TRENDS-in-MEDICINE

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by Lynne Peterson

SUMMARY

- Aragon's ARN-509 data in CRPC looked good, but it is early data.
- Doctors are assuming that Medivation and Astellas' Xtandi will get FDA approval for pre-chemo CRPC. Xtandi and J&J's Zytiga are viewed as comparable, and doctors do not know how to sequence them either pre- or post-chemo until they get more real-world experience with them. Insurance coverage and copays are a real barrier to use.
- An AFFIRM trial analysis found patients did worse when prednisone was added to either Xtandi or placebo, but doctors believe the prednisone patients were sicker, not that prednisone was a culprit.
- Targeted agents continue to fail in CRPC.
- Active surveillance is continuing to increase (now ~30% of patients overall), and the decline in prostatectomies has not yet bottomed.
- In RCC, Aveo and Astellas' tivozanib met the primary endpoint (PFS) but missed on the secondary endpoint of overall survival. Doctors find credible the company's explanation that this is due to crossover.

Trends-in-Medicine
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2013 GENITOURINARY CANCERS SYMPOSIUM
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Nearly 500 abstracts were presented at the 2013 Genitourinary Cancers Symposium – which is co-sponsored by the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO) – and >2,100 specialists attended.

Genitourinary (GU) cancers include cancers of the prostate, kidney, bladder, testis, penis, ureters, and other urinary organs. This year, more than 388,000 will be diagnosed with a GU cancer, and ~60,000 people will die. The most common GU cancer is prostate, with >238,000 men likely to be diagnosed with it this year and 29,000 dying.

The three studies that ASCO considered the most important at the meeting (which is often referred to as the ASCO-GU meeting) dealt with prostate cancer screening in the elderly, duration of anti-androgen therapy, and surveillance for small kidney tumors – not new drugs in development. However, there were several oral talks and posters on drugs that were newsworthy.

CASTRATION-RESISTANT PROSTATE CANCER (CRPC): ANDROGEN SIGNALING INHIBITORS

"Two steps forward, one step backward," that's how William Oh, MD, chief of hematology/oncology at Mount Sinai School of Medicine, described drug development in CRPC.

Comparison of New Approved Drugs in Metastatic CRPC

Drug	Disease state	Comparator	HR	p-value
Dendreon's Provenge (sipuleucel-T)	Chemo-naïve	Placebo	0.775	0.032
Docetaxel	Chemo-naïve	Mitoxantrone	0.76	0.009
Sanofi's Jevtana (cabazitaxel)	Post-docetaxel	Mitoxantrone	0.70	<0.0001
Johnson & Johnson's Zytiga (abiraterone)	Post-docetaxel	Placebo	0.646	<0.0001
Zytiga	Pre-docetaxel	Placebo	0.75	0.0097
Bayer's Alpharadin (radium-223)	Post-docetaxel	Placebo	0.70	0.002

ARAGON's ARN-509 – promising Phase II results

This investigational, next-generation androgen receptor antagonist is different from bicalutamide (AstraZeneca's Casodex) because it has no agonist properties. The results of

the 30-patient Phase I portion of a Phase I/II trial of ARN-509 in metastatic CRPC were presented at ASCO 2012, showing the drug is safe and well tolerated and decreased PSA levels.

The Phase II portion has three parts: non-metastatic CRPC, metastatic CRPC, and metastatic with progression after Zytiga. At ASCO-GU, Matthew Smith, MD, PhD, director of genito-urinary medical oncology at Massachusetts General Hospital Cancer Center, presented the results of the 47 patients in the Phase II group of men with high-risk non-metastatic CRPC. The patients all received 240 mg of ARN-509 daily for continuous 28 day cycles. The study found:

- 91% of patients had ≥50% PSA reduction at Week 24, the primary endpoint. And 91% had ≥50% PSA reduction at Week 12.
- Progression-free survival (PFS) was 88.7% at 12 months.
- The secondary endpoint of time to PSA progression was reached at a median follow-up of 8.1 months.
- The most common treatment-related adverse events were Grade 1-2: fatigue (40%), diarrhea (34%), nausea (21%), abdominal pain (17%), and rash (11%). The Grade 3 adverse events were fatigue, diarrhea, rash, and decreased appetite – each 2%. There were no seizures, and only two patients discontinued due to adverse events.

Dr. Oh, the discussant, said it is possible that more potent androgen receptor (AR) inhibition will lead to better clinical outcomes, but he noted that this study was in non-metastatic patients, and the dose was higher than the approved dose of Medivation and Astellas' Xtandi (enzalutamide, 240 mg), though it is possible there is less toxicity since no seizures were seen in either Phase I or II. The question, he said, is how clinically meaningful the differences are. His comment, "It's too early, but it could be incrementally better."

Dr. Oh added, "I suggest this probably is a next-generation AR antagonist, possibly leading to fewer seizures…The durability [of the PSA response] is encouraging. The toxicity is also encouraging."

JOHNSON & JOHNSON's Zytiga (abiraterone acetate) – pre-chemo results holding up over time

Dana Rathkopf, MD, a medical oncologist from Memorial Sloan-Kettering Cancer Center, presented the third interim survival analysis of the pivotal Phase III COU-AA-302 trial of abiraterone + prednisone vs. prednisone alone in mCRPC pre-chemotherapy (docetaxel). Study COU-AA-302 was the basis for FDA approval in December 2012 of use in pre-chemo patients.

With 56% of overall survival (OS) events, the data showed that Zytiga continues to demonstrate a significant benefit over prednisone alone in terms of both primary endpoints: PFS and OS. The final analysis of this trial will be after 773 events.

Dr. Rathkopf pointed out that this third interim analysis found:

- Zytiga doubled the time to PFS – a 47% reduction in the risk of disease progression (16.5 months vs. 8.3 months, p<0.0001, HR 0.53), with the benefit favoring Zytiga in all patient subgroups. The PFS findings were "highly consistent" between center and investigator reviews.
- Overall survival was 35.3 months with Zytiga vs. 30.1 months with prednisone alone, a 21% decrease in the risk of death. This difference favored Zytiga (p=0.0151, HR 0.79) but did ***not*** cross the boundary for statistical significance. The Kaplan-Meier curves for overall survival were superimposable out to ~18 months, then separated in favor of Zytiga.
- All clinical endpoints continued to show significant improvement with Zytiga. For instance, with Zytiga, 69% of patients had PSA decline ≥50% vs. 29% of prednisone patients. In addition, time to opiate use or need for chemotherapy were both reduced, and quality of life measures were improved.
- Subsequent therapy was common: 65% of Zytiga patients and 72% of prednisone patients got further therapy.
  - Zytiga patients – 57% got docetaxel (Sanofi's Taxotere), 14% cabazitaxel (Sanofi's Jevtana), 9% ketoconazole, 9% Zytiga, and 8% Provenge (Dendreon, sipuleucel-T).
  - Prednisone patients – 63% got docetaxel, 15% Jevtana, 13% ketoconazole, 16% Zytiga, and 6% Provenge.

Doctors questioned at the meeting about the findings said they were pretty much as expected, not a surprise.

COU-AA-302 Updated Results

Measurement	Zytiga + prednisone vs. prednisone		
	Interim analysis #1 (13% OS events)	Interim analysis #2 (43% OS events)	Interim analysis #3 (56% OS events)
Primary endpoint #1: Overall survival			
Mean follow-up	N/A	22.3 months	27.1 months
Actual events	98	333	434
OS	N/A	Not reached vs. 27.2 months (Nss, p=0.0097, HR 0.75)	35.3 vs. 30.1 months (p=0.0151)
Primary endpoint #2: Progression-free survival			
Actual events (investigator)	435	607	644
PFS	N/A	Not reached vs. 8.3 months (p<0.0001, HR 0.43)	16.5 vs. 8.3 months (p<0.0001)

What is the optimal timing for Zytiga? Dr. Oh, again the discussant, said, "Improvement in PFS appears meaningfully better in the pre-chemo setting. Notably, the overall survival benefit is the same (~5 months) irrespective of chemotherapy. It is likely that the maximal benefit of abiraterone is seen when used prior to chemotherapy…On overall survival, a benefit of ~5 months is okay as long as there is evidence it is of benefit to patients."

G-CSF utilization. A J&J retrospective analysis of 278 post-chemotherapy prostate cancer patients from an insurance claims database found that G-CSF use was more common in patients who received Jevtana than Zytiga (66.5% vs. 2.5% of patients, resulting in a slightly higher cost for Jevtana therapy ($2,814) vs. $2,530.

MEDIVATION and ASTELLAS' Xtandi (enzalutamide, MDV-3100) – questions about the impact of prednisone and positive data in chemo-naïve patients

AFFIRM trial. Four new, post hoc, retrospective analyses of the Phase III AFFIRM trial post-chemotherapy (docetaxel) patients with metastatic CRPC were presented at ASCO-GU. The most important – and the one that got the most attention – was an analysis of on-study corticosteroid (mostly prednisone) use in that trial, which was permitted but not required. In that analysis, baseline corticosteroid use (30% of patients) was associated with ***inferior*** overall survival and more adverse events.

Howard Scher, MD, from Memorial Sloan-Kettering Cancer Center, who presented the results, said other studies have suggested that steroids may stimulate prostate cancer growth by activating promiscuous androgen receptors, stimulating human SGK1 gene expression, promoting expression of IL-6, and activating glucocorticoid receptor signaling. He showed a multivariate analysis that suggested that baseline corticosteroid use is an independent predictor of overall survival, with a hazard ratio of 0.54, even after adjusting for prognostic and other factors.

In that study:

- Even baseline use of steroids was worse for overall survival: 10.8 months vs. 18.3 months for no baseline steroids (p<0.001), HR 0.47). Baseline steroid use was worse in both univariate and multivariate analyses.
- Overall survival was better on plain placebo (18.8 months) than on placebo + prednisone (9.6 months) or on Xtandi + prednisone (12.8 months), but the best OS was Xtandi alone (not yet reached).
- Xtandi use improved overall survival regardless of baseline use of steroids.
- Baseline use of steroids also predicted worse PFS and worse time to PSA progression. It was also associated with more Grade 3-4 adverse events.

At first look, the conclusion might be that prednisone is so detrimental that it shouldn't be used at all in these men, and the results could raise questions about the use of Zytiga since prednisone must be given with that. However, Dr. Scher pointed out that the steroid patients were sicker patients.

That point also was hammered home by the discussant, Dr. Oh, who said the MSKCC nomograms would predict 13-month survival for the patients in this study who were on steroids vs. 17 months for patients in the study on no steroids, so "patients receiving corticosteroids were ***much*** sicker and had more advanced disease…Much sicker patients were on steroids, a surprising high number – 46%…We don't know why patients were on steroids. Are steroids bad or are they used in bad situations?…Steroids are actually good in metastatic CRPC – providing pain relief and PSA declines."

Dr. Oh also reviewed survival in three other Phase III trials that had arms with and without steroids.

- In an EORTC trial in 2001, overall survival was not significantly different with prednisone (10.6 months vs. 11.2 months without, p=0.18).
- In the VITAL-2 trial in 2009, docetaxel + prednisone has significantly *better* survival than docetaxel + Aduro BioTech's GVAX (14.8 months vs. 12.4 months, p=0.02).
- In the ASCENT-2 trial in 2011, docetaxel + prednisone was significantly better than docetaxel + Novacea's DN-101 (high-dose calcitriol) – 20.2 vs. 17.8 months, p<0.002).

Impact of On-Study Corticosteroid Use in Phase III AFFIRM Trial

Measurement	Placebo + steroid	Placebo (no steroid)	Xtandi + steroid	Xtandi (no steroid)
Overall survival	9.6 months	18.8 months	12.8 months	Not yet reached
Radiographic PFS	2.9 months	3.0 months	5.6 months	11.1 months
Time to PSA progression	3.1 months	2.8 months	5.6 months	8.6 months
OS for all patients in trial	13.6 months		18.4 months	
Demographics of steroid patients				
Median PSA	177.1 ng/mL	100.1 ng/mL	168.4 ng/mL	77.3 ng/mL
Visceral liver disease at screening	11.2%	6.4%	16.1%	7.5%
>20 bone mets at screening	46.6%	30.8%	47.0%	29.4%
Grade 3-4 adverse events				
	Steroid use		**No steroid use**	
Any treatment-emergent events	63.3%		34.4%	
Infection/infestation	6.6%		4.2%	
Anemia	12.3%		4.8%	

Dr. Oh concluded: "Prednisone and steroid use is really associated with a bad phenotype for the patient and not necessarily causative. We need a prospective trial to explore this, but I didn't see anything to suggest that prednisone was causing worse survival."

Other experts questioned at the meeting agreed with Dr. Oh:

- "That was a post hoc analysis and meant to say that because abiraterone requires steroids, enzalutamide is better…It is marketing…There are enough other data – like in the placebo arms of the original Taxotere studies – to say steroids do some good…[The Scher study] was an attempt to show that enzalutamide would work whether a patient is on steroids or not…but the implication was steroids are bad."
- "It is an interesting observation, but it was a post hoc analysis, and you have to be careful interpreting those data…Patients on steroids tend to be sicker. While it is provocative data, you can't directly apply it to clinical care."
- "We need more data to decide if that steroid observation is, in fact, valid. There needs to be further analysis."

A second poster looked at outcomes in elderly patients in AFFIRM. It found that Xtandi significantly improved outcomes post-docetaxel in elderly patients (age ≥75) vs. placebo. There was no difference in tolerability between the two age groups.

Overall Survival with Xtandi by Age

Age	Survival	
	Xtandi	Placebo
<75	Not yet reached	13.6 months
Age ≥75	18.2 months	13.3 months

A third poster looked at baseline characteristics and efficacy outcomes in AFFIRM. This post hoc analysis found that patients who were on Xtandi the longest tended to have lower baseline disease burden (e.g., lower Gleason score, less concomitant steroid use).

The fourth poster reported on quality of life results in AFFIRM. In this post hoc analysis, quality of life was significantly better with Xtandi than placebo.

The AFFIRM findings raise the level of interest in the PREVAIL trial of Xtandi in chemotherapy-naïve prostate cancer patients. Interim data in that trial are expected in 2H13. Dr. Scher said the "likelihood is that it will be positive."

Phase II trial in chemotherapy-naïve patients. A poster reported on a 67-patient, European, 25-week, open-label, single-arm study in hormone-naïve prostate cancer (all stages) with non-castrate testosterone levels. The study found:

- The primary endpoint was met, with 93% of men having a PSA reduction ≥80% (the primary endpoint). Four men did not, and were considered non-responders, but the principal investigator Bertrand Tombal, MD, PhD, a Belgian urologist, said three of those have since had a response, so updated data to be presented at ASCO 2013 will have a 99% rate.
- Responses occurred early (by Week 5) and were observed through the end of the study (Week 25).
- The most common adverse events were gynecomastia (36%), fatigue (34%) and hot flush (18%).

Dr. Tombal said, "We did not anticipate the efficacy results. We were quite surprised by the size of the response…Now I feel safe testing this."

What will the design of the Phase III trial be? Dr. Tombal said the LHRH (luteinizing hormone-releasing hormone) drugs never had to show an improvement in overall survival, just a decrease in testosterone, so the design of the Phase III trial needs to be discussed with regulators, "The hurdle is how to get it registered in a reasonable time frame."

Experts who saw the poster agreed that these findings confirmed what they already believed – that Xtandi is as effective as Zytiga pre-chemo and likely to get FDA approval for that indication.

Seizures. Doctors said that so far they have not seen any seizures in Xtandi patients in real-world usage.

Sequencing of CRPC Therapies

Currently, drug regimens are described as pre-chemotherapy or post-chemo, but Oliver Sartor, MD, a medical oncologist from Tulane University School of Medicine, said those distinctions may not be appropriate any longer, "The definition of pre- and post-docetaxel is not biologic in origin. It was a regulatory-related division instead of a biologic division. The question now on everyone's mind is how we redefine therapies in the setting of these highly active drugs. For instance, there are data that suggest docetaxel is not very active post-abiraterone and that cabazitaxel could be different. So, as we go forward, it will be critical to define this. This is something new about which we currently know very little."

Pre-chemotherapy

Generally, doctors asked about choosing among available therapies pre-chemo described it as "six of one, half dozen of another." They don't see big differences between Zytiga and Xtandi, except that Zytiga is approved in that setting, and Xtandi is not, and that Zytiga requires concomitant prednisone. Once Xtandi gets the pre-chemo indication – and every doctor questioned believes it will – the choice will be a toss-up. In the meantime, there is very little off-label use of Xtandi pre-chemo.

Doctors want to get experience with both Zytiga and Xtandi and see how they work in their own hands, but as Dr. Oh put it, "Both abiraterone and enzalutamide are effective."

Most doctors predicted that the uptake of Zytiga – and Xtandi when it gets the indication – will be very quick, with the limiting factor insurance coverage. Dr. Sartor said, "Uptake pre-docetaxel will be very, very fast…But insurance is limiting uptake both pre-chemo and post-chemo. Copays also can be quite substantial, so there are patients who are not getting these drugs because the copays are onerous and unacceptable to patients. The out-of-pocket cost to patients can be $2,000 a month. I have patients paying that. Out-of-pocket expenses are a huge issue, and that is not being adequately addressed. Many insurers are keeping copays that high. I have many patients today who can't get the drugs because the copays are so high."

Provenge, on the other hand, is generating very little excitement, and there wasn't much discussion about it at the meeting. When asked about it, doctors generally said its adoption is better in academic centers than community practices. Edward Messing, MD, a surgeon from the University of Rochester Medical Center and president of the Society of Urologic Oncology (SUO), explained, "Right now, except for abiraterone, there is Provenge, which is a tough drug to give. In a city like Rochester NY, it is difficult because of having to ship off site…I don't do it. It is tough for urologists and radiation oncologists to do in their office because you need infusion capabilities. The average urologist doesn't have that facility. The large urology groups are 12%-13% of all urologists. For the remaining 80%, that is a treatment which is very, very tough to do.

Comments on sequencing pre-chemo included:

- *Dr. Messing:* "For metastatic prostate cancer, the standard treatments are LHRH agonists, and most of us [urologists] would be willing to play around with 1-2 rounds of hormonal therapy. After that, we refer to medical oncologists. So, abiraterone and enzalutamide will be in our hands as well as medical oncologists, and they will move up…LHRH will still be first, and then these will be second line. I won't do a second anti-androgen after one anti-androgen or ketoconazole. You won't do those games any more."
- *Leonard Gomella, MD, chairman of the department of urology at Jefferson Medical College:* "As time goes on and as experience grows with both…clinicians will decide…They will have to build experience with the drugs…Figuring out sequencing will consume us in CRPC for the next 3-5 years. The only thing generally being accepted in the world of sequencing is if you are going to use immunotherapy – like Provenge – it should be one of the earlier agents. Using it later probably won't offer the same benefit. But sequencing enzalutamide, abiraterone, cabazitaxel, and alpharadin will consume everyone for the next 3-5 years and will become a more and more difficult question to answer. As more options become available, tracking survival in the absence of clinical trials will be difficult."
- *Dr. Sartor:* "Either hormonal therapy will be an option… Some patients who can't get prednisone or don't want it – and I do have a little more concern using prednisone long-term in asymptomatic patients because of the increased risk of diabetes, osteoporosis, myopathy, etc. – will get enzalutamide. And there are certain patients with a questionable history of seizures, where you want to avoid enzalutamide and use abiraterone. But I think that patients who are asymptomatic and on long-term treatment may benefit from a non-steroidal regimen."
- *Dr. Scher:* "Pre-docetaxel I generally use enzalutamide because I don't do prednisone early, but abiraterone works. It is something you need to discuss with patients…There are some patients where enzalutamide works, and some where abiraterone works."
- *John Araujo, MD, PhD, a genitourinary oncologist from MD Anderson Cancer Center:* "I use abiraterone because enzalutamide is not approved for pre-docetaxel use, but the choice is insurance driven, and it is hard to get either covered."
- *Virginia:* "To me it is a question of why I would use a drug with steroids when I don't have to."
- *Michigan:* "The pre-docetaxel choice will be insurance-driven…When to use enzalutamide is not clear, but if you want to eliminate prednisone, then go with enzalutamide."
- *Belgium:* "The prednisone with abiraterone is a problem. Enzalutamide is better. In the European Union, the problem is reimbursement."
- *Germany:* "I mostly use abiraterone now, but if AFFIRM is true, I'll switch to enzalutamide. I'll talk with my colleagues when I get home."

Could the choice of anti-androgen be left to the patient much the way patients choose multiple sclerosis drugs or anti-TNF inhibitors for rheumatoid arthritis? Dr. Gomella said that is possible. He said doctors could outline the various possible drugs to patients and let them make informed decisions, "That certainly might happen in prostate cancer, but doctors have a lot of influence and say based on their comfort level."

How will doctors choose between Zytiga and Xtandi when both are approved in the pre-chemo setting? Dr. Messing said, "It is hard in the absence of comparative data to figure it out. Urologists will be more comfortable with enzalutamide because it doesn't require a steroid. To an internal medicine doctor, giving 5-10 mg of prednisone is nothing, but urologists don't give it at all. They worry about ulcers, suppression, and all the other things that are probably irrelevant at that dose…That is a hurdle that will make enzalutamide more attractive. The thing that makes enzalutamide a little less attractive and needs to be considered is, if used very early, it has the risk of gynecomastia, so it requires breast irradiation first…which is easy, but not cheap …but not scary."

How quickly will Zytiga and Xtandi be adopted in the pre-chemo setting? Dr. Messing said, "I think it will be very rapid. Once both are approved, almost everyone will go on one of these after an LHRH – unless insurance companies won't pay for it." Hong Zhang, MD, PhD, a radiation oncologist from the University of Rochester Medical Center, added, "The adoption is happening right now."

What about the cost of moving Zytiga and Xtandi into this setting? Dr. Messing said, "Of course, it is expensive…to society…The question is do they have a bigger bang when moved forward. At the end of the road, they have a three-month overall survival advantage, which sounds pretty trivial…but if they give a man nine months of a completely normal state before chemotherapy, that may be different. It depends on what their bang is for that."

Why choose Zytiga or Xtandi instead of Casodex? Dr. Messing said, "You know in salvage with Casodex, you get 2-3 months of PSA benefit and very little else. If Zytiga demonstrates a 9-month benefit, that is three times as long. In someone with metastases, it would be hard to deny abiraterone."

Post-chemotherapy

Doctors said that post-chemo is mostly Zytiga, with the balance split between Xtandi and Jevtana. Xtandi is really just getting going in this indication.

A U.S. Oncology study, sponsored by Sanofi, but conducted by Ian Schnadig, MD, an Oregon medical oncologist and GU chair of the Pathways Task Force, Pharmacy and Therapeutics Committee at McKesson Specialty Health, looked at usage patterns in first-, second-, and third-line treatments. The preliminary data from the study found that over one year:

- 80% of patients went on to second-line therapy, but only 20% got a third-line drug.
- Second line, 48% of patients got abiraterone second line, 31% cabazitaxel.
- Third-line patients, 7% had docetaxel-abiraterone-cabazitaxel (DAC) in that order, and 14% had docetaxel-cabazitaxel-abiraterone (DCA), in that order.

Dr. Schnadig said the preliminary data suggest that for second-line patients DA is superior, and for third-line patients DCA is superior.

Asked what he, himself, does post-docetaxel, Dr. Schnadig said, "I generally use abiraterone first because of my comfort level and familiarity with it. I've used enzalutamide a handful of times so far – when abiraterone was given pre-docetaxel."

Pre-emptive radiation. Dr. Zhang and Dr. Messing urged more consideration of radiation of oligometastases. Dr. Messing explained, "Metastases in prostate cancer and breast cancer, in the majority of cases, wind up in the same sites. So, if you saw someone with one or two mets, you possibly could go ahead and not only treat those sites but treat other areas likely to be the next sites – oligometastatic therapy. That might offer some patients long-term remission or potentially a cure." Dr. Zhang added, "It is a pre-emptive strike, and you may buy quality of life."

Duration of Anti-Androgen Therapy

An 18-month course of androgen blockade may be enough. That was the finding from a study presented by Abdenour Nabid, MD, a Canadian radiation oncologist. However, the study was not definitive.

Dr. Nabid led a 630-patient Phase III study comparing anti-androgen therapy for 18 months vs. 36 months in high-risk prostate cancer patients undergoing radiotherapy. With a mean follow-up of 77 months, he found that anti-androgen therapy can safely be reduced from 36 to 18 months, and 18 months of anti-androgen therapy could represent a threshold effect with no further benefit.

Reducing the duration of anti-androgen therapy is important because of the side effects of hormone blockade, which include loss of libido, hot flashes, decline in intellectual capacity,

fatigue, decrease in muscular strength, increase in abdominal fat, osteoporosis, and more.

Bruce Roth, MD, a medical oncologist from Washington University School of Medicine, said the ideal duration of anti-androgen therapy has been a question, "In early trials, it was given for three years, and then trials were done with two years. Can we get by with less than 18 months?…We can't tell if 12 months is inferior to 18 months…but at least this is a reduction…***This may change standard of care***."

Asked if he would recommend stopping anti-androgen therapy in men who are currently on it and have been on it at least 18 months, Dr. Nabid said, "I think it is possible. My hope is that the duration of 18 months becomes standard…But right now, if you go by the guidelines…before these data are published…probably you can reduce it to 24 months."

Asked if he is comfortable enough with these data to change his practice, Dr. Roth said, "I would be willing to do that…I personally would feel comfortable…It is a question of how best to treat high-risk disease. The vast majority of large tumors (T3-4) are treated with radiotherapy and anti-androgen therapy vs. surgery…On the other hand, among men with a high Gleason or high PSA, there are a significant number of those undergoing prostatectomy, whether that's right or wrong. It is less likely a urologist will say no surgery for a patient with a component of a high Gleason or elevated PSA or a large tumor…Thousands of patients would potentially have high-risk disease…These are the people with the highest rapid progression." Dr. Messing added, "About 16%-17% are Gleason ≥8. That is a PSA-driven diagnosis. The majority of those people are elderly…so a substantial proportion of T1c disease represents the majority of prostate cancer currently diagnosed in the U.S. Fifteen percent of those are going to be high-risk disease, and a much larger number of those are elderly than younger. So, you are left with a substantial number managed with radiotherapy and anti-androgen therapy. If 250,000 are diagnosed with prostate cancer, and 16% are T1c, then up to 10,000-15,000 men are in this high-risk category of T1c, and most of those will be managed by hormones and radiation."

Anthony D'Amico, MD, PhD, a radiation oncologist from Harvard Medical School, discussed this study, emphasizing that non-inferiority does not mean equivalence. He pointed out that Dr. Nabid's study was designed as a superiority study, but the wide confidence intervals make the results less clear, "What we can say rigorously now is that 36 months is not superior to 18 months, but 18 months ***may*** be inferior to 36 months…For high-risk prostate cancer patients 36 months is too much, 6 months is too little, but 18 months of therapy may be just right – but the word is ***may***."

CASTRATION-RESISTANT PROSTATE CANCER (CRPC): INVESTIGATIONAL THERAPIES

ACTIVE BIOTECH and IPSEN's tasquinimod – development continues

There were no data on this quinoline-3-carboxamide linomide analog at ASCO-GU. However, Nicholas Vogelzang, MD, chair and medical director of the Developmental Therapeutics Committee of US Oncology Research, said, "It is a different mechanism of action, so there could be a role for it because it is throwing a curve ball at the cancer…It should be combinable with androgen-receptor antagonists…But cost will be the rate limiting issue. That's why I prefer sequential therapy."

AMGEN's AMG-208 – interesting early activity

The results of a first-in-man study in solid tumors were presented in a poster on this oral MET inhibitor. The maximum tolerated dose was 400 mg. The most common toxicities were nausea and hypertension. The researchers concluded that it has "broad anti-tumor activity," especially in the 10 prostate cancer patients. Among those prostate cancer patients, there was 1 CR and 2 PRs by local read, but no PRs by central read. The poster included pictures of scans of a prostate cancer patient whose spinal mets disappeared on AMG-208. However, activity did not correlated with MET testing.

BAYER's Alpharadin (radium-223) – don't rule this out

Doctors at ASCO-GU insisted this alpha-emitting radiopharmaceutical will have a role in post-chemo CRPC despite the issues with previous radiopharmaceuticals. They said use may be restricted to certain centers, but they also said it ***will*** be used. Dr. Gomella said, "The big challenge with it is probably at the local level in the number of centers able to offer it to their patients because there are NRC-related [Nuclear Regulatory Commission-related] issues since the drug is manufactured outside the U.S…That will be one of the initial challenges – the distribution network – but I think it will be used. Physicians have to understand we have a certain track record with radiopharmaceuticals that urologists or oncology-related specialists may feel are substandard…Alpharadin is completely different and has a completely different toxicity profile. So, it has to be an educational effort."

Dr. Sartor said, "It is highly active, with minimal toxicity. It is incredibly well tolerated. There will be challenges in the

uptake of a radiopharmaceutical given that prior radiopharmaceuticals have not been a success…but given the activity and the minimal toxicity, I think this will be a popular drug and one that patients will ***demand***. It has expanded access, and I get patients from all over the country – ***physician*** patients – who come to my center for treatment with it. I honestly believe this is a drug that will succeed because of its merits. Every radiopharmaceutical in the past had insurmountable barriers, but I believe the barriers in this case will be surmountable."

A poster was presented at the meeting with an updated analysis of the effect on pain in the Phase III ALSYMPCA trial in CRPC patients with bone metastases. In the study, Alpharadin prolonged median time to external beam radiotherapy (EBRT), significantly prolonged median time to initial opioid use (38% risk reduction vs. placebo).

CASTRATION-RESISTANT PROSTATE CANCER (CRPC): TARGETED THERAPIES

The message about targeted therapies was: they don't work in CRPC. One after another they have failed.

What do these failures mean for other investigational therapies? Dr. Oh, the discussant, said there has been "compelling" preclinical data in prostate cancer for a VEGF role, but mice do not have predictability in sepsis and perhaps they don't in CRPC as well. He noted that the Phase III VEGF trials have repeatedly shown no advantage on survival and greater toxicity, speculating that this could be because the disease is too advanced, VEGF is the wrong target, there is a poor therapeutic index, or multiple growth pathways may be involved.

Yet, Dr. Oh held out some hope for a combination of MET inhibition and VEGF inhibition. He said the COMET-1 trial in metastatic CRPC of prednisone vs. Exelixis' Cometriq (cabozantinib, XL-184), a tyrosine kinase inhibitor (TKI) approved to treat medullary thyroid cancer, may help answer that question.

Phase III Targeted Therapy Trials in Prostate Cancer

Drug	Target	Overall survival	PFS	Toxicity
Roche/Genentech's Avastin (bevacizumab)	Anti-VEGF antibody	No difference	Better	Worse
Pfizer's Sutent (sunitinib)	VEGFR TKI	No difference	Better	Worse
Celgene's Revlimid (lenalidomide)	PDGF	Worse	Worse	Worse
Sanofi and Regeneron's Zaltrap (ziv-aflibercept)	VEGF Trap	No difference	No difference	Worse

The latest targeted therapy failures were:

- **Bristol-Myers Squibb's Sprycel (dasatinib).** Dr. Araujo reported on a study of docetaxel ± Sprycel in metastatic CRPC, "The overall survival curves were virtually identical. Dasatinib did not improve overall survival (21.2 months vs. 21.5 months). There was no advantage in any subgroup analysis, and there were no meaningful changes between the two arms on secondary endpoints, except time to first skeletal-related event [SRE], which was 31.1 months with placebo and not reached with dasatinib…This is being investigated."

  Dr. Araujo added, "We need to understand something more before we add these drugs to docetaxel. I worry that we are missing something. Maybe persistent AR signaling is the resistance mechanism, so targeted therapies don't work in CRPC."

  Dr. Oh said the apparent benefit of Sprycel on SREs may be due to differences in bisphosphonate use in the two arms.

- **Sanofi and Regeneron's Zaltrap (ziv-aflibercept).** Ian Tannock, MD, PhD, a medical oncologist from Canada, reported on the results of the Phase III VENICE trial of docetaxel/prednisone ± ziv-aflibercept for first-line treatment of metastatic CRPC. Again, there was no difference in overall survival, "The survival curves were basically superimposable." He said the quality of life data will be presented at ASCO in June 2013, but the adverse events were higher with Zaltrap, and fatal adverse events were higher (5.6% vs. 3.3%). His conclusion: VENICE is yet another negative trial where a targeted agent has been added to docetaxel + prednisone.

  A doctor in the audience commented, "I find those fatalities shocking. How did that happen?" Dr. Tannock answered, "We are looking into that…Apart from the fact that most of those people died from infection, I can't say much about it."

- **Astellas/OSI Pharmaceuticals' linsitinib (OSI-906).** Cleveland Clinic researchers reported on a Phase II trial of this IGF-1R inhibitor that also failed. The drug was safe, but PSA decreases were "modest" and transient.

Targeted therapy with results still pending

- **OncoGenex Pharmaceuticals' OGX-427.** There was no discussion of this heat shock protein inhibitor at ASCO-GU, but, given the history of targeted agents, doctors questioned about OGX-427 were not too optimistic about it. The investigator-initiated Phase II PACIFIC trial of OGX-427 in combination with Zytiga and prednisone in

metastatic CRPC has just started enrolling patients. The primary endpoint is PFS at 60 days.

Another investigator-sponsored Phase II trial is looking at OGX-427 + prednisone in CRPC. The primary endpoint is disease progression at Week 12 post study treatment. Preliminary data from this study were presented at ASCO-GU 2012.

Two Phase II trials and a Phase I trial are also underway in bladder cancer: BOREALIS-1, BOREALIS-2, and OGX-427-BL-01.

PROSTATE CANCER: SCREENING

A study found that older men and black men are more likely to have intermediate-risk or high-risk prostate cancer than low-risk younger men or white men, suggesting that screening may be more valuable than previously thought in these patients. The study also suggested that a life expectancy ≥10 years might be a better criteria for screening than age <75.

Dr. Zhang, a radiation oncologist, reported on this population-based study – using the SEER database from 2004-2008 of 70,345 men with Stage T1cN0M0 prostate cancer (which is prostate cancer diagnosed by needle biopsy due to elevated PSA but no other clinical signs of disease).

Dr. Roth said, "We hear recommendations all over the map for PSA screening – everything from the American Cancer Society's old position of everyone over age 50 to the U.S. Preventive Services Task Force's [USPSTF's] recommendation that no one should be screened. It is not that simple, and that answer is somewhere in between. This gives us information on older patients, that the concept that older patients (over age 75) would all have indolent prostate cancer and may die of something else may not be true…So, numeric age is probably not a good determinant of who should and should not get PSA screening…Maybe numeric age is not the best way to determine who should and should not get screened. Maybe life expectancy is. A 10-year life expectancy might warrant a discussion with the patient of whether PSA screening should be done."

Study of Men with T1cN0M0 Prostate Cancer

Measurement	Low-risk	Intermediate-risk	High-risk
Definition	PSA <10 Gleason ≤6	PSA 10-20 Gleason 7	PSA >20 Gleason ≥8
Historic 10-year survival	91%	84%	80%
Diagnosis in this cohort	47.6%	35.9%	16.5%
Median age	67	70	72
Black	13.1%	16.3%	17.7%
Odds ratio for older vs. younger man (age ≥75 vs. <50)	---	4.47	9.39
Odds ratio for black vs. white men	---	1.50	1.84

PROSTATE CANCER TREATMENT: PROSTATECTOMY VS. RADIATION VS. ACTIVE SURVEILLANCE

Has there been a change in patients presenting with early, low grade prostate cancer due to changes in PSA screening?

- Dr. Roth said he doesn't think the new guidelines on prostate screening have been out long enough to have much impact yet, "We know fewer are screened, but how that affects the makeup of the patients presenting is too early to see. We are all seeing a decrease in the percent of people screened, but what that translates to, I don't think we know."
- Dr. Messing also thinks it is too early to know the entire impact, "It is too soon to say…but I certainly believe there are fewer patients being referred because of elevated PSA because fewer people are being tested…There is absolutely no doubt most urologists are seeing fewer patients because of an elevated PSA, so there are fewer referrals because the original PSA is done by the primary care doctor. The reason it takes time to see the effect [of reduced screening] is that a lot of people were already in the hands of the urologists. Primary care doctors are ordering PSA less commonly, but they are still ordering them…and I am a believer that the PSA test has a place."
- Dr. Gomella said he is already seeing an impact, "I have men who come in with clear prostate cancer and high PSAs who are refusing to be diagnosed because they read an article that said it doesn't matter. So, patients I know in my heart are in trouble or will get in trouble have this message that PSA is not a good test, that PSA is a bad test…There is no question there are fewer referrals. Our colleagues not only at Kimmel Cancer Center, but in the U.S. are seeing a 25% reduction in referrals for either elevated PSA or newly diagnosed prostate cancer. It is conflicted right now because the American Cancer Society guidelines, which were recently revised, continue to recommend screening with an educated patient. In fact, the fine print of the USPSTF is a little contradictory because after giving the big message about not screening, they default to the bottom line that you should give patients the option if they are informed…So it is a little bit of a schizophrenic message. But we are seeing a lot of primary care doctors backing away from screening, and we are seeing a drop in patients coming in around the country."

What percent of patients opt for active surveillance, for prostatectomy, or for radiation today?

- Dr. Roth, a medical oncologist, said it depends a lot on the patient's age, comorbidities, and even distance from the doctor, "Some patients live 70 miles away from radiotherapy and can't come five days a week for 7.5 weeks…There are people who mentally want it [the cancer] out…It is really very individual…And it depends on who presents the choices to the patient. If the urologist does the biopsy…it is likely that surgery will be at the top of the list…There are more people opting for active surveillance, and it has become more widely accepted…I think it is more prevalent for someone to choose that approach and for urologists to offer it than 10 years ago."
- Dr. Messing, a urologist, said, "It depends on the patient's age, but the choice is changing rapidly…My guess is that nowadays roughly half of patients with low-risk prostate cancer, which is <50% of men diagnosed, are being offered and encouraged to do active surveillance…and I think they are doing it…In my group it is clearly true. So, one-quarter of all men with prostate cancer are undergoing active surveillance. There was a big rise in prostatectomies when robotic surgery came in, and that is still the major treatment for men under age 70…Only ~25% of men <70 are getting radiation, but after age 75, almost everyone gets radiation [if not active surveillance]."
- Dr. Zhang, a radiation oncologist, agreed, saying, "In the SEER database for 2004-2008, 25%-30% of men diagnosed with T1c prostate cancer were not being treated [were getting active surveillance]."
- Dr. Gomella estimated that about one-third of men are choosing surgery, one-third radiation, and one-third active surveillance, adding, "But the trend is for more active surveillance."
- A Canadian radiation oncologist estimated that 25% of Canadian patients and 35% of U.S. patients get active surveillance; 45% of both U.S. and Canadian patients get radiation; and the rest get surgery.

Experts said that an increase in active surveillance (the preferred term but sometimes referred to as watchful waiting) more than a drop in prostate cancer screening is decreasing the number of prostatectomies performed each year. And experts don't think the decline in prostatectomies has bottomed yet because active surveillance is continuing to increase.

- SUO president Dr. Messing said, "Prostatectomies at our institution are down 20% from two years ago, and I think it is still declining."
- Dr. Zhang agreed, "I think it will continue to decline."
- Dr. Gomella said, "I don't think we have bottomed on that…Active surveillance is coming out of both radiation and surgery…My gut feeling is it is a little more out of radiation because those are the patients who probably are a little older and more candidates for radiation."

Have the data that outcomes are worse with the robot caused any pullback in use of or enthusiasm for robotic prostatectomies [with Intuitive Surgical's da Vinci]? Dr. Messing said he doesn't do robotic prostatectomies but four members of his department do use da Vinci, "The chief advantage of the robot is that it is less of a whack…Patients feel more comfortable after, and there is no question when my [open prostatectomy] patient is in the same room with a patient undergoing a robotic procedure that there is a difference in the patients…so that attraction exists. All the robot has to be is approximately equal in outcomes to be better." Dr. Gomella added, "The penetration of the robot is such that it is unlikely to change a huge amount."

How are these trends likely to change over the next couple of years? Dr. Messing said, "I believe the vast majority of low-grade disease receives no treatment, and one-third get delayed treatment for disease progression or because they or their wives can't stomach no treatment, which is not a small issue. In terms of surgery vs. radiation, for younger men surgery is still the majority, and for older men, radiation is the majority. I don't think this will change a great deal." Dr. Gomella is worried, "There are some sobering observations made by epidemiologists…who predict that if current changes in screening for prostate cancer continue to decline, by 2021 or so we will probably return to the 1994 levels of death from prostate cancer. So, we are probably going to go backwards." A Canadian doctor said active surveillance is likely to continue to increase, reducing both radiation and surgery equally.

RENAL CELL CARCINOMA (RCC)

A retrospective cohort study looked at real-world patterns in third-line treatment of metastatic RCC in the U.S. The researchers, led by Sumanta Kumar Pal, MD, a medical oncologist from City of Hope Comprehensive Cancer Center, used a claims database of 812 RCC patients and found that the "therapeutic scenario for metastatic RCC is rapidly changing in the U.S."

- The most common first-line agent was Sutent (52%), and the most common second-line agents were Pfizer's Torisel (temsirolimus) and Novartis' Afinitor (everolimus).
- The most common third-line choice was Torisel in 2007 but Afinitor and GlaxoSmithKline's Votrient (pazopanib) in 2009.

- The results are in line with the National Comprehensive Cancer Network (NCCN) guidelines, with VEGF and mTOR being the most common prescribed first- and second-line agents, respectively.

Another poster reported on the results of a large, retrospective chart review, looking at outcomes of second targeted therapy for metastatic RCC. Eric Jonasch, MD, a genitourinary oncologist from MD Anderson Cancer Center, and colleagues found that ~25% of patients had dose adjustments on their second targeted therapy, most commonly because of drug toxicity. They also found that treatment duration, PFS, and overall survival in community practice were longer than seen in pivotal trials, which may be due to different patient populations, change in monitoring, and definitions of progression.

Surveillance beats surgery for small kidney tumors

William Huang, MD, a urologic oncologist from New York University Langone Medical Center, reported on a retrospective cohort study of 7,418 kidney cancer patients with small (<4 cm) tumors from 17 cancer registries, 78% of whom got surgery (either partial or radical nephrectomy) and 22% got only surveillance. Over 10 years, only 3% of patients in either group died of kidney cancer, and there was no difference whether they got surgery or not.

However, surveillance was associated with a significantly lower risk of cardiovascular events and a significantly lower risk of all-cause death. Dr. Huang concluded that surveillance did not increase the risk of dying of kidney cancer, and surgery increased the risk of CV complications and poorer overall survival, making surveillance a reasonable option for patients, especially those who are older or have considerable comorbid conditions.

Dr. Roth commented, "The majority of these [smaller] lesions are asymptomatic and found incidentally…When these patients get referred to urology, there is a question on how to approach these small cancers…Despite the fact that these days the majority of these can be done with partial nephrectomy and laparascopically, you are still taking tissue out…This shows not intervening not only won't have a negative impact, but it may be a negative impact to do surgery on these patients because they will have an increased risk of CV events and maybe CV mortality."

How common are these small kidney tumors? Dr. Huang said the overwhelming majority – at least 2/3 – are still treated with surgery, and surgery is standard of care for small renal masses.

AVEO and ASTELLAS' Tivopath (tivozanib)

A few days before ASCO-GU, the companies announced the results from the Phase III TIVO-1 trial in patients with advanced renal cell carcinoma (RCC), but the survival results were formally presented at the meeting in four separate posters. It had previously been reported that the trial met the primary endpoint, showing significantly better PFS than Bayer's Nexavar (sorafenib). The key results at ASCO-GU were:

- Tivozanib failed to show any significant benefit on overall survival, a secondary endpoint. In fact, overall survival was actually numerically (but not significantly) shorter with tivozanib – 28.8 months vs. 29.3 months. The company claimed that "differential use of second-line therapy" confounded the survival results because crossover was allowed.
- More Nexavar patients got second-line anti-VEGF therapy than tivozanib patients (70% vs. 10%). In fact, 156 of 158 control patients eventually got tivozanib, so crossover was very high.
- Most of the patients in the trial were enrolled in eastern and central Europe.
- More tivozanib patients remained progression-free and on randomized therapy than control patients (27% vs. 12%).

Survival. *Is that explanation for the failure on overall survival credible?* Most, but not all, doctors at the meeting said yes. A Texas doctor said, "When you don't see an overall survival benefit, it puts a damper on it. At the end of the day, you want to see an improvement in survival. I don't think the explanation is credible; there are too many confounders."

Dr. Vogelzang said, "I think the crossover explanation is credible…The issue for the FDA is the overall survival looks different, even if it is non-significant…This looks at least as good as sunitinib and pazopanib…The issue is there were so few U.S. patients. Overall survival could actually be worse with a hazard ratio of 1.25. It looks different, but it is probably not, but it looks like the lines [Kaplan-Meier curves] separate. You could argue two things: (1) that tivozanib is very powerful, and second treatments have become less important when first-line drugs are highly effective, or (2) that tivozanib is toxic, and patients didn't want that drug class again."

The principal investigator, Robert Motzer, MD, an oncologist from Memorial Sloan-Kettering Cancer Center, said, "The slightly longer median overall survival for sorafenib is intriguing…In the trial design, when patients were randomized to sorafenib and progressed, they were offered tivozanib. We did

this for the benefit of the patients…Many of the patients randomized to tivozanib, when they progressed, didn't get any other targeted therapy where there was no targeted therapy available [e.g., eastern Europe]. The sorafenib patients had a higher number of treatments – most had two or more – whereas most tivozanib patients had only one drug."

Dr. Motzer added, "The take-away is that sequenced therapy is better. Access to more drugs is better for patients. The more drugs patients have access to, the better. And survival is better with these targeted therapies. Before targeted drugs, survival was ~1 year, and with targeted drugs, it is being pushed out to 29 months…I don't put much stock in exploratory post hoc analyses…but the average overall survival was ~1 year before these drugs, and now it is >28 months, which shows progress …The overall survival comparison is not what doctors focus on. If anything, they focus on median PFS. They shouldn't do cross trial comparisons of that, but they do."

Subgroup analysis. In the 16 subgroup analyses reported, PFS was clearly better with tivozanib in three pre-specified subgroups: patients from North America/western Europe, patients with an ECOG score 0, and patients with no prior systemic therapy. The exploratory subgroups that favored tivozanib included patients with favorable MSKCC prognostic factors, patients with ≥2 organs involved.

On the pre-specified subgroup of North American patients, Dr. Motzer cautioned that the numbers were small. Dr. Vogelzang agreed, adding, "The confidence intervals were too wide to make much of this."

Patients who developed hypertension, another exploratory subgroup, had significantly longer PFS than patients who did not develop elevated blood pressure.

Quality of life. Quality of life was not worse with tivozanib than Nexavar, but it wasn't significantly better either.

Biomarker analysis. A pre-specified biomarker analysis *suggested* that a 9-gene signature representing hypoxia deregulation might predict non-responder, but the data are very preliminary. Murray Robinson, PhD, senior vice president for translational medicine at Aveo, also said the study provided more insight into the patients who do not respond to tivozanib. He explained that 15% of clear cell RCC is a different tumor molecularly, and his studies found, "The reason VEGF inhibitors work so well in RCC is that most clear cell cancer has a particular deletion/mutation, and the 15% who don't have the mutation don't respond to tivozanib." However, those patients generally do respond to Nexavar.

QT prolongation. Last year at ASCO-GU, the company presented a poster on the results of an open-label, non-randomized, single-arm, 50-patient QT study of tivozanib 1.5 mg/day in patients with advanced solid tumors. On the primary endpoint of change from baseline in QT interval corrected for heart rate (QTcF), the maximum mean change was +9.3 ms at 2.5 hours after dosing on Day 21. On average for all post-dose time points, QTcF was +2.2, and QT was 5.6 ms. The graphs over time indicated that QT clearly increases when the drug is administered, the rate comes down before re-administration, then increases again, though the increases are relatively small. The company's chief medical officer said that the increase appears to plateau by Day 21, when the drug is at steady state.

That study raised a number of questions (See ASCO-GU 2012 report) than it answered, so it seemed logical to look for more QT data at this year's meeting. There wasn't any. Asked about QT prolongation, Dr. Motzer said, "I personally don't think it is an issue…We did EKGs and studied the patients well. I am not aware of any QT issue with this trial." Aveo's Dr. Robinson said, "There is no QT issue with tivozanib…The FDA is very comfortable with the hypertension management we put in place."

Usage. *How would tivozanib be used if it were FDA approved?*

- *Dr. Motzer:* "I would give patients the option of sunitinib, pazopanib, or tivozanib. Pazopanib is my recommendation now…In the U.S., doctors don't have a lot of hands-on experience with tivozanib yet, but as they got more hands-on use with it – and if the safety profile holds up – use will increase…In an era of comparable efficacy and overall survival, safety is becoming a big factor…The choice will be between pazopanib and tivozanib, and we need more experience to choose one over the other, but it ***seems*** that tivozanib has the best safety."
- *Another doctor (not involved in the trials):* "We use temsirolimus in poor risk RCC patients. If patients don't look like they will tolerate treatment well, we go to pazopanib because it is the best tolerated. Then, we go to sunitinib. There are no data for what we do, but it is our approach…I really don't think we know yet if tivozanib is more tolerable than pazopanib. We need to try it in the real world first to know."
- *Dr. Vogelzang:* "In my experience, tivozanib is a very tolerable drug, very easy to give. Although there is hypertension and an increase in red blood cells, it is pretty impressive. You really do block VEGF…This looks at least as good as sunitinib and pazopanib. It is attractive because you might not have to immediately switch to a second-line treatment, so you could coast a while…My sense is these [tivozanib,

sunitinib, and pazopanib] are all the same. Tivozanib is a very easy drug, but so is pazopanib – and so is sunitinib when given on a 2-week on/1 week off schedule…Doctors are slow to change, but they may change faster to a 2/1 sunitinib schedule…My take-home is that sunitinib will be very hard to displace. Pazopanib use will increase now that the COMPARZ trial is done…Pazopanib, sunitinib, and tivozanib are not distinguishable on efficacy."

- *Ronald Bukowski, MD, an oncologist from the Cleveland Clinic:* "The choice will depend on the adverse events. Doctors will stay with what they are comfortable with unless there is a clear difference…Community doctors will stick with what they are used to…If efficacy is similar, then tolerance is the issue. Pazopanib is a little earlier than the old sunitinib schedule." However, he agreed that many doctors are already switching to a 2/1 schedule for sunitinib.

Tivozanib was submitted to the FDA, which accepted the NDA, and the PDUFA date is July 28, 2013.

mTOR inhibitor safety

A meta-analysis of eight oncology trials with a total of 2,990 patients, led by Toni Choueiri, MD, a medical oncologist from Dana-Farber Cancer Institute, found that treatment-related fatalities occurred more than twice as often in patients treated with mTOR inhibitors approved for use in RCC vs. control – 3.1% overall with Afinitor and Torisel vs. 1.2% for the controls. That's a relative risk of 2.33 for mTOR inhibitors vs. controls (p=0.003). There was no significant difference between Afinitor and Torisel.

However, Dr. Choueiri emphasized that "both study drugs, everolimus and temsirolimus, benefit the overall patient population with their approved indications, including renal cell carcinoma…[But] the risks associated with these drugs may be greater once they are introduced [more widely] to the real-world oncology population."

Seattle Genetics' SGN-75

A poster presented the results from a 58-patient Phase I trial of this antibody-drug conjugate (anti-CD70) in metastatic RCC. The study established the half-life (6-11 days) and the maximum tolerated dose (3 mg/kg Q3W), but the efficacy signal was weak – 2 PRs, no CRs, 12 stable disease.

The surprise was a significant rate of ocular adverse events: 66% all grades, 28% Grade ≥3. The events were mostly dry eye, corneal epithelium defect, and blurry vision. The researchers said these side effects "appeared reversible to Grade 1 or baseline," but it is an odd cluster of events.

Genomic Testing

The three main genomic tests available for prostate cancer patients are finding limited use, at least so far. One of the key barriers is lack of good reimbursement. Test company sales reps said that lack of clear Medicare coverage limits use. If there were a Medicare code, they predicted that it would make a "huge" difference and boost use, though admitting that it is "still difficult to change doctors' practices." One pointed out that insurance carriers are "very interested" if the test can save them money on other procedures and tests.

- **Genomic Health.** The company was scheduled to present data on the validation of its biopsy-based genomic prostate score (GPS) as a predictor to improve prostate cancer patient selection for active surveillance – and the study was even highlighted in the press materials for the meeting, but the company withdrew the poster, ostensibly to present it instead at the American Urological Association meeting in San Diego in May 2013. Genomic Health did not even have a booth at the ASCO-GU meeting.
- **MDxHealth.** The company's ConfirmMDx test was launched in May 2012, and the company has tripled its sales force to market it. And that marketing is focused on men with negative prostate cancer biopsies as a test to help avoid a repeat biopsy. A sales rep said 43% of men who get one biopsy have a repeat biopsy in 12-18 months. He also said that in January 2013 Medicare issued a new miscellaneous code that covers this test, which costs $2,000-$2,400. So far, most orders for this test have been coming from urologists, and the company reportedly has ~200 customers who have ordered the test.
- **Myriad Genetics.** The company's Polaris test, which is used for men with positive prostate cancer biopsies, is being ordered by pathologists, radiation oncologists, and urologists, but a sales rep said who orders it varies by geography. For this ~$3,400 test, the company bills Medicare, so the doctor doesn't have to do that. There is no Medicare code for this yet.

Dr. Gomella, a urologist, said, "The Genomic Health test is the most applicable because it looks at progression. The others tend to look at the development of metastases and spectrums farther down the line…The MDx test is practical. We know everyone needs a second biopsy on active surveillance after the first biopsy. The question is if they need a third or fourth biopsy. But I don't order it. We have significant challenges in the practical world in getting the tests paid for and the copays covered. The manufacturers really have to help with that."

However, doctors weren't sure that clear Medicare coverage would lead to a sudden surge in use. Dr. Gomella said, "We would begin to use them selectively in certain settings…That is not a sudden floodgate. We have all been there with new diagnostic tests that come and go…They get big uptake and excitement, then die off. It will be a slow uptake. The proof will be in the pudding when doctors try it themselves."

MISCELLANEOUS TIDBITS

Other items of interest highlighted by ASCO

- **Anticoagulants.** A study suggested that therapeutic anti-coagulation improves outcomes in men receiving docetaxel for metastatic CRPC. The study had "compelling" results that anticoagulants can improve outcomes after treatment for prostate cancer, though more studies are likely needed before this becomes a widespread practice.
- **Argos Therapeutics' AGS-003.** A study of AGS-003 + Pfizer's Sutent (sunitinib) in unfavorable risk metastatic renal cell carcinoma doubled survival, but an expert said the findings need to be confirmed in a larger number of patients. The new data in a poster at ASCO-GU was 39.5-month survival vs. ~22 months in all-comer control or ~27 months with intermediate disease patients. A researcher called it "Provenge-plus for RCC," adding, "Patients whose CD8 cells are increased seem to be responders, so we may have a biomarker."
- **Bristol-Myers Squibb's nivolumab (BMS-936558, MDX-1106, ONO-4538).** The company presented a poster with an updated analysis from the CA-209-003 trial of this anti-PD1 antibody. The new information was prolongation of the response in responders and the design of the ongoing Phase III trial. That pivotal, 822-patient Phase III trial started in October 2012, randomizing patients 1:1 to nivolumab 3 mg/kg IV every 2 weeks vs. Afinitor 10 mg/day orally. The primary endpoint is overall survival. Five other Phase III trials in various cancers are underway, and another is expected to start soon. All the trials have a prospective/retrospective biomarker analysis. More data are expected at ASCO 2013.
- **Eisai's lenvatinib (E-7080).** The results of the Phase Ib portion of a Phase I/II trial of this multi-targeted kinase inhibitor were presented in a poster, indicating that the dose for the Phase II portion of the study would be 18 mg QD in combination with Afinitor 5 mg QD. Treatment-related adverse events did not appear to be increased with the combination. Grade ≥3 treatment-related adverse events included proteinuria, hypertriglyceridemia, diarrhea, and fatigue. Partial responses were seen in 33.3% and stable disease in 22.2% of patients who got lenvatinib 18 mg QD + 5 mg Afinitor QD.
- **Merck's Proscar (finasteride).** A poster reported on a long-term survival study of finasteride for chemoprevention. The study found that giving it for seven years did not decrease overall mortality from prostate cancer but did significantly reduce the risk of a prostate cancer diagnosis.
- **Pfizer's Inlyta (axitinib).** This tyrosine kinase inhibitor (targeting VEGF, PDGF, and cKIT) missed the primary endpoint in a first-line metastatic RCC trial, failing to show statistically significant improvement in PFS vs. Nexavar. Inlyta delayed disease progression by 10.1 months, which was a >50% improvement vs. Nexavar, but the hazard ratio (0.77) did not reach the target of a 44% reduction (HR 0.56). Inlyta is approved to treat second-line RCC.