.7 months. Three patients discontinued treatment due to Avastin toxicity.

GENENTECH's Avastin (bevacizumab)

A poster by researchers from Virginia Mason Medical Center in Seattle reported on their study of Avastin in 18 patients with high risk prostate cancer. They found that Avastin does not appear to exacerbate acute radiation toxicity, and further study of Avastin + IMRT and combined with androgen blockade is warranted given there is no Grade 4 toxicity.

A Phase III trial of docetaxel + prednisone ± Avastin in CRPC is underway. Enrollment of 1,020 patients was completed in December 2007. The primary endpoint is overall survival. It will be about two years before the data are mature.

What do doctors think of the outlook for Avastin in prostate cancer? They are waiting for data from an ongoing CALGB study of docetaxel ± Avastin. The trial is either closed or nearly enrolled, but the data are not expected until 2009. Dr. Howard Sandler of the University of Michigan Medical Center said, "VEGF inhibitors make sense in most cancers. Avastin has really been beneficial in every tumor it has been tried in – colorectal cancer, renal cell cancer, breast cancer. And preliminary data from CALGB suggest it may be beneficial in prostate cancer, so I am optimistic about that study." Dr. Eric Klein of the Cleveland Clinic said, "It is too early to say. It does seem like there is some activity. The trials are early, but it is promising."

Safety of Avastin in High Risk Prostate Cancer

Adverse event	Toxicity from Day 1		Acute toxicity within 90 days of start of IMRT	
	Grade 2	Grade 3	Grade 2	Grade 3
Hypertensions	61%	17%	11%	6%
Proteinuria	33%	6%	22%	0
Leukopenia	28%	0	28%	0
Fatigue	11%	6%	11%	0
Diarrhea	6%	0	6%	0
Hemorrhoids	6%	0	6%	0
Cystitis	6%	0	6%	0
Bilirubin	6%	0	---	---
Confusions	6%	0	---	---
Lack of motivation	6%	0	---	---
Headache	6%	0	6%	0
Urinary frequency	6%	6%	---	---
Liver enzyme increase	0	6%	0	6%
Hyponatremia	0	6%	---	---

MEDIVATION's MDV-3100

There were no data on this CYP17 inhibitor at ASCO-GU, but several speakers mentioned it. It was discovered by Dr. Charles Sawyer, a very respected researcher, and licensed to Medivation. Dr. Roth said, "Few people have as much basic science respect as Sawyer…so that gives real credibility to the drug…He is completely credible." A speaker said a Phase I/II program is underway at Memorial Sloan Kettering Cancer Center (MSKCC), with the outcome of that expected later this year. Dr. Oh said, "The preclinical data have been very promising, but it is way too early to say whether it will succeed." Dr. Gelman said, "Last year they showed data that, in instances where bicalutamide is ineffective, this drug induces a reduction in tumor size and a certain percentage of animals have complete responses."

NOVARTIS'S RAD-001 (everolimus)

mTOR inhibition remains an interesting avenue of research, and Novartis sources were very enthusiastic about RAD-001. Key data are expected at ASCO 2008 on this, but at ASCO-GU Duke researchers reported on 19 patients in a Phase II study in metastatic CRPC which found that continuous administration of 10 mg/day was well tolerated, with stable disease in "some" patients, but no objective or PSA responses so far. Median TTP was 85 days. The side effect that has been a concern with all mTORs is pneumonitis, and that was not reported in this study, though 5% of patients had pulmonary infiltrates.

PROTOX THERAPEUTICS' PRX-302

Researchers reported on a Phase I study of 24 patients of transperineal intraprostatic delivery of PRX-302, a genetically altered protoxin. The study found no drug-related serious adverse events, one Grade 3 adverse event (liver enzyme elevation) that was asymptomatic and resolved in a week. PSA levels decreased in 63% of patients. Further studies are planned.

Other novel agents in development

Dr. Tomasz Beer of Oregon Health Sciences University (OHSU) pointed out that there are not a lot of data on treatments for mCRPC beyond docetaxel. Dr. Michael Carducci, a urologist from Johns Hopkins, warned that the new androgen receptor agents "require using trial designs and treatment settings where the comparators and endpoints are tricky." Dr. Gelman said, "I believe that we will need multi-agent therapy…I think it will require agents that affect different androgen receptor resistance mechanisms – for example, a kinase inhibitor and a third generation anti-androgen."

Novel Therapies for CRPC

Drug or class	Notes
Cytotoxic chemotherapy	
Overall	TTP/PFS 2-3 months, median survival 11 months
EMD Serono's Novantrone (mitoxantrone)	TTP/PFS 2-3 months
Carboplatin	TTP/PFS 3 months
Pharmion/GPC Biotech's satraplatin	33% reduction in risk of progression, but no survival difference. Unlikely to be approved in prostate cancer
Bristol-Myers Squibb's ixabepilone	TTP/PFS 2.2 months
Vinorelbine ± estramustine	TTP/PFS 1.4 months
Ongoing trials	
Sanofi-Aventis's XRP-6258	A cousin of docetaxel in Phase III
Ixabepilone + mitoxantrone	Phase II
E-7389	---
Cell Therapeutics's Xyotax (paclitaxel polyglumex)	Phase II
Nexavar + previous chemotherapy	Phase II
AstraZeneca's Iressa (gefitinib) + etoposide	---
Cell Genesys's GVAX + docetaxel	Vaccine. Exploratory Phase II analysis suggested survival benefit with high dose
Dendreon's Provenge (sipuleucel-T)	One trial of this vaccine showed no benefit in TTP but 4.5 month benefit in survival in an exploratory analysis. Final data should be mature in 1-1.5 years
CTLA-4 blockage	---
Merck's odanacatib (MK-0822)	Being studied in both prostate and breast

RENAL CELL CARCINOMA (RCC)

Sutent and Nexavar are already approved in RCC, but there are a relatively long list of other agents also in development to treat this cancer, including Avastin.

PFIZER's Sutent (sunitinib)

The ***good news*** for Pfizer at the meeting was that new data on Avastin + IFN didn't appear more effective than Sutent in first-line RCC, and Sutent has the advantage of being an oral agent. The other good news was that it appears that patients who progress on Sutent can have the drug stopped and then respond again once it is restarted.

The ***bad news #1*** was that a 48-patient retrospective study by Stanford researchers found that the rate of cardiac toxicity – specifically symptomatic Grade 3/4 heart failure – with Sutent in RCC and gastrointestinal stromal tumor (GIST) is almost twice as high in the real world (15%) as had been reported in the clinical trials (8%). The adverse effects were observed as early as 22 days and as late as 435 days after the start of Sutent and persisted in three patients even after Sutent was discontinued and heart failure medication was started. Patients with a history of heart failure, a history of coronary artery disease, or a low body mass index (BMI) were more likely to experience heart failure on Sutent.

The retrospective study was performed at Stanford University after doctors there observed a higher than expected incidence of ***symptomatic*** heart failure. The researchers suggested that the cardiotoxicity may be related to dose: "It is possible those patients with lower BMIs have a higher effective serum level of drug with dose-related pharmacodynamic effects at the level of the cardiomyocyte."

These findings led the researchers to recommend close monitoring of patients on Sutent. Dr. Melinda Telli of Stanford said, "Our data demonstrate the need for routine cardiac monitoring in patients receiving sunitinib. Cardiac adverse effects need to be carefully examined in future trials of sunitinib to determine the factors that place patients at risk for this complication." Another expert commented, "This is important, and we haven't given it enough scrutiny. It doesn't mean we shouldn't use sunitinib, but we need to screen patients for underlying risk factors for heart disease…It also probably wouldn't influence the choice between Sutent and Nexavar because the collective sense is that Sutent has more anti-cancer activity (than Nexavar)."

An expert from M.D. Anderson Cancer Center said that guidelines are in the process of being written by a group of cardiologists, internists, and oncologists around the country and should be completed in 2Q08 or 3Q08. Then, they will submit the report to the National Cancer Institute (NCI). He added, "At our institution we have largely adopted guidelines…In order to be enrolled in any VEGF trial, the patient has to have a blood pressure <140/90, which is substantially lower than NCI which is 150/100, so we lowered the bar as part of the standard of care as standard practice at our institution…The task force will specifically address VEGF."

The ***bad news #2*** was that combination therapy with Sutent + Avastin does ***not*** appear to be safe, at least not in the dose combinations tested so far. Dr. Jorge Garcia of the Cleveland Clinic said no new patients are being enrolled in trials of this combination after a researcher at another institution reported a case of microangiopathic hemolytic anemia (MAHA), a serious condition which he dubbed "TTP-lite." He said the Cleveland Clinic hasn't seen this side effect, but he explained that it is very serious and raises questions about whether either Pfizer or Genentech will now move forward with the combination. Dr. Garcia said, "There will be no more trials with this combination for the time being. This is a serious adverse event. Lowering the dose is not the solution." More data on this toxicity are expected at ASCO 2008.

The study by Dr. Garcia and colleagues of Sutent + Avastin was a Phase I trial in advanced solid tumors. An MTD (defined by DLTs during the first cycle) was not reached at Sutent 50 mg/day 4 weeks on followed by 2 weeks off plus Avastin 10 mg/kg every 2 weeks. Only one DLT occurred during the study, a Grade 4 hypertension, with hypertension the most common Grade 2/3 toxicity. There was no microangiopathic hemolytic anemia in this study. The objective response rate was 29% (all PR), and 35% of patients had stable disease. To date, 55% of patients had discontinued treatment, 7 of these due to adverse events.

The ***puzzling news*** was that the incidence of brain metastases has increased with Sutent. Experts were quick to say that they do not believe Sutent is causing brain mets, but they said they are seeing more brain mets in patients who have been treated with Sutent, and they speculated that this is because the patients are living longer. However, they also commented that the brain mets appear to be larger in size, and they weren't sure if that could be related to the drug. One expert said, "Don't stop Sutent because of brain mets because Sutent controls the RCC."

A study is expected to be published soon in which 300-400 patients on Sutent who developed brain mets were evaluated. An expert said, "It may be that, in patients treated with targeted agents, the cancer may escape into sanctuary regions (e.g., the brain)."

Dr. Brian Shuch of UCLA reported on his retrospective analysis of 138 RCC patients who developed brain mets – most before Sutent was introduced. He found that if patients were aggressively screened, one-third had asymptomatic CNS disease, but size not the number of tumors influenced symptoms and surgical intervention. Survival was also longer than previously reported with aggressive therapy, and it was determined more by performance status and not the extent of CNS disease. He suggested that these patients should no longer be excluded from trials, and he recommended that all patients with extracranial disease should be screened for brain mets.

Safety in Phase I Trial of Sutent + Avastin in Solid Tumors

Adverse event	Sutent 25 mg + Avastin 5 mg/kg n=3	Sutent 37.5 mg + Avastin 5 mg/kg n=7	Sutent 37.5 mg + Avastin 10 mg/kg n=3	Sutent 50 mg + Avastin 10 mg/kg n=12	Sutent 50 mg + Avastin 5 mg/kg n=6
DLTs	0	1 Grade 4 hypertension	0	0	0
Hypertension	0	4 Grade 3	2 Grade 2	6 Grade 3	3 Grade 3
Hand-foot syndrome	1 Grade 3 2 Grade 2	0	1 Grade 3	0	1 Grade 3
Proteinuria	0	0	0	1 Grade 2 1 Grade 3	0
Fatigue	1 Grade 2	2 Grade 3 1 Grade 4	1 Grade 2	2 Grade 2 1 Grade 3	1 Grade 2 1 Grade 4
Thrombosis	0	1 Grade 3 DVT	0	0	0
Hemorrhage	0	0	0	1 Grade 2 epistaxis	0
Nausea/diarrhea/ anorexia	1 Grade 2 nausea 2 Grade 2 anorexia	1 Grade 3 anorexia	1 Grade 2 nausea 1 Grade 2 diarrhea 1 Grade 2 anorexia	1 Grade 2 vomiting	1 Grade 2 taste change
Hematologic adverse events					
Neutropenia	1 Grade 2	0	0	2 Grade 2 3 Grade 3	0
Anemia	1 Grade 2	0	0	0	0
Thrombocytopenia	1 Grade 2	1 Grade 3	1 Grade 2	1 Grade 2 1 Grade 3 1 Grade 4	0
Lymphopenia	0	2 Grade 3	0	1 Grade 2	0

BAYER/ONYX's Nexavar (sorafenib)

Dr. Garcia presented the results for 37 patients in a Phase II study of Nexavar in clear-cell metastatic RCC refractory to either Sutent or Avastin. Currently, there is no standard of care after front-line therapy with either a VEGF inhibitor or an mTOR inhibitor, though some small studies have suggested VEGF therapy can be given sequentially. Nexavar is commonly used second line after prior VEGF therapy, but that hadn't been studied before. The trial was powered to show at least a 20% tumor burden reduction rate, and it showed almost twice that (38%), which he called "modest efficacy." Other findings included:

- 16 patients discontinued due to progressive disease and 4 to adverse events.
- One patient died of disease-related liver failure.
- 8 patients had their dose escalated – all in the first 45 days.
- No new adverse events were seen with Nexavar.
- Patients who experienced Grade ≥3 adverse events with prior Avastin or Sutent therapy were more likely to experience a Grade ≥3 adverse event with Nexavar (but p=Nss).
- Prior response to Avastin or Sutent did not appear to predict for or against a subsequent response to Nexavar.

Second-Line Nexavar after Sutent or Avastin in mRCC

Measurement	Nexavar in Avastin-refractory patients n=15	Nexavar in Sutent-refractory patients n=22
Demographics		
Mean duration of prior therapy	6.4 months	14.6 months
Median number of previous cycles	6	9
Median time from discontinuation of prior treatment to start of trial	4 weeks	7.6 weeks
Prior PR	13%	45%
Prior SD	20%	23%
Results		
OR	3% (1 patient)	
SD	40%	
Primary endpoint: tumor burden reduction rate	38%	
Median PFS	3.7 months	4.4 months

GENENTECH's Avastin (bevacizumab)

New data on Avastin from the Phase III CALGB-90206 trial in RCC were somewhat disappointing. The efficacy of Avastin + interferon (IFN) was better than IFN alone in terms of PFS and ORR – but only comparable to other trials of Sutent (a PFS of ~11 months) – and toxicity was greater with the combination. Dr. Brian Rini of the Cleveland Clinic said no prior trials have shown a benefit with adding agents to IFN.

Phase III Results for IFN ± Avastin in RCC

Measurement	Avastin 10 mg/kg on Days 1 and 15 + IFN 9 MU TIW n=369	IFN 9 MU TIW n=363	p-value
Secondary endpoint #1: PFS	8.5 months	5.0 months	<0.0001 (HR 0.71)
PFS by MSKCC risk group			
Favorable	11.1 months	5.7 months	<0.05
Intermediate	8.4 months	5.3 months	<0.05
Poor	3.3 months	2.6 months	Nss
Response			
Secondary endpoint #2: ORR	25.5%	13.1%	<0.0001
CR	3.4%	1.3%	<0.0001
PR	23.4%	12.7%	<0.0001
Duration of response	11.9 months	8.7 months	Nss
Grade 3-4 adverse events			
Any	79%	61%	---
Fatigue/asthenia/malaise	37%	30%	---
Anorexia	17%	8%	---
Proteinuria	15%	<1%	---
Hypertension	10%	0	---
VTE	2%	1%	---
Hemorrhage	1%	<1%	---
GI perforation	<1%	0	---
Arterial ischemia	1%	0	---

At the 5th pre-planned interim analysis, the DSMB recommended release of the data, which showed a similar benefit on both ORR and PFS to a previous trial, AVOREN. The trial is still ongoing awaiting enough events to determine the primary endpoint, overall survival.

So how would oncologists choose between Sutent and Avastin when and if Avastin gets approved for use in RCC? Oncologists said:

- "The PFS is a little lower than what was shown in the AVOREN trial, and the ORR is a little less than in AVOREN. But Avastin + IFN is in the ballpark of Sutent. The Avastin toxicity is bad when a patient gets it, but a lot of patients don't experience the toxicity. More patients can tolerate Avastin than Sutent. The majority of patients do well with Avastin. Sutent has a chronic, irritative toxicity."
- "Avastin actually has a little better side effect profile – less fatigue – but when you add the IFN, then the side effect profile is similar to Sutent…The activity (efficacy) of Avastin and Sutent are comparable, but Sutent is easier to administer. However, reimbursement may dictate the choice of agent."
- "Doctors may prefer Avastin because they get more 'chair' time (office visit charges) with it."

- "How to choose is something well worth thinking about. I would avoid the hype going on right now. None of these are great agents (in RCC)."
- *(Urologist):* "All of them – Sutent, Avastin, and Nexavar – are all sort of the same. I start with Nexavar, and if a patient fails that, I go to Sutent. Medical oncologists often use Sutent and switch to Nexavar if a patient fails Sutent…I see no reason to choose Avastin over Sutent if the cost is the same."
- "There is no advantage to Avastin…I wouldn't choose Avastin. I think it is much easier to take a tablet (Sutent) than get IFN or Avastin IV injections."
- *Canada:* "Avastin has no traction in Canada because it is too expensive."
- "I think this plus the AVOREN trial establishes Avastin as front-line therapy, and it will be used often when it is FDA approved (for RCC)."
- "The tolerability of Avastin is better – less fatigue and less hand-foot syndrome – than Sutent."
- "Right or wrong, Avastin will become the standard in RCC and replace Sutent."
- "Avastin + IFN is too difficult a regimen. The combination won't replace Sutent in RCC."
- "The combination of bevacizumab + IFN is better than IFN alone. What we don't know is if the combination is better than Avastin alone. The toxicity for the combination appears more severe than Avastin monotherapy."

European researchers presented a poster with the results of a 649-patient study looking at the efficacy and safety of Avastin + IFN in subgroups of patients with mRCC. The researchers concluded:

- The combination significantly increases PFS, independent of baseline characteristics of age, CL, or VEGF level.

Avastin + IFN in mRCC

Measurement	IFN n=327	Avastin + IFN n=322	Hazard ratio
Median PFS in patients with:			
Favorable MSKCC risk score	7.6 months	12.9 months	0.60
Intermediate risk score	4.5 months	10.2 months	0.55
With ≥3 of 6 poor risk features	2.3 months	3.8 months	---
Grade 3 adverse events in patients age <65			
Any	45%	58%	---
Anemia	5%	2%	---
Fatigue	7%	9%	---
Asthenia	8%	7%	---
Grade 3 adverse events in patients age ≥65			
Any	48%	66%	---
Anemia	6%	4%	---
Fatigue	9%	18%	---
Asthenia	5%	14%	---

- The Avastin dose intensity was not affected by age or decreased renal function, though the IFN dose was lower in those subgroups.
- There was a slightly higher incidence of Grade 3 adverse events in patients age ≥65.
- Avastin adverse events were independent of renal function.
- Patients with renal impairment are expected to derive similar efficacy benefit from Avastin as patients without renal impairment.

MERCK's Zolinza (vorinostat), an HDAC inhibitor

Researchers from Johns Hopkins presented a poster on 7 patients from an ongoing Phase I/II trial of vorinostat + Avastin 200 mg BID (on a 14-day schedule every 3 weeks) in RCC. They said the PK was as expected, and they observed "prolonged stable disease." The DLT is thrombocytopenia. Dr. Roberto Pili of Johns Hopkins said that only one Grade 4 thrombocytopenia was observed, and that occurred after 3 cycles, and he doesn't believe that Avastin is increasing the toxicity of vorinostat.

NOVARTIS's RAD-001 (everolimus)

A poster by researchers at the University of California, San Francisco, reported on the findings from a Phase I dose escalation study of the combination of RAD-001 and Nexavar in RCC. They found that:

- RAD-001 had no apparent effect on Nexavar levels.
- A 2.5 mg daily dose of RAD-001 is tolerable, and additional patients are being accrued to further explore the toxicity of a 5 mg daily dose of RAD-001. None of the patients at 2.5 mg/day experienced a dose-limiting toxicity, but two of 4 evaluable patients at the 5 mg dose had DLTs (Grade 4 uric acid and Grade 3 lipase with Grade 2 pancreatitis).
- Other Grade ≥3 toxicities included lymphopenia, syncope, and hypophosphatemia at 2.5 mg/day, and hypophosphatemia, diarrhea, hyponatremia, dental infection, edema, and photosensitivity at 5 mg/day.
- Best objective responses in 10 evaluable patients were: 3 confirmed PR and 2 SD.

Future therapy options: combination or sequential therapy?

Oncologists just don't know yet whether combination therapy or sequential therapy with targeted agents is better, what combinations, or which sequence of drugs should be used. One expert suggested:

- Avastin followed by Sutent on progression.
- Nexavar followed by axitinib on progression.

- Avastin + IFN, and then at first side effect drop the IFN and keep the Avastin. If that fails, Sutent, Nexavar, and Wyeth's Torisel (temsirolimus) all are possible.
- Sutent, followed by Nexavar or Torisel on progression. A trial of this is ongoing now.

Dr. Thomas Hutson of Baylor-Sammons Cancer Center noted, "Our clinical development of novel agents is outpacing our ability to know how to use these agents optimally." There have been no head-to-head trials of the new agents, and no data on sequencing, and until there is, he predicted, "The community standard will remain sequential use of single agents…On the sequencing Nexavar and Sutent, at the end of the day, there is a lack of cross-resistance…We have seen activity when one is used first and the other second, but we can't say which is better first."

Dr. Robert Motzer of MSKCC discussed combination therapy. He made several points, including:

- "One of the most compelling combinations is **temsirolimus + IFN**, where the survival was less for the combination than temsirolimus monotherapy …And that is something that we have to keep in mind as we move forward with targeted + targeted combinations."
- "One of my concerns with the **Nexavar + IFN** combination is the fact that the patients on the studies had such a high percent of dose reductions and of patient withdrawals from the studies for toxicity. In one study, 65% had dose reductions and nearly 30% came off for toxicity."
- "For most of us the door has been closed for adding **EGFR inhibitors**."
- "With the combination of **sunitinib and bevacizumab**, we got to full doses without excessive DLT. It appeared very promising, but with time what we found was the toxicity was excessive…and resulted in our inability to treat patients long-term. That has really given me a caution on these combination therapies as chronic treatments."
- "There is a common adverse event theme; they all seem to have rash, cardiac, cytopenia, and GI side effects."

Sequential and Combination Therapy in mRCC

Drug or combination	Response in MSKCC good patients	Response in MSKCC intermediate patients
Initial therapy in untreated patients		
Sutent + IFN	35%	56%
Torisel	---	26%
Avastin + IFN	29%	56%
Sequential treatment algorithms		
Type of RCC	**Prior therapy or risk**	**Order of agents**
First-line clear-cell	Good or intermediate	Sutent or high dose IL-2 in selected patients ***or*** Avastin + IFN
	Poor risk	Torisel
First-line non-clear-cell	All	Torisel
Second-line clear-cell	Prior cytokines	Nexavar or possibly Sutent
	Prior VEGF, TKI	Different TKI or mTOR inhibitor
	Prior Avastin	Sutent
	Prior mTOR	No data on what to give
Combination therapies		
Combination	**Phase studied**	**Outcomes**
Torisel + IFN	Phase III	Inferior survival to Torisel monotherapy
Sutent + IFN	Phase I	Unfavorable toxicity profile that compromised Sutent dosing
Avastin + IFN	Phase III	Combination better than IFN alone but is combination better than Avastin alone?
Nexavar + IFN	Phase II	High response rate but toxicity
Nexavar + Torisel	Ongoing	Full dose Torisel and half dose Nexavar is regimen for Phase II
Sutent + Avastin	---	Excessive toxicity at full doses
Nexavar + Avastin	---	Key toxicities are hypertension and hand-foot syndrome. Is half dose of each better or a full dose of one?
Torisel + Avastin	---	Promising combination with full dose of both, but limited safety data

Adverse Events with Combination Therapy in mRCC

Drug	Rash or hand-foot syndrome	Hypertension	Cytopenia	GI
Sutent	Yes	Yes	Yes	Yes
Nexavar	Yes	Yes	Yes	Yes
Avastin	---	Yes	---	Yes
Torisel	Yes	--	Yes	Yes

UROTHELIAL CANCER (UC)

Researchers at MSKCC presented research that, using immunohistochemistry (IHC) to assess the HIF and mTOR pathways, found that HIF-1 and mTOR are both overexpressed in invasive UC. Several trials are ongoing or planned at MSKCC targeting the

HIF-1 or mTOR pathways, including these trials in metastatic UC:

- **First-line therapy.**
  - Phase II trial of gemcitabine (Lilly's Gemzar) + Nexavar in patients with normal renal function.
  - Phase II trial of gemcitabine + Avastin in patients with poor renal function.
- **Second-line therapy.**
  - Phase II trial of Sutent.
  - Phase II trial of docetaxel ± AstraZeneca's vandetanib (ZD-6474).
  - Phase II trial of Novartis's RAD-001.

BAYER/ONYX's Nexavar (sorafenib)

A Phase II Canadian study found Nexavar was well tolerated but failed to show a significant response as a single-agent in first-line advanced or metastatic UC. There were no CRs or PRs, and only 4 patients had stable disease. Median TTP was 1.9 months, and median survival was 5.9 months. A researcher concluded, "There is probably not a role for Nexavar mono-therapy (in UC)…I think Sutent may be better." Additional data are expected at ASCO 2008.

PFIZER's Sutent (sunitinib)

Preliminary results from 21 patients in an ongoing, multi-center, open-label, Phase II study in Spain, looking at Sutent as first-line therapy in patients with advanced UC ineligible for cisplatin-based chemotherapy, indicated that Sutent has sufficient benefit in these "unfit" patients to allow initiation of chemotherapy to be delayed. The median TTP was similar to that obtained with standard chemotherapy in this patient population.

Phase II Trial of Sutent in Advanced UC

Measurement	Best tumor response by RECIST		
Objective response	14.3%		
CR	0		
PR	14.3%		
SD	64.3%		
Median TTP	6.0 months		
Adverse events			
	Grade 1-2	**Grade 3**	**Grade 3-4 hematologic**
Fatigue	37.5%	6.25%	0
Hypertension	25.0%	6.25%	0
Hand-foot syndrome	25.0%	0	0
Vomiting	18.7%	0	0
Cutaneous rash	12.5%	0	0
Hematuria	12.5%	0	0
Stomatitis	6.25%	0	0
Epistaxis	6.25%	0	0
Thrombocytopenia	N/A	N/A	20%
Lymphopenia	N/A	N/A	6.7%

BLADDER CANCER

ASTRAZENECA's vandetanib (ZD-6474) , an EGFR/ VEGFR inhibitor

A cell-line study by researchers at the University of Colorado found that ZD-6474 showed *in vitro* activity in bladder cancer cells. It also had synergistic activity with chemotherapy at a low dose. The researchers concluded, "The addition of ZD-6474 to cisplatin-based chemotherapy regimens merits further study."

INTUITIVE SURGICAL's DaVinci for robotic surgery

Three posters from Dr. Khurshid Guru and colleagues at Roswell Park Cancer Institute in Buffalo NY reported on the use of the DaVinci robot to perform radical cystectomies. Among the reported findings were:

- The learning curve for this procedure is 10-29 cases.
- Intraoperative and short-term post-operative outcomes compare favorably to open radical cystectomy, the current gold standard for treatment of invasive bladder cancer.
- The procedure can be done regardless of BMI, but a wider excision is needed for patients with a higher BMI.

WYETH's HTI-286

Researchers from the University of British Columbia reported on a preclinical, proof-of-concept study which found that intravesical HTI-286, a synthetic analogy of hemiasterlin, a marine sponge product which they discovered and then licensed to Wyeth, showed promising anti-tumor activity and minimal toxicity in cell lines and in a mouse model of high-grade bladder cancer. A researcher said, "It is not clear if Wyeth will pursue this indication. I think they tried it a couple of years ago in NSCLC, where they saw stable disease, but not enough effect to go forward. However, we may try to license it back from Wyeth to run a trial."

TESTING

ESOTERIX ENDOCRINOLOGY's ultrasensitive testosterone (UST) assay

One of the definitions of CRPC is testosterone ≤50 ng/dL. Esoterix Endocrinology, in conjunction with Cougar, is developing an ultrasensitive testosterone assay that will measure much lower levels. Oncologists weren't sure there is a real need for this test, but a Cougar official said that the company wanted this assay because "abiraterone decreases testosterone to very low levels, and we wanted to see what is going on." He added, "It is now a research test, but it could become more widely used in the future." An oncologist said, "There is a very small percent of people who escape in terms of serum tests from LHRH therapy – perhaps 1%-2% if we tested lower would have a test above the castration range…but it is a small percentage, and all I want to know is if it is in the castrate range or not. I might make a change in therapy based on intratumoral levels, which is not what that test is giving me. A serum test is unlikely to change anything." Another expert said, "There is a difference between serum and intraprostatic testosterone, so unless it better reflects what goes on inside the prostate, I don't see the utility."

NANOSPHERE's Verigene ultrasensitive PSA test

Most medical oncologists not only didn't see a need for a new nanotechnology test that measures super low levels of PSA, some even actively opposed such a test. Among the comments were:

- *U.K.:* "There is demand for a supersensitive PSA test. The test we have now can vary up to 5% when repeated in the same lab and up to 30% from one lab to another."

- "Where ultrasensitive PSA would be helpful is after a radical prostatectomy, but before it would be used in the U.S. there would have to be outcomes studies that show that earlier treatment improved outcomes or reduced the need for treatment (chemotherapy)."
- *Missouri:* "There is no proven utility yet in any prostate cancer disease state. Detection alone doesn't mean that the information is useful."
- *Utah:* "The standard PSA test already causes a lot of angst. What if you left 3% of normal prostate tissue (after a radical prostatectomy). That would be expected to produce some PSA. So, I'm not sure a more sensitive test would be useful – unless you could measure velocity – and you can already do that with current tests. And existing tests can measure down to 0.2 ng. But it could be marketable; patients might want the test even if physicians don't. I don't think I would ever order a PSA test more sensitive than what we now have."
- *North Carolina:* "I doubt there would be any demand for a more sensitive PSA test. We already have an ultrasensitive assay, and most people don't know what to do with measurement at that level. A patient who has recently had a prostatectomy with a negative PSA has a risk of progression at 10 years of 1%, so how do you do better than that? Even if you could measure PSA doubling time from 0.001 to 0.002 or 0.004, there still are no data that predict doubling at that level is meaningful…At the American Urological Association meeting this year, a doubling from 0.01 to 0.02 to 0.04 was shown to be only modestly predictive of the real doubling time (0.2 to 0.4 to 0.8), and some would argue that even at that level PSA doubling is not accurate…It is a big stretch, given what we know today, to say those very, very low levels can tell us what will happen. Nano levels scare me even more."
- "If PSA is rising post-prostatectomy, then it means the patient has metastases. But with the nanotest we would be treating solely on rising PSA, when the patient has no evidence of metastases. I don't think that is appropriate."
- *Statistician:* "There are no clinically meaningful data on doubling time at those levels."
- *Texas:* "There are a lot of problems with using PSA…It doesn't matter how sensitive the test is because there is no evidence that early intervention is beneficial."
- *Michigan:* "There is a supersensitive PSA test already. We can order that now. But it may, in a sense, be too sensitive. It is conceivable that after surgery there is a tiny bit of PSA, and if there is an extremely low level of PSA, it is possible it could be from that...Or, it could be from benign glands somehow left behind at the time of surgery…So, my own personal practice is not to use this supersensitive test but to use 0.3 ng/ml as a cut-off. The Europeans use 0.2 ng/ml, and the American Urological Association uses 0.4 ng/ml…Neither the AUA or European Association of Urology (EAU) advocates using the supersensitive assay following surgery."
- "I'm not sure (existing) ultrasensitive PSA assays have improved therapy at all because until you have a therapy that, when given with small volume recurrence, can be proven to be curative, essentially all you are introducing is lead time for recurrent disease…Unless you could have intervened and changed the natural history of the disease by detecting earlier recurrence, it doesn't make any difference…Quality of life decreased when our lab switched to ultrasensitive PSA because patients with undetectable PSAs before (with 0.1 the lowest measurable level), then had a 0.07 level, and the distress level was unbelievable. Unless you are prepared to change therapy – and say why you are changing it in asymptomatic patients when there is no curative therapy to give – What is the value of having a patient worry for a longer period of time?…Maybe the test would have value as an end-point in a clinical trial, but not for general use in the population…And in post-prostatectomy patients, knowing that there is a very low PSA level doesn't help unless there is proof that the therapy you are adding is curative…There is a small percentage of patients who probably would benefit from radiation therapy for small volume recurrence, but the majority of patients in that situation are not cured despite radiation therapy, and we don't think hormonal therapy in that situation is curative. If you could prove you could cure a patient with small volume recurrent, that is great...but not everyone who recurs will die of prostate cancer…You have to dial in restraint when you order the PSA, not after it comes back positive. Then it is too late."
- "Those (ultrasensitive) PSA assays have been around a long time and have never gained clinical traction because there is so much variability in the clinical behavior of a person with rising PSA. It probably wouldn't change what you do. But it might be useful for testing the activity of new drugs."
- "We already have one (supersensitive PSA test)…That already exists down to levels as low as 0.01 ng/ml or even lower…The problem with going further is that we don't learn any more with PSA if you find tiny amounts…We need a better biomarker than PSA in the blood. We are also learning that what is going on in the blood may not reflect what is going on in the tumors…In the tumors, they are like little factories making their own hormones and PSA. They may be making their own machinery to sustain themselves, and whatever they leak into the bloodstream is what we measure, but it may not be what is important – which is what is in the tumors…I don't think we will get a lot more bang for the buck with slightly better PSA tests."

PSA Clearance test

French researchers presented a poster on a new concept for measuring PSA – PSA Clearance (CL_{PSA}). The idea is to use this to predict biochemical release risk in patients with prostate cancer in the first month following radical prosta-

tectomy. The new measure uses a specialized CL_{PSA} software program commonly used as a tool for measuring PK values to determine CL_{PSA} based on four PSA assays in the first month after surgery. It's kind of an area under the curve analysis. When applied to 67 patients, the researchers found that if a patient's CL_{PSA} is >0.0480, the patient wouldn't relapse.

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