Trends-in-Medicine

October 2009

by Lynne Peterson

SUMMARY

The positive news:

♦ **Amgen's denosumab** is safe and effective for skeletal-related events.

♦ **Amgen's Vectibix** is effective first-line in metastatic colorectal cancer but only if the patients are KRAS-wild type.

♦ **Roche/Plexxikon's PLX-4032** improves survival in metastatic melanoma.

♦ No new safety signals were seen with **Roche's Tarceva** in non-small cell lung cancer.

♦ **Regional hyperthermia** improves mortality in sarcoma patients.

The negative and mixed news:

♦ **Bayer/Onyx's Nexavar** improves survival in metastatic breast cancer, but side effects are a concern.

♦ No first-line benefit was shown for **Lilly/Bristol-Myers Squibb's Erbitux** in metastatic colorectal cancer.

♦ **Roche's Avastin** showed no survival benefit in malignant melanoma.

Trends-in-Medicine
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ECCO-15 – ESMO-34
The 15th Congress of the
EUROPEAN CANCER ORGANISATION (ECCO)
and The 34th Congress of the
EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY (ESMO)

Berlin, Germany
September 20-24, 2009

Among the key news at ECCO-15/ESMO-34 was:

- **Bone metastases** – The efficacy of Amgen's denosumab for skeletal-related events in cancer patients was confirmed in two studies, and safety was reassuring. Denosumab is easier to take than Novartis's Zometa (zoledronic acid), and patient demand is expected to be high, but doctors are worried about how it will be priced.
- **Metastatic breast cancer** – Surgical removal of a primary tumor (which is rarely done today) improves survival in metastatic breast cancer. In the SOLTI trial, Bayer/Onyx's Nexavar (sorafenib) significantly improved progression-free survival (PFS) but had a high rate of hand-foot syndrome, which doctors generally thought was manageable.
- **Colorectal cancer (CRC)** – In the PRIME trial, Amgen's Vectibix (panitumumab) was effective first-line, while in the MRC-COIN trial Lilly/ImClone/Bristol-Myers Squibb's (U.S.) and Merck KGaA's (Europe) Erbitux (cetuximab) failed to show a benefit first-line. However, doctors weren't convinced there is an efficacy difference between the two drugs first-line, calling it a class effect. Vectibix may now pick up a ***little*** more market share because it is easier to give and a little less expensive than Erbitux, but Erbitux has more data, which is important to oncologists. Oncologists now appear convinced that both drugs should only be used in KRAS-wild type patients, which are about 60% of CRC patients. In other news, aspirin may be a beneficial preventive agent after all, at least in some patients.
- **Metastatic melanoma** – Roche/Plexxikon's PLX-4032 improved survival in early-stage trials, while Roche's Avastin (bevacizumab) failed to show either a PFS or overall survival (OS) benefit.
- **Non-small cell lung cancer (NSCLC)** – In the SATURN trial, Roche's Tarceva (erlotinib) was effective with no new safety signals.
- **Ovarian cancer** – The data are very early but very promising for Eisai/ Morphotek's farletuzumab (MORAb-003).
- **Prostate cancer** – Gonadotropin-releasing hormone agonists carry greater cardiac risks than anti-androgen therapy.
- **Sarcoma** – Regional hyperthermia appears beneficial.

Most Common Cancers

Cancer	Number of cases worldwide	Number of cases in Europe	By gender
Lung	1.52 million	386,000	No. 1 for men
Breast	1.29 million	430,000	No. 1 for women
Colorectal	1.15 million	412,000	---
Stomach	934,000	~81,000	No. 1 in developing countries
Prostate	N/A	346,000	No. 2 for men

The scope of the cancer problem

According to ECCO/ESMO ~12.4 million people are diagnosed with cancer every year, including more than 3 million Europeans. It has been estimated that, if current trends continue, the number of new cases diagnosed annually will rise to 26.4 million by 2030.

Endpoints

Dr. Jose Baselga of Spain, the current president of ESMO, said PFS is the key measure in breast cancer trials – but not necessarily in other cancers. He explained, "PFS is becoming the primary endpoint in the breast cancer field…We have multiple therapeutic options that interfere with survival. If you have only one active agent, then PFS correlates with OS…but in breast cancer you have multiple lines of therapy, so overall survival can be influenced not only by the agent you are studying, but also the therapy you receive afterwards. So, to look at survival is very, very difficult. I think we should move to the idea that PFS is our optimal endpoint. Having said that, PFS is loaded with issues: How do you assess it? The trials have to be extremely well controlled to be objective and prevent bias. But I think in the community there is the unanimous belief that that is the preferred endpoint."

Dr. J. Gordon Mcvie of Italy agreed that breast, prostate, and kidney cancer are special situations, where overall survival gets clouded by multiple therapies, putting more reliance on PFS, "Nothing is more important than overall survival – ever! PFS is a convenience for doctors and pharmas to shorten the time. It's a shortcut. It is better than no endpoint. What is happening now in breast cancer is that there are 100 molecules in the pipeline, like planes circling an airport. But if you were looking at NSCLC, melanoma, or glioblastoma, then PFS equals OS. In breast cancer and prostate cancer – and now kidney cancer – we have a battery of salvage options, and crossover screws up the survival studies. However, if there is no PFS, it is most likely there will be no survival benefit. However, the monoclonal antibodies are much slower at shrinking tumors…The metastatic disease problem is not OS but the quality of survival…These are important palliative medications, so survival endpoints are secondary."

Cancer research priorities

Dr. Richard Sullivan of the U.K. said that public sector spending for cancer research is €14 billion annually, but less than 3% of this is spent on "low and middle income 'relevant' cancer research."

What needs to be done? Dr. Sullivan suggested, "We need to be much more holistic about prioritizing funding for cancer research…Societies and membership bodies need to 'debate' policy papers on cancer research investment. We need a more global perspective. There is a disturbing trend to say that funding is becoming more nationalistic, and there is a need for a global fund to fund research…as with HIV."

Dr. Sullivan proposed a new concept: A Global Cancer Fund.

Dr. Sullivan said, "There is no shortage of cancer drugs coming through the pipeline, and the whole area of drug research is quite healthy. What we need is a reapportioning of budgets from the charitable sector and public funders to carve out space for other areas of cancer research that are largely invisible to a lot of policymakers." Dr. Sullivan wants to see more studies aimed at improving surgery, pathology, and diagnostic and staging imaging, and more research on prevention.

New European Academy of Cancer Sciences

The formation of a European Academy of Cancer Sciences was announced at ESMO. The Academy's goal is to inform and educate policymakers about the needs of the oncology community. ECCO president Dr. Alexander Eggermont, a professor of surgical oncology at the University of Rotterdam in the Netherlands, said, "We hope that, by keeping a close eye on policy developments that might affect cancer and offering expert advice to those responsible for decision-making, we will be able, in the future, to avoid some of the recent decisions that have had so much potential to harm cancer patients and the oncology community." For example, Dr. Eggermont said the Clinical Trials Directive (in the U.K.) has had a "devastating" impact on academic clinical researchers and has greatly reduced the amount of academic clinical research in oncology in Europe.

The virtual Academy has 114 founders, with 30 chosen on the basis of their experience and reputation. Those 30 then voted for the other members. Among the members are Sir Richard Peto, the biostatistician from Oxford.

One of the first projects of the Academy will be to prepare a paper on what needs to be done to boost cancer research in Europe. The Academy is hoping to issue that next year.

Cervical cancer screening

With the current push for human papilloma virus (HPV) vaccination, Dr. Jack Cuzick of the U.K. pointed out that Pap smear screening for cervical cancer will become less cost-effective in the future, "Screening will be more difficult and less cost-effective in vaccinated women. We can probably test

at longer intervals…It will be important to have registries to know who is vaccinated and who isn't."

He said that is a reason to move, instead, to HPV testing with objective, automated methods, "We are bogged down now in a technology that is 50 years old…(HPV) is a much better test… And women will be able to use a tampon or spatula and send a sample in (for HPV testing)…It is time right now to move to HPV vaccination and HPV screening." However, he noted that screening will remain important until the vaccine becomes widely (used).

The unanswered question is: What does this mean for the companies that provide Pap smear testing?

BONE METASTASES

Bone is a common site for metastases – ~70% of breast cancer metastases are to bone, and ~90% of prostate cancer metastases are to bone. The clinical consequences of a bone metastasis are: (1) skeletal-related events (SREs) such as fracture, radiation, surgery, or spinal cord compression, (2) hypercalcemia, and (3) pain. Currently, intravenous bisphosphonates – most often Zometa – are used to delay or prevent SREs.

Incidence of Bone Metastases in Cancer

Cancer	Approximate incidence of bone metastases
Myeloma	100%
Prostate	90%
Breast	70%
Thyroid	60%
Lung	35%
Melanoma	30%
Kidney	23%

AMGEN's denosumab

Amgen was heavily promoting denosumab at ECCO-15/ESMO-34. This included special media events for ***selected*** media only – not reporters from the major U.S. media outlets. According to ESMO sources, this was an invitation-only media dinner for media whose coverage of ESMO was "sponsored by Amgen." While Amgen sources insisted that this is a common practice in Europe, none of the European reporters questioned in the press room were supported by Amgen or any other pharma or biotech company.

Denosumab is a monoclonal antibody in development to treat osteoporosis and to prevent bone metastases (mets) in cancer patients. In August 2009 an FDA advisory panel recommended ***against*** approval of denosumab for postmenopausal osteoporosis over concern for tumor promotion. An Amgen official said, "In Europe, (regulators) have guidance on the treatment of osteoporosis, where the draft guidance for the FDA has both prevention and treatment…(The FDA concern) was raised around the prevention claim."

Denosumab will be sold as Prolia for osteoporosis, but Amgen apparently plans a different name for it in cancer since the dosing will be very different. Thomas McCourt, the head of marketing for Prolia (osteoporosis), recently left Amgen to go to Ironwood Pharmaceuticals, but Amgen officials brushed this aside, insisting it was having no impact on the launch plans. There were no rumors circulating at the meeting, no discussion about it, and no speculation on why this happened.

Asked when Amgen plans to file in Europe and the U.S. for a bone metastases indication, an Amgen official said, "The (data from these breast and solid tumor trials) have really just been released. We are looking at the option of filing on two studies…A third study (in prostate SREs) is to be completed sometime in 2010…There are pros and cons of submitting on two studies vs. three, and we haven't made a decision on that …but I expect a decision 'soon.'"

Amgen has not said how it plans to price denosumab, and the pricing – like the name – is likely to be different in cancer. Speakers and company officials repeatedly pointed out that the cost of Zometa is not just the cost of the drug but also the cost of nursing time, infusion supplies, etc.

Before ESMO, Amgen released top-line data from two trials – one in breast cancer and another in multiple myeloma and solid tumors (other than prostate or breast). At ESMO, more details from these trials were released. Both trials measured the effect of denosumab on SREs and pain.

One of the concerns with denosumab has been a worry that it might be tumorgenic, that it might spur primary tumor growth while inhibiting bone mets. Most oncologists questioned believe the new data should put an end to this concern. An Amgen official said, "What are the potential reasons RANKL could cause tumors? One is the theoretical effect on the immune system that has not been proven to have an effect. There is no evidence with Prolia or in these two (cancer) studies that answers that for me. Second is the structure of the TNF superfamily. There is no evidence that denosumab cross reacts with TRAIL in the preclinical setting, so denosumab should not bind up TRAIL. So, if you give a higher dose, and if there were cross reactivity, you would bind up TRAIL…So, in terms of robustness, I am reassured, and we have continued to monitor patients. We will monitor the original patients for a decade." An investigator said, "With the data from these two trials, there is no concern about infection causing risk (of tumor promotion)." Another investigator commented, "In our trials…we had immunosuppressed patients, and we didn't see an increase in infectious complications. That is very encouraging. If any patient was going to get an infection, it would be the patient on chemotherapy, and we didn't see that."

Asked about data indicating Zometa actually has an anti-tumor effect, Dr. Alison Stopeck of the Arizona Cancer Center said, "That is hypothetical at this point and not proven."

Asked if denosumab will be used off-label in cancer if it is approved for postmenopausal osteoporosis (PMO), a U.S. investigator said no, "I won't get paid for it if used off-label. It is a different dose (in cancer) than for PMO, and it is a different schedule than PMO, so I don't see how you would get it paid for...But I would use it (off-label) in adjuvant patients. For patients without breast cancer but who have osteopenia or osteoporosis secondary to an aromatase inhibitor, I would consider using denosumab on the dose recommended and approved (for PMO)."

Zometa is associated with some renal toxicity, and this adverse event appears lower with denosumab. The question is how significant the renal toxicity side effect actually is in patients with bone metastases. While most oncologists questioned said "a lot" of their patients have renal issues, they generally did not consider renal toxicity to be an important differentiator between the two drugs. An Amgen official said, "Renal toxicity is a real issue with some patients, but it depends on the cancer. The vast majority of multiple myeloma patients have renal issues, and so does a large number of patients getting platinums as well as a lot of the elderly."

How was PFS measured in the denosumab SRE trials? An Amgen official said PFS data were collected, determined, and reported by the investigators, not as adverse events but as progression. There was no central review. Investigators had to record a progressions event and detail how it was determined. The Amgen official said, "It was a double-blind, double-dummy study, so there was no need for a central reviewer."

Asked about crossover in both denosumab studies (breast and solid tumors), Dr. Stopeck said that patients continued to get the planned denosumab doses through the entire study, that patients did not come off denosumab or switch to Zometa unless they withdrew consent or died; there was no crossover.

- Denosumab was ***not superior*** to Zometa on time to first-and-subsequent SREs, and denosumab was not better in pain prevention or improvement.

New data at ESMO showed:

- Time to disease progression was exactly the same between the two drugs. No PFS data were presented.
- OS was similar.
- Osteonecrosis of the jaw (ONJ) was comparable with both drugs.
- Time to first on-study SRE or hypercalcemia, in a post hoc exploratory analysis, was significantly longer with denosumab.
- A post hoc analysis found some tumors that appeared to respond better to each agent.

Asked if the results justify the likely higher cost of denosumab, Dr. David Henry of Pennsylvania, the principal investigator, said, "In the U.S., Zometa requires more chair time…so you have to consider that when you compare the cost of denosumab and Zometa."

Asked about the potential impact of denosumab on bone metastases, Dr. Henry said, "That's pure speculation. In the adjuvant setting, Zometa has wonderful data that is an exciting avenue for the future of this drug (denosumab)."

Asked what percent of solid-tumor cancer patients without breast or prostate cancer currently get Zometa, Dr. Henry estimated ≤50%, adding, "We use a lot of it for patients with bone mets."

Study 244: Denosumab in solid tumors/myeloma (*but not breast or prostate cancer*)

This international, double-blind, randomized, active-controlled, Phase III trial enrolled 1,776 adults with solid tumors and bone metastases who had no current or prior IV bisphosphonate therapy.

What was known before ESMO is that:

- Denosumab was ***non-inferior*** to Zometa on the primary endpoint of time to first on-study SRE. However, denosumab did not show superiority on this endpoint.

Denosumab Efficacy in Solid Tumors and Multiple Myeloma (*non-breast, non-prostate*)

Measurement	Denosumab 120 mg SC Q4W n=886	Zometa 4 mg IV Q4W n=890	Hazard ratio	p-value
Primary endpoint: **Non-inferiority** in time to first on-study SRE	20.6 months	16.3 months **Non-inferior**	0.84	0.0007
Secondary endpoint #1: **Superiority** in time to first on-study SRE	20.6 months	16.3 months **NOT superior**	0.03	Nss, 0.06 adjusted
Secondary endpoint #2: **Superiority** on time to first-and-subsequent on-study SRE	392 SREs	436 SREs	0.90	Nss, 0.14
Exploratory post hoc analysis: Time to first on-study SRE or hypercalcemia of malignancy	19.0 months	14.4 months	0.83	0.02
Time to pain improvement	85 days	85 days	1.01	Nss, 0.93
Time to experiencing moderate or severe pain	57 days	36 days	0.93	Nss, 0.17
OS	Median survival ~12 months		0.94	Nss, 0.43
Overall disease progression	Median time to disease progression ~6 months		1.00	Nss, 1.0

Denosumab Safety in Solid Tumors and Multiple Myeloma (*non-breast, non-prostate*)

Measurement	Denosumab	Zometa
Overall survival by tumor type *		
Favors	Bladder NSCLC	Endometrial Multiple myeloma
Possibly favors	Renal, small cell lung, melanoma, NHL, thyroid, pancreatic	Renal, unknown primary, cervical
Adverse events **		
Any adverse event	96%	96%
Infections	40.8%	39.7%
Serious adverse events	63%	66%
Infectious serious adverse events	14.6%	13.4%
Adverse events leading to discontinuation	10%	12%
Acute phase reaction (first 3 days)	6.9%	14.5%
Potential renal toxicity	8.3%	10.9%
Renal failure	2.3%	2.8%
Acute renal failure	1.3%	1.8%
Hypocalcemia	10.6%	5.6%
ONJ overall	1.1%	1.3%
ONJ in Year 1	0.5%	0.6%
ONJ in Year 2	1.1%	0.9%
New primary malignancy	0.6%	0.3%
Anemia	28%	33%
Nausea	28%	30%
Fatigue	24%	25%
Dyspnea	25%	23%
Favors	Anemia, pyrexia, peripheral edema chills	Hypocalcemia

* neither therapy favored in head & neck, gastric, soft tissue sarcoma, neuroendocrine, or ovarian cancer

** neither therapy favored other adverse events

Asked about the incidence of ONJ, Dr. Henry said, "In the U.S., we worry about ONJ, but it is very rare."

Study 136: Denosumab in breast cancer

Before ESMO, Amgen reported that denosumab showed superiority over Zometa in this 34-month, randomized, double-blind study:

- Primary endpoint of time to first on-study SRE (HR=0.82, p=0.01).
- Time to first-and-subsequent SREs (HR=0.77, p=0.001), improved by 23% with denosumab.
- OS comparable (HR 0.95, p=0.50).

New data at ESMO:

There was no indication of tumor progression with denosumab. The new data showed denosumab:

- Primary endpoint: curves continue to diverge.
- Time to first on-study SRE: 26.5 months with Zometa and not yet reached for denosumab.
- Time to first-and-subsequent SRE – the curves continue to separate throughout the course of the trial.
- Has not yet reached median time to first on-study SRE. For Zometa the median time was 806 days.
- Denosumab showed no imbalance in time to cancer progression (HR 0.99).
- OS and time to progression (TTP) were both identical between the 2 drugs. (NOTE: This trial did not measure PFS; it measured TTP.)
- Infections were comparable.
- Serious adverse events were comparable.
- Serious infections were comparable.
- ONJ was numerically but not statistically more common with denosumab.

Dr. Stopeck, the principal investigator for this study, said there was no evidence of any tumorgenicity with denosumab, "My trial certainly showed no evidence of tumor progression...And in all honesty, I would hypothesize the drug's method of action would make it anti-tumor, so I am not surprised by these results at all."

Dr. Stopeck also was very pleased with the efficacy of denosumab, "The trial was very positive… Denosumab was superior to Zometa not only in delaying SREs but also in improving pain control, with less toxicity, so there really is no downside to the drug. It really is a positive drug and a positive trial...After you get your first SRE...the curves continue to separate which means...denosumab patients had less subsequent and fewer initial SREs…You are continuing to get a benefit. There is a 23% risk reduction of getting a first-and-subsequent SRE…(This was an important study because) it showed everything positive you can imagine. It decreased time to SRE, had less toxicity than the current standard of care, and is subcutaneous, so it adds tremendous convenience. So, in every way, it was a win, win, win."

Denosumab will improve quality of life for breast cancer patients, Dr. Stopeck believes. She said, "Denosumab can prevent SREs, which are really devastating to breast cancer patients. I like to think of breast cancer as a chronic disease, and if you develop a fracture or pain or require surgery, that is devastating to your quality of life…And I can't say how nice it is to have a subcutaneous drug. Breast cancer can be maintained for years on hormone therapies – oral drugs – and having a drug that is better, safer, and subcutaneous so they don't have to come to the cancer center for an IV infusion is better for them maintaining as normal a life as possible. You want your patients to have as normal a life as possible."

Asked about the renal adverse events, Dr. Stopeck said, "In terms of renal toxicity, there was a huge difference in favor of denosumab. In this trial, we dose reduced Zometa per the package insert while denosumab was not dose reduced for anything."

Asked about the ONJ cases, Dr. Stopeck said, "Obviously, I would have loved if ONJ didn't occur in either arm...It is a very small number, but we will dig deeper in patients who develop this (ONJ)...Denosumab is reversible, and Zometa is not...so there is a possibility that perhaps we have a more reversible type of ONJ with denosumab. It will take several months to dig down into the data (and see if this is true)... Initially, I saw a lot of patients with ONJ...and now that I know the risk factors, much fewer of my patients get it…I've gotten good at avoiding it…I haven't seen a case now in several years where initially I had half a dozen (with Zometa and pamidronate)."

How will the oncology community view these data? Dr. Stopeck said, "Obviously, we don't know the cost (of denosumab). Will that make a difference? Yes. Will patients prefer this drug? Yes. There is no pain, no flu-like symptoms, and it is subcutaneous injections. Having a Portacath on your chest is a constant reminder of your breast cancer, and there is a cost involved in that…I've had a couple of patients asking when the trial would be open, so they could use a subcutaneous injection because they refused to get a Portacath... Emotionally, that can be tough...So, for those types of patients, it is a no brainer to switch to denosumab immediately. It's easier, less toxic, and more efficacious...In the U.S. Zometa is expensive when you consider the drug, the chair, nursing time, facility time, etc. In the U.S. we charge for all that. So, denosumab will have a huge advantage in those terms...It's about $1,500 a shot for Zometa monthly with everything included."

What will make breast cancer doctors use denosumab? Dr. Stopeck said, "Preventing SREs is primary for the patient and the oncologist. Once a patient gets a fracture and needs radiation, it is very limiting to me…I don't like to send patients for radiation oncology because that means they are getting radiation to a part of the body that inhibits my future therapies…And if a patient fractures something, it is devastating to them...And it is a risk factor for worsening survival once you get surgery...That is No. 1 for me...And patients will love the less toxicity. More than 25% of breast cancer patients have flu-like syndrome after a (Zometa) infusion for 1-3 days that keeps them in bed, and denosumab doesn't have that."

Is the delay in time to SRE clinically meaningful? Dr. Stopeck said, "Yes...When you take the totality of data...it is better, prevents future SREs, maintains pain control, and does this with less toxicity."

How much will denosumab expand the number of breast cancer patients on therapy for SREs? Dr. Stopeck said, "I don't give Zometa to elderly patients because of borderline renal insufficiency...In a year, 10%-15% more patients will be on therapy (with approval of denosumab)."

Asked about the rigor around the TTP analysis, Dr. Stopeck emphasized that TTP was not the primary endpoint. She said TTP was based on the investigator, who checked a box that said a patient progressed, but patients could stay in the trial even if their disease progressed and the anti-tumor therapy was changed.

What's next? Dr. Stopeck said Amgen is planning a trial of denosumab in the adjuvant setting, "I think it is absolutely safe enough (for that setting), and if nothing else, it will prevent them from getting bone loss on their aromatase inhibitors."

Asked about the importance of denosumab being a fully human antibody, Dr. Stopeck said, "A fully human antibody means patients won't develop antibodies, so they can continue to receive the drug for years and years."

Asked if denosumab should be used first- or second-line, Dr. Stopeck said, "I don't see any downside to using denosumab for first-line." Dr. Henry added, "While superiority was not met (in solid tumors), the convenience and lack of renal monitoring is such a convenience for patients that it moves in my mind to first position."

Denosumab Efficacy in Breast Cancer

Measurement	Denosumab 120 mg SC Q4W n=1,026	Zometa 4 mg IV Q4W n=1,020	Hazard ratio	p-value
Primary endpoint: Time to first on-study SRE	Not yet reached	26.5 months	0.82	0.01
Time to first-and-subsequent on-study SRE	---	806 days	0.77	0.001
Time to first on-study SRE or hypercalcemia of malignancy	Not yet reached	25.2 months	0.82	0.007
Time to worsening of bone pain	88 days	64 days	0.87	0.009
OS	---	---	0.95	Nss, 0.50
TTP	---	---	0.99	Nss, 0.90
Adverse events				
Any adverse event	96%	97%	---	---
Infections	46%	49%	---	---
Serious infections	7%	8%	---	---
Serious adverse events	44%	46%	---	---
ONJ	20 patients (2.0%)	14 patients (1.4%)	---	Nss, 0.39
Renal toxicity	4.9%	8.5%	---	---

Prostate cancer study

An Amgen official said the denosumab prostate TIBL trial is "focused on the appropriate measure in prostate cancer patients with androgen sensitivity…They looked at changes in PSA (prostate specific antigen) levels over time…That was a pre-specified robust analysis and essentially showed no difference…We looked at survival as well, and that was the same. In terms of other pre-specified analyses, there were bone scan data that showed similar outcomes. So, based on PSA, bone scan, and survival equivalence, we concluded there isn't any issue there. The FDA did its own analysis."

Asked if Amgen did its own analysis like the FDA, the official said, "We focused on the pre-specified outcomes."

The prostate SRE trial will report next year. No interim analysis is planned. The official said, "One could predict (based on mechanism of action, etc.) the results should be robust."

Denosumab vs. Zometa

Dr. Mcvie said that the issue isn't PFS or OS differences but the effect on time to first skeletal-related events (SREs), "SRE is more important than PFS…Two or 3 extra months free of bone pain will impress me…But the competition for denosumab, zoledronic acid, is very cheap, and I'm damn sure denosumab won't be as cheap as zoledronic acid." He emphasized that there are 40 years of research with bisphosphonates (e.g., Zometa) and predicted that doctors in some countries will use Zometa first, switching to denosumab if Zometa fails. But he said other countries, where cost is less an issue, may use denosumab first.

Oncologists said that most of their patients with bone metastases get Zometa. In one year, they estimated that denosumab would take share from Zometa, which most prescribe monthly, but it will not expand the market. Comments included:

- *Italy #1:* "Forty percent of my patients (with bone mets) get Zometa, but a year after denosumab is approved, it will be 30% denosumab, 10% Zometa because of the convenience and method of action of denosumab."
- *U.K.:* "About 10% of my patients with bone metastases are on Zometa, which I give some Zometa monthly and others every three months. It varies greatly…People will change to denosumab, but it will take time. Eventually, denosumab will expand the market, but again, time is an issue. It needs to get in the guidelines and in electronic prescribing. I doubt there will be much, if any, off-label use in the U.K…Even though there is ONJ with denosumab, the method of action may swing people in favor of it to reduce or avoid ONJ (vs. Zometa)."
- *Italy #2:* "If denosumab were available, I would use it. If I were convinced by the trials that denosumab is better than Zometa, then I'd use it 100%, but I'm not completely convinced yet, so I would try it in a few patients… Denosumab is unlikely to expand the use of these two agents because right now I don't use Zometa in patients with a few months of life left…Denosumab is easier to use, but if a patient has a short life expectancy, I'd probably prefer radiotherapy or morphine…When I use Zometa, it is 4 mg every 4 weeks. I participated in a trial of Zometa every three months. That trial is closed, and we are waiting for the results."
- *Denmark:* "We are using oral, daily ibandronate (GlaxoSmithKline's Boniva) instead of Zometa right now. I participated in a denosumab study, but we can't just change (to denosumab if it were approved) because of cost. The decision process is long and troublesome…Even if it were reimbursed, I wasn't won over by the data yet."
- *U.S.:* "About 70% of my metastatic breast cancer patients are on Zometa – all of the patients with bone metastases. The denosumab data look good. It's tough to predict how much denosumab will be used in a year, but my bias is in favor of denosumab. The deciding factor will be cost. A lot of doctors and patients will be biased toward more denosumab – if it is reimbursed."
- *Germany:* "I will get information on denosumab when I get home (from ESMO). I won't switch to denosumab right away because of cost and because bisphosphonates are easy to get, cheap, work, and have good and long-term data. Bisphosphonates are standard-of-care, and a good standard-of-care…I don't think denosumab will change practice a lot...Medical advertising to consumers is illegal in Germany, but the media are legal advertising. Amgen takes advantage of this by sponsoring and promoting informational websites through an organization."

BREAST CANCER

BAYER/ONYX's Nexavar (sorafenib) – beneficial in breast cancer

In data presented at ESMO, Nexavar significantly reduced PFS in advanced/metastatic breast cancer by 42%, and the benefit was there whether it was first- or second-line therapy. The problem was two side effects: a 45% rate of hand-foot syndrome and a 53% rate of diarrhea.

SOLTI-0701 was a randomized, double-blind, placebo-controlled, Phase IIb trial of capecitabine ± Nexavar in women with locally advanced or metastatic breast cancer conducted in Spain, France, and Brazil. Nexavar, an oral multikinase inhibitor, is already approved for treatment of renal cell and hepatocellular carcinoma, and it now looks promising in breast cancer. SOLTI is one of four Phase IIb studies making up the TIES breast cancer program.

Dr. Baselga of Spain, the principal investigator of SOLTI, dismissed concerns about the hand-foot syndrome side effect, saying, "This is an effect we were anticipating. During the study there was a learning curve by the investigators to identify it earlier, to manage it appropriately with local therapy and dose reductions, and, as the study evolved, the complications

decreased in frequency…We are investigating supportive treatment strategies to manage hand-foot syndrome."

How much of a problem for usage is the hand-foot syndrome side effect? Most oncologists did not see it as a barrier to use. They said it means having to manage the patients more carefully – giving a drug holiday or stopping Nexavar altogether when symptoms develop – but they indicated hand-foot syndrome is manageable and will not discourage most patients. But a few worried about the impact of dose adjustments on efficacy of the chemotherapy. Comments included:

- *Italy:* "Patients will still take Nexavar, and I'll just stop the drug if hand-foot syndrome occurs."
- *Denmark:* "Hand-foot syndrome would keep me from using it."
- *U.K.:* "Hand-foot syndrome is a common side effect with targeted therapies that differs from traditional chemotherapy. It is undoubtedly unpleasant and a nuisance, but patients don't die from it. It needs to be managed, but it can be managed. We will need to explain to patients that if their hand or foot starts to get sore, they need to tell us so we can modify the dose. The effect builds up over time, but it is reversible."
- *U.S.:* "Hand-foot syndrome is a big deal. The issue is how severe and how symptomatic the patients are. That is a problematic side effect...It can be managed, but the issue will be whether it impacts treatment activity. There is no medication to treat it, and lowering the dose may negatively affect treatment…So, it is not clear where I would use Nexavar (in breast cancer)…Avastin has its own problems…PFS needs to be 2-3 months to be meaningful. It's a judgment call. There is no magic number for PFS."

Results of SOLTI-0701 Phase IIb Trial of Nexavar in Breast Cancer

Measurement	Sorafenib 400 mg BID + capecitabine n=115	Capecitabine 1000 mg/m^2 n=114
Primary endpoint: PFS	6.4 months (HR 0.576, p=0.0006)	4.1 months
PFS in first-line therapy	7.6 months (HR 0.498, p=0.0022)	4.1 months
PFS in second-line therapy	5.7 months (HR 0.652, p=0.0339)	4.1 months
Responses		
ORR	38.3% (Nss, p=0.1229)	30.7%
Complete response	1.7%	0.9%
Partial response	36.5%	29.8%
Stable disease	43.5%	37.7%
Progressive disease	10.4%	23.7%
Adverse events		
Hand-foot syndrome	89%	63%
Diarrhea	53%	30%
Mucosal inflammation	32%	19%
Asthenia	24%	27%
Rash	22%	8%
Hypertensions	17%	12%
Musculoskeletal pain	12%	6%
Neutropenia	11%	4%
Grade 3 adverse events more common with Nexavar		
Hand-foot syndrome	45%	13%
Rash	3%	0
Fatigue	2%	1%
Musculoskeletal pain	2%	0
Dyspnea	5%	3%
Neutropenia	4%	2%
Discontinuations		
Any	65%	79%
Due to adverse events	15% *	7%
Due to progressive disease	45%	66%
Due to death	0	1%

*** Most commonly hand-foot skin reaction (8 patients vs. 2 patients) and diarrhea**

How does Nexavar compare to Avastin for breast cancer? A U.K. oncologist said, "Avastin has the advantage of more patients treated, so the data are more robust. But Nexavar is a small molecule and a new class. Nexavar's use will depend on Bayer's strategy – as combination therapy, sequential therapy, etc. With more drugs for breast cancer, it makes the path less clear…Myself, I would need more information on the side effects before I would use it. It's like the choice between Herceptin (Genentech, trastuzumab), which is an injection, and lapatinib (GSK's Tykerb), which is a tablet, since their efficacy is comparable."

ROCHE's Avastin (bevacizumab) – trial suspended

Shortly after ESMO, Roche announced that the National Cancer Institute and the Eastern Cooperative Oncology Group (ECOG) had suspended enrollment in a Phase III Avastin breast cancer study (E5103) after six patients developed congestive heart failure (CHF). However, Roche still believes the number of CHF cases are still within the reported rates for Avastin. The data safety monitoring board is evaluating the information from this pre-planned cardiotoxicity analysis, and what happens next depends on that review. The study was specifically designed to look at cardiovascular (CV) safety.

Breast Cancer Therapy Approaches

Line of therapy	Option 1	Option 2	Option 3	Option 4	Option 5
1st line	FOLFIRI/Avastin	FOLFOX	EGFR inhibitor/FOLFOX	EGFR inhibitor/FOLFIRI	FOLFOX
2nd line	FOLFOX	FOLFIRI	??	FOLFOX	EGFR inhibitor/FOLFIRI
3rd line	EGFR inhibitor	EGFR inhibitor	??	??	??

E5103 is a multicenter, randomized, double-blind, placebo-controlled Phase III trial of Avastin plus chemotherapy as adjuvant treatment following surgery in women with either lymph node-positive or high-risk, lymph node-negative breast cancer. The primary endpoint of the study is disease-free survival. Cardiotoxicity is a secondary endpoint.

Surgery for metastatic breast cancer

A retrospective study from the Netherlands found that surgical resection of the primary tumor in women with metastatic breast cancer almost doubles survival (in this study to 31 months vs. 14 months without surgery). A multivariate analysis showed that surgery is an independent prognostic factor for overall survival (HR 0.62), with a 38% reduction in mortality risk by removal of the primary tumor.

It is not the practice in the U.S. or Europe to operate on these women, and the ESMO president said this study ***will not change practice***. But it is likely to get a lot of play in the media, so women with metastatic breast cancer may start demanding the surgery. And not a small number of patients are affected: 31% of breast cancer patients have distant metastases at initial presentation, with a median survival of 1-2 years.

COLORECTAL CANCER (CRC): EGFR INHIBITORS

EGFR inhibitors have proven efficacy in refractory metastatic cancer in KRAS-wild type (WT) tumors, but in first-line therapy, the results have been mixed. The CRYSTAL and OPUS trials showed a first-line benefit with Erbitux. The CAIRO-2 and PACCE trials showed no benefit to an EGFR inhibitor added to oxaliplatin-based chemotherapy plus Avastin.

The data at ESMO did not resolve this. Rather, they added to the mixed results. Vectibix was effective first-line on PFS but not overall survival, and Erbitux failed first-line in the MRC-COIN trial. Oncologists, asked about these conflicting findings, generally said that they still believe EGFR inhibitors work first-line, and they believe it is a class effect – that both Vectibix and Erbitux are effective. Thus, none predicted that Erbitux would lose its first-line approval in Europe as a result of COIN.

The question, thus, is how doctors now view Vectibix vs. Erbitux and how they will choose between them. Comments included:

- *U.K.:* "I think there will be a way to identify patients for Vectibix and Erbitux…It is not clear where Vectibix should be used yet…The 1.6 month improvement in PFS is really thin, and clinical trials are the best results. When it is used in the real world, that number nearly always drops."
- *Italy:* "We only use Vectibix after Erbitux, not first-line, because of reimbursement, and that won't change until reimbursement changes."
- *Australia:* "We use both Vectibix and Erbitux pretty equally, so our use will stay about the same over the next year…Neither is very available because there is no reimbursement for them…To move into first-line, Vectibix needs good studies, but it is easier to give Avastin + chemotherapy. EGFR inhibitors are just easier for me to use second-line…I haven't seen any evidence to say there is a major difference between Vectibix and Erbitux, and you can't base your decision (on what to use) on one trial. I also have questions about U.K. data…There is no advantage of Vectibix over Erbitux or vice versa."
- *Belgium:* "I'm using mostly Erbitux now, and in a year, it will still be 70% Erbitux because we don't have any data with Vectibix for potentially operable patients. Logically, you could extrapolate to that, and a lot of my colleagues will do that, and they will change completely to Vectibix, but I'll reserve it for third-line – and not in operable patients."
- *Spain:* "Over the next year, I may use more Vectibix because it has less toxicity than Erbitux, and it is cheaper, with the same efficacy…Erbitux is useful first-line, but the studies don't demonstrate that yet. In Spain, we have a new law that lets us use therapies without asking for permission (as we had to do in the past)…The real study we need is chemotherapy + Avastin vs. chemotherapy + an EGFR inhibitor…We use FOLFIRI + Avastin first-line for most patients…I'm using an EGFR inhibitor more after second-line, but still not often. After ESMO, we will ask to use an EGFR inhibitor first-line. I think it is better than either current first-line."
- *France:* "ESMO will change what we do. We'll use Vectibix earlier; it is less allergic, and there are fewer acute side effects. I think Vectibix is easier to use, but there aren't any head-to-head trials comparing Vectibix and Erbitux. Efficacy is comparable…Currently we are using almost all Erbitux, but in a year we may be doing 50% Vectibix."
- *India:* "We use only Erbitux because panitumumab is not available yet. We use Avastin in KRAS-mutant patients. If Vectibix were available, I would choose one or the other – Vectibix or Erbitux – and probably Vectibix because it is a humanized antibody, but the lack of data on Vectibix is an issue."

The term first-line in connection with the EGFR inhibitors can be confusing, so a variety of treatment approaches are being used.

An Italian oncologist believes there may actually be a significant difference in how Vectibix and Erbitux work. He said, "They are not exactly the same molecule." He explained that the focus has been on inhibition of the EGFR, which both agents accomplish. However, he said there is a new focus on

the impact on the immune system, which Erbitux but not Vectibix does, "If I have to give a monoclonal antibody to a patient, knowing Erbitux can both turn off the EGFR receptor at the tumor but also bring NK (killer) cells directly to the tumor – an antibody dependent cellular cytotoxicity (ADCC) effect – I'm going to choose Erbitux." However, an Amgen official dismissed the role of ADCC, saying, "The role of ADCC in cancer is not that clear. I believe the major option is to block the EGFR receptor. That is the key pathway. There is a possibility there is an immune component, but that has never been proven."

AMGEN's Vectibix (panitumumab)

Vectibix is approved for use as monotherapy for metastatic CRC (mCRC) in patients with KRAS-wild type (WT) tumors, but the uptake has been limited and slow. New data presented at ESMO could give use a boost.

PRIME Trial (Study 203) – in first-line mCRC Vectibix effective in KRAS-WT but harmful in KRAS-mutant patients

Prior to ESMO, Amgen announced only that the PRIME trial met its primary endpoint, with no details.

PRIME was a randomized, open-label, multicenter Phase III trial of FOLFOX4 [oxaliplatin/5-fluorouracil (5-FU)/leucovorin)] ± Vectibix as first-line therapy in patients with previously untreated mCRC.

In PRIME, KRAS status was prospectively collected. Originally, the trial was designed to compare the treatment effect in the whole population, but the study was amended to focus on the KRAS-WT subset prior to the primary analysis.

At ESMO, Dr. Jean-Yves Douillard of France, the principal investigator, reported that Vectibix significantly prolonged PFS in KRAS-WT patients but had a ***detrimental*** effect in KRAS-mutants. However, the PFS difference was only 1.6 months, causing some doctors to question the clinical significance. And Vectibix did not show any survival benefit. Dr. Douillard said, "The trial confirmed that the only patients benefiting from panitumumab (first-line) are KRAS-WT, but more importantly, in the KRAS-mutated patients there is a detrimental effect which is significant – a shorter progression-free survival. So, not only is panitumumab beneficial in WT, but it is detrimental in the mutated patients…KRAS is a major biomarker to decide on a treatment in CRC…In second-line therapy, panitumumab is not harmful, but in first-line it is… Prospectively, this confirms that patients with KRAS-mutation should not receive treatment with Vectibix, and it should be restricted to patients with wild type status."

The results showed:

- **KRAS-WT patients**
  - PFS was significantly improved by 1.6 months when Vectibix was added to FOLFOX4 in KRAS-WT patients (9.6 months vs. 8 months). These data were called "very mature."
  - Response rates were 55% Vectibix vs. 48% without it, but this was not statistically significant.
  - PFS favored Vectibix in most subgroups, but there was no benefit to Vectibix in women and in people age ≥65. In patients with ECOG performance status 2, PFS actually favored FOLFOX4 alone.
  - Overall survival (in an interim analysis) was ***not*** significantly better with Vectibix, though Dr. Douillard described it as trending in favor of Vectibix.

Vectibix Results in PRIME Trial in First-Line mCRC

Measurement	KRAS-WT		KRAS-Mutant	
	Vectibix + FOLFOX4 n=325	FOLFOX4 n=331	Vectibix + FOLFOX4 n=221	FOLFOX4 n=219
Primary endpoint: PFS	9.6 months (p=0.0234, HR 0.80)	8 months	7.3 months (p=0.0227, HR 1.29)	8.8 months
Overall survival, median (interim analysis)	20.3 months (Nss, p=0.16, HR 0.83)	17.2 months	15.1 months (p=0.004, HR 1.53)	18.7 months
Responses				
Response rate	55% (Nss, p=0.068)	48%	N/A	N/A
CR	0	0.3%	N/A	N/A
PR	55%	47%	N/A	N/A
Stable disease	30%	36%	N/A	N/A
Progressive disease	7%	11%	N/A	N/A
Grade 3/4 adverse events				
Any adverse event	84%	69%	80%	73%
Fatal adverse events	5 patients	6 patients	8 patients	3 patients
Skin toxicity	36%	2%	30%	1%
Neutropenia	42%	41%	37%	47%
Diarrhea	18%	9%	20%	10%
Neurologic toxicity	16%	16%	16%	17%
Stomatitis	9%	1%	6%	3%
Hypomagnesaemia	6%	0	6%	<1%
Infusion-related reactions	<1%	0	<1%	0

➢ **KRAS-mutant patients**

- PFS was significantly ***worse*** with the addition of Vectibix in KRAS-mutant patients.
- Overall survival was significantly ***worse*** with Vectibix. Dr. Douillard said, "Based on this survival interim analysis…we can prove there is a detrimental effect…in patients with KRAS mutation."
- Numerically, there were more deaths with Vectibix. Dr. Douillard said, "It is true there were more toxicity-related deaths in mutant patients, but it does not seem to be related to either Vectibix or FOLFOX …There was some pulmonary embolism in slight excess."

Dr. Douillard pointed out that Vectibix is better tolerated than Erbitux, and no premedication with steroids or antihistamines was needed. He emphasized the lack of allergic reactions and no need for renal monitoring as additional reasons to choose Vectibix over Erbitux.

Asked why first-line mCRC patients did worse with Vectibix than second-line patients, Dr. Douillard said, "Second-line patients are naturally selected…Roughly 60% make it to second-line…So, you have already selected patients…It may also be a drug effect…It could be an oxaliplatin issue. The detrimental effect was seen with Erbitux and FOLFOX but not reported with FOLFIRI (irinotecan/5-FU/leucovorin)…so, it could be an oxaliplatin issue. That is a hypothesis only, but we have to look at that in detail."

Are these data sufficient to get a broader label in Europe? Dr. Douillard believes the data are sufficient.

There will be more data from PRIME analyses at ASCO GI in January 2010.

Study 181 – in second-line mCRC Vectibix more effective in KRAS-WT, no impact in KRAS-mutant

This study showed that KRAS status determines who responds to Vectibix, but, unlike in first-line, there was no detriment to KRAS-mutant patients from taking Vectibix – it just didn't provide any added efficacy. Study 181 was a randomized, multicenter, Phase III study. FOLFIRI ± Vectibix (6 mg/kg Q2W) was given to patients as second-line therapy in mCRC patients previously treated with 5-FU, based on a prospective determination of KRAS status.

Vectibix Results in Study 181 in Second-Line mCRC

Measurement	KRAS-WT		KRAS-Mutant	
	Vectibix + FOLFIRI n=597	FOLFIRI n=486	Vectibix + FOLFIRI	FOLFIRI
Primary endpoint #1: PFS	5.9 months (HR 0.73, p=0.004)	3.9 months	Nss difference	
Primary endpoint #2: OS	14.5 months (HR 0.85, p=0.115 Nss)	12.5 months	Nss difference	
Response rate	35%	10%	N/A	N/A

Dr. Marc Peeters of Belgium, the principal investigator, said a 2-month improvement in OS is significant, "If you look at the curves, there is a real difference between both arms, which means there is a risk reduction of 27% with Vectibix, and this is clinically significant…In this population which has already received chemotherapy, and some who already received Avastin. This is an important gain, and in general, clinically significant."

But Dr. Peeters cautioned that Vectibix only works in WT KRAS, not mutant KRAS, "(Second-line) there is no benefit in the mutant population, but no negative effect in the mutants, meaning if you add panitumumab to chemotherapy in mutants, you have no negative effect on the outcomes. If you look to other trials (e.g., oxaliplatin), you see a negative effect on the outcome when you add an EGFR inhibitor…You need to test first. If you want to treat with panitumumab, you need to know (KRAS status)…Your patient has to be tested for KRAS, and then, if and only if your patient is WT, can you go with panitumumab."

MERCK KGAA/LILLY/IMCLONE/ BRISTOL-MYERS SQUIBB's Erbitux (cetuximab)

MRC-COIN trial of Erbitux + chemotherapy in first-line mCRC – no benefit first-line

This 1,630-patient, randomized trial, conducted in the U.K. and Ireland, had two parts, and each part was presented at ECCO/ESMO separately on a different day.

Part 1 – Arm A (continuous) vs. Arm C (intermittent) chemotherapy. Patients in both these arms could get either oxaliplatin/5-FU/folinic acid (OxMdG) Q2W or oxaliplatin/capecitabine (Xelox) Q3W at the option of the physician or patient, but the choice had to be made *before randomization*. As in the Vectibix PRIME trial, the analysis was changed prospectively to focus on KRAS-WT patients. KRAS data were available on 84% of patients.

This part of the trial was aimed at answering the question: In patients with mCRC is it best to give continuous chemotherapy or treat for 12 weeks, break treatment until progression, and then restart the same chemotherapy? What this trial found was that, overall, chemotherapy helps patients with mCRC, but there is a small survival advantage to a continuous strategy, though that comes at a cost of 10 weeks more chemotherapy, which means not only the extra time but more side effects and toxicity. Dr. Richard Adams of the U.K., a COIN investigator, said, "We see an increase from 5% to 18% of severe nerve damage in the hands and feet (peripheral neuropathy). Hand-foot syndrome is also increased (with intermittent therapy), and this is related to the oxaliplatin."

Dr. Adams said this part of the study was "not market-driven …It is about quality of life as much as anything else." He added that these findings mean doctors and patients should discuss the options: "We are left with (the need for) a discussion with patients on the pros and cons, saying to patients, 'At the end of 12 weeks, you have a choice.'"

Part 2 – Arm A (continuous chemotherapy) vs. Arm B (Erbitux). There was no benefit on PFS or survival with the addition of Erbitux to oxaliplatin-based chemotherapy in KRAS-WT patients or in all patients overall, but there was increased toxicity. The primary investigator, Dr. Timothy Maughan of the U.K., said, "PFS was the most surprising. I think none of us would have predicted this…but there was no benefit." Dr. Adams said the findings from this part of COIN suggest that patients with unresectable liver mets might benefit from Erbitux (or Vectibix) first-line, but not most patients.

However, researchers found a "suggestion of benefit" for PFS in patients getting Erbitux + OxMdG and a suggestion of detriment in patients getting chemotherapy including capecitabine (Xelox), and they urged caution in the selection of the chemotherapy to be used with Erbitux in clinical practice. The suggestion was that capecitabine negatively affected the Erbitux results. Dr. Adams said there is a non-significant trend indicating that the OxMdG patients may be the ones who get the benefit from Erbitux in first-line. Dr. Maughan said,

Erbitux Results in MRC-COIN Trial in First-Line mCRC

Measurement	Arm A: Continuous chemotherapy n=8	Arm B: Erbitux n=362	p-value	HR
Baseline				
Number	367	362 patients	---	---
KRAS-WT	57%	54%	---	---
KRAS-mutant	41% *	44% *	---	---
Overall survival				
Primary endpoint: KRAS-WT	17.9 months	17.0 months	Nss, 0.68	1.038
Secondary endpoint #1: KRAS-mutant	14.8 months	13.6 months	Nss, 0.80	0.98
Secondary endpoint #2: "All" wild type KRAS	20.1 months	19.9 months	Nss, 0.86	1.02
Secondary endpoint #3: "Any" mutant KRAS	14.4 months	12.7 months	Nss, 0.96	1.00
Progression-free survival				
Secondary endpoint #4: All patients	8.6 months	8.6 months	Nss, 0.60	0.96
PFS "all wild type"	8.8 months	9.2 months	Nss, 0.36	0.92
PFS "any mutation"	6.6 months	6.3 months	Nss, 0.33	1.08
Responses				
KRAS-WT overall response at 12 weeks	50%	59%	0.015	ORR 1.44
All patients best overall response (CR/PR) at 12 weeks	45%	49%	Nss, 0.124	ORR 1.17
KRAS-mutant overall response at 12 weeks	41%	40%	Nss, 0.877	ORR 0.97
KRAS-mutant overall response at any time	46%	43%	Nss, 0.449	ORR 0.88
Wild type best overall response at any time	57%	64%	0.049	ORR 1.35
All patients best overall response at any time	51%	53%	Nss, 0.428	ORR 1.08
Adverse events in KRAS-WT patients				
Any hematologic Grade 3-4	21%	16%	---	
Any non-hematologic Grade 3-4	62%	77%	<0.001	
Death within 30 days of last treatment	8%	11%	---	
Treatment-related death within 30 days of last treatment	1%	1%	---	
Adverse events in all patients				
Any hematologic Grade 3-4	17%	19%	---	
Any non-hematologic Grade 3-4	57%	74%	<0.001	
More common	---	Nail changes, skin rash, hand-foot syndrome, diarrhea, alopecia, hypomagnesaemia, anorexia	<0.05	
Grade ≥3	---	Hemoglobin, nail changes, diarrhea, skin rash, hand-foot syndrome, hypomagnesaemia, anorexia, stomatitis	<0.05	
Death within 30 days of last treatment	9%	12%	---	
Treatment-related death within 30 days of last treatment	1%	1%	---	

*In the rest the test failed

"We compared these results to other trials…which didn't include panitumumab, which probably should have been included...but there was no favor to Erbitux where no capecitabine was used."

A full analysis of the toxicity, dose delivered, and dose intensity will be presented in the future, perhaps at ASCO GI 2010.

Vectibix vs. Erbitux

Erbitux currently is used more commonly in mCRC than Vectibix, and many oncologists not involved in the Erbitux and Vectibix trials who were questioned at ESMO were dubious that the EGFR inhibitor data at the meeting would lead to significantly increased use of either agent. Vectibix investigators were more optimistic about the outlook for Vectibix use, saying Erbitux has outsold Vectibix because Vectibix is only labeled in most of Europe for single agent use after chemotherapy failure, while the Erbitux label is for use in combination with chemotherapy. However, an Erbitux investigator argued that neither agent generally should be used either first- or second-line but should be reserved for third-line.

Asked how they choose between Vectibix and Erbitux and how they will make that decision post-ESMO, doctors pointed out that there are no head-to-head data on the two agents, but all agreed that efficacy, skin toxicity, and diarrhea are comparable. The advantages cited for Vectibix were: no need for premedication, ease of administration, no immediate allergic reaction, every two-week dosing, and probably cheaper.

Comments included:

- *Dr. Douillard, a Vectibix researcher:* "Panitumumab has no allergic reactions. There have been a few cases of sudden death with Erbitux in patients – especially in the U.S. – with pre-existing allergies. Panitumumab is easier to administer, a fully human antibody, and doesn't require pre-treatment. And it is given Q2W instead of weekly… By restricting panitumumab to KRAS-WT, it is more effective and more cost-effective." Vectibix is a little less expensive in both Europe and the U.S.
- *Dr. Adams, an Erbitux researcher:* He believes that first-line therapy should be oxaliplatin or irinotecan, second-line whichever of these was not used first-line, and then the EGFR inhibitors can be used third-line, "It depends on what you (are used to), the cost, and convenience to patients. What I personally use is Erbitux, but I don't have a hang-up between them, and I think they've shown the same efficacy. I think either could be used. I don't think (the data at ESMO) will change my practice. I think it comes down to cost. They give the same benefit…My personal conclusion is that (both EGFR inhibitors) should stay third-line until we have further evidence about which combination of drugs to use…The majority of patients are getting a benefit from chemotherapy first-line…I would not feel confident in using Vectibix or Erbitux in the first-line metastatic setting because I don't think it would be to the benefit of my patients. It would cause them to have toxicity without benefits. What is important to patients is quality of life, toxicity, and how long they are going to live. It doesn't matter if you use an EGFR at the beginning or the end. Why not bolt it on at the end instead of putting it in the front…In the U.K., the panitumumab and COIN data will not change practice."
- *Dr. Peeters, a Vectibix researcher:* "You can say the efficacy is in the same line (with Vectibix as Erbitux), but there are other points that favor panitumumab: It is given every two weeks, it is very convenient for the patient because there is no premedication. But a head-to-head trial has never been done."

Asked if Erbitux is more potent than Vectibix, Dr. Douillard said, "There is no head-to-head trial…The hazard ratio in the (Erbitux) OPUS trial was 0.65, and in PRIME (with Vectibix) it was 0.80, but the analysis of OPUS was censored at 12 months, and in PRIME we waited until the curves merged at 27 months. If we had calculated HR at 12 months, it would have been the same…The Avastin HR for disease-free survival (DFS) looked fantastic at 6 months, a little less at 12 months, and at 2 years, nothing. So the HR varies with time. If you really want the exact HR, you have to wait long enough for the curve to merge to calculate the difference in the area under the curve (AUC) all along."

Asked if there was anything in the Vectibix data at ESMO that would encourage doctors to switch from Erbitux to Vectibix, Dr. Peeters said, "Besides PFS and OS, we have seen a very high response rate. This is very exceptional. And there is better safety and convenience. So, there is an argument to say there is a place for panitumumab."

Asked how he uses Vectibix himself, Dr. Peeters said, "In Belgium, Vectibix is only registered in monotherapy, so we can't use it (second-line in combination with chemotherapy) outside clinical trials."

Didn't Erbitux have longer PFS in the CRYSTAL trial than Vectibix in PRIME? Dr. Douillard said, "The PFS benefit in CRYSTAL was 2 months, and we have 1.6 months, but the way they (CRYSTAL) calculated PFS was not the same. We included all progressions and all death due to disease, which CRYSTAL did not do. So, we have a more restrictive approach to death."

KRAS Testing

Dr. Douillard estimated that 50%-60% mCRC patients in European community practices currently are being KRAS tested, but he predicted that, based on data at ESMO, this will increase over the next year. Several other oncologists who treat mCRC agreed, and most said it should now be part of the workup when the primary tumor is resected.

A larger percent of mCRC patients get tested in Europe than in the U.S., Dr. Douillard said. A source blamed that on the fact that there is no FDA-approved KRAS test in the U.S. yet.

Dr. Adams said that the trials at ESMO have reinforced the importance of KRAS testing, "It is still an important biomarker for both drugs. The question really comes back to whether you feel these drugs should be used first-, second-, or third-line. If you are not going to use them first- or second-line, there is no point in doing KRAS. But if you are going to use them first- or second-line, then actually you need the biomarker in that stage…Unless you want to downsize liver mets (in a first-line patient), you can wait to KRAS test third-line."

Dr. Adams also wondered if there are biomarkers besides KRAS that may further define who will benefit from EGFR inhibitors like Erbitux and Vectibix, "Does COIN say to us that there are biomarkers we are missing, that KRAS is not enough? Is it saying that EGFR inhibitors…don't have a benefit in first-line and are better in second-, third-, fourth-line where they have a very good record, and the trials agree? That is my leaning at the moment. I think there will be (other) biomarkers. I think going back to this (COIN) data and trying to find biomarkers which identify subgroups will be very useful, and that requires a prospective trial to assess that. For the moment, it puts the drugs (Erbitux and Vectibix) outside the window of the first-line setting."

ASPIRIN

Longer term follow-up has found that 600 mg of aspirin daily ***does*** significantly improve survival in ***some*** CRC patients after all. Dr. John Burn of the U.K. reported on investigator-initiated, long-term follow-up of the patients in the CAPP trial (which found no effect of aspirin in preventing CRC in patients with a gene predisposing them to the disease). When CAPP ended – with 29 months of follow-up – there was absolutely no benefit to aspirin. But at three years after the study ended and aspirin use was discontinued, the investigators found a survival benefit – a 40% reduction in the rate of CRC (HR 0.60). Dr. Burn said, "The effect takes three years to begin, but persists for five years after…I think the reason four or five trials have failed to support (aspirin use in CRC)…was they were too short, when, in fact, the benefits are probably not seen in the general population for 10 years. The trials simply weren't long enough."

Interestingly, aspirin did not work the way the investigators expected. It did not prevent adenomas from forming, but it stopped patients from getting cancer. Dr. Burn said, "This calls into question the idea that the benefit is from prevention of adenoma formation."

Dr. Burn noted that benefits of giving 600 mg of aspirin a day outweigh the side effects, at least in this younger patient (average age 45) population:

- 11 bleeds with aspirin vs. 9 in placebo.
- 3 cardiovascular events with aspirin vs. 8 with placebo.

MELANOMA

ROCHE/PLEXXIKON's PLX-4032 – surprisingly positive results in *metastatic* melanoma

At the American Association for Cancer Research (AACR) meeting in April 2009, researchers said one of the drugs to watch in melanoma is PLX-4032, an ***oral*** RAF inhibitor, and they were right. Results of a Phase I extension study of PLX-4032 were presented at ESMO, and it showed rapid and dramatic shrinking of melanoma tumors and metastases. BRAF is implicated in 50%-60% of melanomas and 5% of CRC. Dr. Paul Chapman of Memorial Sloan-Kettering Cancer Center in New York, the principal investigator, said, "(In these mutations) BRAF is always turned on, leading to an abnormal cellular proliferation, and we think this is what drives the melanoma."

This study was small (31 patients), looking only at patients with the BRAF mutation (not wild type BRAF) who were taking the highest PLX-4032 dose (960 mg BID) in a larger dose-finding study. Most of the patients were stage M1c, which means metastatic disease to distant organs, which has a very poor prognosis.

ESMO officials were excited about the results. Dr. Chris Twelves of the U.K. said, "These are data the likes of which have never been seen in melanoma…This is really unheard of and, if it pans out, will be a once-in-a-generation therapy…It is potentially remarkable data."

The study showed that 70% of patients (19 of 27 evaluable as of August 21, 2009) met the criteria for partial response (tumor shrinkage of ≥30% for at least a month, the RECIST standard). Another six patients also showed a response, but it was too early to determine if they met the RECIST criteria for partial response (PR). Two of the PR patients actually had a complete response (CR). Median PFS has not yet been reached. The overall response rate is 70%, which compares to ~14% that would have been expected with chemotherapy.

Patients responded quickly, often with startling results within 15 days but at least within 8 weeks. In one patient, a rib metastasis not only disappeared, but new bone grew back, something which really surprised investigators.

While PLX-4032 is not a cure, Dr. Chapman called it a "huge step forward." He warned that it is not yet known how long the response to PLX-4032 will last, and some patients have had their cancer progress after initially responding. He said, "This is impressive…A lot of these patients were pretty sick, but many of them had a significant and rapid improvement in the way they function. We've had patients come off oxygen, and we've got several patients who have been able to come off narcotic pain medication soon after starting treatment."

The main side effects so far have been non-melanoma skin cancers, such as squamous cell skin cancer, a less serious, treatable cancer. Dr. Chapman said, "Although these are very

easy to cut out, it is something we are keeping a close eye on." Dr. Twelves warned against thinking that PLX-4032 swapped one cancer (melanoma) for another (squamous cell carcinoma).

About 3% of patients experienced Grade 3 adverse events, mostly fatigue, rash, and photosensitivity, and ~25% of patients had to have the dose reduced or take a drug holiday for 1-3 weeks due to adverse events, but none had to discontinue therapy. Dr. Chapman said, "When people go out in the sun with this drug, especially in the summertime, even fairly trivial exposure can result in significant sunburn."

Going forward, experts agreed that melanoma patients will all have to be tested upfront for BRAF status.

ROCHE's Avastin – fails in melanoma but the story may not be entirely over

Avastin failed to show a benefit on PFS or OS in a Phase II melanoma study. The randomized BEAM trial studied chemotherapy (carboplatin + paclitaxel, CP) ± Avastin in patients with previously untreated advanced melanoma.

Nonetheless, the principal investigator, Dr. Steven O'Day, director of the melanoma program at the Angeles Clinic and Research Institute in Los Angeles CA, called the results "extremely encouraging." He emphasized that there was a consistent trend in favor of a benefit on disease stabilization, tumor shrinkage, and survival – even in patients with the worst prognosis – at ~6 weeks. No new toxicities were observed.

The initial ESMO abstract suggested a survival benefit of a little over 3 months (p=0.04), but Dr. O'Day said that was an immature endpoint, and the plan was to do some follow-up analysis. That was completed the weekend before ESMO started. In that analysis, the 3-month survival benefit didn't change, but it was no longer statistically significant. Dr. O'Day said, "That happens with smaller studies…which is why it is important to follow patients longer term."

Asked where this study leaves Avastin as a therapy for melanoma, Dr. O'Day said, "It is still very encouraging data because all of the efficacy parameters – PFS, OS, response rate, stable disease at 6 months – are consistent in this trial, and there is about a 20% improvement in each of these. It all holds together well. There are strong data that angiogenesis is a pivotal part of melanoma. And we already have data that Avastin in another disease has improved survival. I think melanoma is an excellent prototype disease that is very vascular. These data are very encouraging and will prompt, I hope, a further large, Phase III study." ECCO president Dr. Eggermont, a melanoma expert, said, "Avastin…will probably go to Phase III (in combination with chemotherapy)…The (Avastin study) was relatively small…but the trend doesn't change, and that is the basic message on Avastin…The PLX story is simply spectacular because it is like Gleevec (Novartis, imatinib) in GIST. What is very encouraging is the response rate in non-mutated is zero, so we know exactly what we are doing. It is so specific (in its inhibition) that the side effect data are very encouraging…So, it makes sense that the chances of it panning out are greater."

Will Roche conduct a Phase III trial? That has not been decided, and since Roche now has the rights to the Plexxikon drug, the answer is even cloudier. Dr. O'Day said Roche is in the process of making a decision whether to go ahead with a Phase III trial in melanoma. Other experts at ESMO said they hope – and believe – that Roche will do the Phase III trial.

How do Avastin and PLX-4032 compare? Dr. Chapman said, "We should not expect PLX-4032 to be useful in BRAF-WT (which is 40% of patients) only in mutated patients...I would have predicted Avastin would be equally effective regardless of BRAF status…so you would have at least two options… They haven't been given together, but…if you shrink the tumor too much with PLX-4032, it may not be as sensitive to VEGF inhibition, so you would have to think about that. But there is no reason you couldn't combine them from a toxicity point of view." Dr. Twelves of the U.K. said, "We are talking about control not cure of melanoma, so patients might need one drug first-line, and the other second-line."

Asked if any studies in melanoma have shown an OS or PFS benefit, Dr. Chapman said, "Actually, almost no studies have looked at survival in melanoma. Dacarbazine (DTIC) has never been compared to observation, so we don't know that. DTIC vs. the Dartmouth regimen failed to show a survival benefit of combination chemotherapy vs. DTIC." Dr. Eggermont added, "It is safe to say the last 30 randomized Phase III trials, which ranged from a single-drug to 2-3-4-5-6-drug combinations have all failed to have an impact on overall survival. There were a couple that had an impact on PFS, so PFS in melanoma has not panned out as being a reliable surrogate endpoint. What we have been able to do in those trials is significantly increase toxicity. We are very good at that."

Results of Phase II BEAM Trial of Avastin in Advanced Melanoma

Measurement	CP + Avastin n=143	CP alone n=71	Hazard Ratio	p-value
Primary endpoint: PFS	5.6 months	4.2 months	0.783	Nss, 0.14
OS	12.3 months	9.2 months	0.79	Nss, 0.19
Objective response rate	25.5%	16.4%	---	Nss, 0.1577
Stable disease or better at 6 months	50.4%	37.4%		
Exploratory analyses				
OS in patients with M1c	---	---	0.64	---
OS in patients with M1c and elevated LDH	---	---	0.53	---

NON-SMALL CELL LUNG CANCER (NSCLC)

ROCHE's Tarceva (erlotinib) in NSCLC – effective with no new safety signals

The randomized Phase III SATURN study in chemotherapy-naïve advanced NSCLC patients who had undergone 4 cycles of first-line platinum-based doublet therapy showed a significant 41% improvement with Tarceva vs. placebo in both progression-free survival and overall survival. The PFS and OS results held up for all subgroups evaluated – gender race, type of NSCLC, and smoking history. The results also held up by biomarker status, favoring Tarceva for all measures.

Dr. Federico Cappuzzo of Italy said, "What we observed is that there is a non-specific group of patients driving the survival benefit…which is consistent with the previous trials…There was a huge benefit in EGFR-positive patients, but there was a benefit in all patients. The magnitude of the benefit is lower in patients without EGFR mutations, but we have a benefit regardless in terms of PFS."

Asked how Tarceva compares to:

- **Alimta** (Lilly, pemetrexed) in NSCLC. Dr. Cappuzzo said, "The results in SATURN are quite similar to the results of the Alimta trial, with the important difference that Tarceva is effective in patients with EGFR mutations, even in squamous cell. For Alimta we have no data on EGFR mutation presence."
- **Iressa** (AstraZeneca, gefitinib). Dr. Cappuzzo said, "Iressa is an alternative that we could consider, but there is no reason to give it after Tarceva. It's a choice between the two. There is no reason to give one after the other… But I can't give Iressa without EGFR testing, and I can give Tarceva without EGFR testing. If I can't perform EGFR testing for any reason, I give Tarceva…At the present time, I can test no more than 20% of patients – even if I wanted to test them all – because in ~50% we don't have tissue available. In the remaining ~50%, sometimes the tissue is not enough for additional tests or it is not available."

Results of Phase III SATURN Trial of Tarceva in First-Line NSCLC

Measurement	Tarceva n=437	Placebo n=447	p-value	HR
Co-primary endpoint #1: PFS at 12 weeks	53%	40%	<0.0001	0.71
Co-primary endpoint #2: PFS at 24 weeks	31%	17%		
PFS in EGFR+	---	---	<0.0001	0.10
PFS in EGFR-wild type	---	---	0.0185	0.78
Other results				
OS in all patients	---	---	0.0088	0.81
OS in patients with non-squamous disease	13.7 months	10.5 months	0.0194	0.79
OS in EGFR-wild type	11.3 months	10.2 months	0.0245	0.77
OS in EGFR mutations	Not reached	23.8 months	Nss, 0.6810	0.83
Safety				
Withdrawal due to any adverse event	5%	2%	---	---
Dose modification/ interruption due to an adverse event	16%	3%	---	---
Rash – any grade	60%	9%	---	---
Rash – Grade 3	9%	0	---	---
Diarrhea – any grade	0	4%	---	---
Diarrhea – Grade 3	2%	0	---	---
Quality of life data for Tarceva vs. placebo				
Time to deterioration in quality of life	---	---	0.008	0.96
Time to analgesic use	---	---	0.0199	0.66
Time to pain	---	---	0.0080	0.61
Time to cough	---	---	Nss, 0.2546	0.77
Time to dyspnea	---	---	Nss, 0.2054	0.75

OVARIAN CANCER

EISAI/MORPHOTEK's farletuzumab (MORAb-003) – very early but very promising

Farletuzumab, a humanized monoclonal antibody to folate receptor alpha – when combined with carboplatin and a taxane – appears to stabilize ovarian cancer for an indefinite time. Farletuzumab normalized CA125 (a marker of ovarian cancer) in 88.6% of patients in platinum-sensitive relapse in a 58-patient, Phase II study at 20 sites in the U.S., Germany, and the Netherlands. In 20.5% of patients, the second progression-free interval was as long or longer than the first progression-free interval.

Phase I results were reported at ASCO 2009, and Dr. Deborah Armstrong of Johns Hopkins Kimmel Cancer Center reported on Phase II results at ESMO. In this study, symptomatic patients were treated with their original carboplatin/taxane regimen plus farletuzumab (100 mg/m^2 weekly) for 6 cycles, then responders were put on farletuzumab maintenance therapy. Asymptomatic patients were treated with single agent farletuzumab until progression and then crossed over to the combination arm. On average, the first progression-free interval for these patients was 15.5 months, and all had carboplatin/taxane first-line.

Farletuzumab results included:

- 26 patients entered the combination arm to start.
- 28 patients entered the single agent arm to start. Seven of these discontinued therapy, and the remainder went on to combination therapy on progression. At Week 9, 38.5% had stable disease.

- 2 patients discontinued due to bowel obstruction, and one withdrew consent.
- Median PFS currently is 13.1 months. Of the 44 evaluable patients who got combination therapy at some point, 9 (20.5%) had a second progression-free interval longer than the first. Second progression-free intervals ranged from 11.8 months and still responding to 34.1 months and still responding, compared to a range of first responses of 11.3-26.4 months.
- Farletuzumab shrank or eliminated the tumor in 70% of patients.
- The response data (by RECIST) were available on 43 patients, showing: 7% CR, 63% PR, 23% SD, and 7% progressive disease, for an ORR of 69.8%.
- Grade 3 adverse events occurred in 9 patients: headache as part of infusion reaction, abdominal complaints as part of disease progression, peripheral occlusive disease, bronchitis, herpes zoster, diarrhea, and neutropenia.

The dose used in this study was 100 mg/m^2, except for a few patients with a lower lead in for safety reasons. Dr. Armstrong said, "we could go to 400 mg/m^2 based on the Phase I studies, but pharmacology said 100 is probably sufficient. In the future, we are moving to mg/kg dosing because that seems to provide less swings, and we are going to a lower dose to see if we can get by with an even lower dose."

No receptor saturation studies have been done yet because there hasn't been a reliable assay for the folate receptor, but Morphotek has been working with another company to develop an assay and believes that it is nearly ready.

A Phase III trial is already underway and enrolling patients under a special protocol assessment (SPA) with the FDA. The goal is to enroll 900 patients in 30 countries in North America, South America, Europe, Asia, and Australia. It is an event-driven trial, and the primary endpoint is PFS, which a company official said the FDA insisted on. Overall survival is a secondary endpoint. Results are expected in early 2012.

At ASCO 2009 and again at ESMO researchers reported data questioning the value of basing early treatment on rising CA125 levels alone after finding that strategy did not improve overall survival, median survival, or quality of life. One researcher said, "There is no benefit of routine measurement of CA125 after chemotherapy." This might raise questions about the single agent arm of the farletuzumab study, but Dr. Martin Phillips, the chief medical officer for Morphotek, said the results in the combination only arm of the trial were similar to the overall trial results."

PROSTATE CANCER

U.K. researchers at ESMO were recommending oncologists consider the possible cardiac side effects when they prescribe endocrine therapy for prostate cancer and suggested they might want to refer patients to a cardiologist before starting treatment. Mieke Van Hemelrijck, an epidemiologist from King's College in London, their retrospective study using a Swedish database of ~80,000 men, said, "We estimate that, compared with what is normal in the general population, ~10 extra ischemic heart disease events a year will appear for every 1,000 prostate cancer patients treated with (endocrine therapy)."

Not all types of endocrine therapy appear to carry the same risk. Injections of gonadotropin-releasing hormone (GnRH) agonists, which reduce the production of testosterone from the testicles, appear to pose a greater risk than anti-androgen therapy, which blocks testosterone from attaching to prostate cells but doesn't reduce the amount of circulating testosterone. Van Hemelrijck said, "The hypothesis is that testosterone is protective for the heart, so it could be the risk of anti-androgen therapy is less severe than other therapies because there is still circulating testosterone…However, anti-androgens are sometimes given more to men who are a bit more healthy than the ones who get GnRH…Quality of life is better with anti-androgens, but they are not necessarily quite as effective (in preventing prostate cancer)."

What are the implications of this research? It may simply make doctors more cautious about watching for cardiac signs, but it also could have a dampening effect on the use of GnRHs.

SARCOMA

Hyperthermia – beneficial administered regionally

Evidence is building that ***regional*** hyperthermia is beneficial in causing tumor necrosis. Dr. Rolf Issels of Germany presented data on the use of hyperthermia from a Phase III study of 341 patients with soft tissue sarcomas of the abdomen who were treated in Europe and the U.S. between 1997 and 2006. At 34 months, overall survival was not statistically different with the hyperthermia, but among the 269 patients who completed the full treatment (either four cycles of chemotherapy alone or four chemotherapy cycles plus eight heat treatments), the heat-treated patients had 44% lower mortality.

Dr. Issels used BSD Medical's BSD-2000 3D regional hyperthermia treatment system which heats the tumors to 40-43°C (104-109.4°F) via electromagnetic waves. There are two options:

- A $500,000 desktop on a cart version that is used for superficial tumors such as melanoma. This machine takes about 1 hour per treatment.

- A $1 million, more powerful unit that can treat solid tumors of the pelvic area. This treatment takes about 1.5 hours, including preparation time.

A BSD official said ~20 units currently are operable in the U.S., ~18 in Germany, and ~10 in the rest of Europe. Although many patients have been treated worldwide, the device does not yet have FDA approval. The FDA reportedly wants a more rigorous clinical trial.

Dr. Issels said the heat not only kills cancer cells but also seems to make chemotherapy work better by making cancer cells more sensitive to the chemotherapy, "The patients receiving the targeted heat therapy fared better on all outcome measurements…They were 42% less likely to experience a recurrence of their cancer at the same site or to die than those who were getting chemotherapy alone, survival an estimated 120 months before local progression of their disease, compared with an estimated 75 months (for chemotherapy alone). Similarly, the average length of time that patients remained disease-free was 32 months in the group that got both treatments, compared with 18 months in the group that got chemotherapy alone – an improvement of 30%."

The most frequent side effects of hyperthermia was mild-to-moderate discomfort (45%) and blisters (17.8%). One patient suffered severe burns.

♦