- VOLUME 2 -

IN THE UNITED STATES DISTRICT COURT
IN AND FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION and NOVARTIS AG, Plaintiffs, vs. BRECKENRIDGE PHARMACEUTICALS INC., Defendant.	:	CIVIL ACTION NO. 14-1043 (RGA)
NOVARTIS PHARMACEUTICALS CORPORATION and NOVARTIS AG, Plaintiffs, vs. ROXANE LABORATORIES, INC., Defendant.	:	CIVIL ACTION NO. 14-1196 (RGA)
NOVARTIS PHARMACEUTICALS CORPORATION and NOVARTIS AG, Plaintiffs, vs. PAR PHARMACEUTICAL, INC., Defendant.	:	CIVIL ACTION NO. 14-1289 (RGA)

Wilmington, Delaware
Tuesday, August 30, 2016
8:30 o'clock, a.m.

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BEFORE: HONORABLE RICHARD G. ANDREWS, U.S.D.C.J.

don't know that. There's nothing on that to indicate where it was published, or that it was, in fact, in the European Journal of Cancer.

THE COURT: Mr. Brown, how do you know it was published in the European Journal of Cancer?

MR. BROWN: Well, we provided the citation to them. It has been in the expert reports and everything throughout the case.

The first we heard of the authenticity, other than there was some boilerplate objections across the board, but the first time we heard this articulated was last night.

We already the found the cover page of the document and I think we've got librarians looking for it.

But --

THE COURT: All right. Well, I'm not going to exclude it on the basis of this, so, Ms. Jacobsen, you might as well address it in your -- in the testimony.

I assume Dr. Ratain -- Dr. Ratain's document, I assume he will say, yes, I

know it came from the cancer journal. The cover page is not going to upset me.

All right. Can we give this back to Ms. Jacobsen?

MS. JACOBSEN: Thank you.

So, your Honor, plaintiff's next witness is Dr. Howard A. Burris, III.

Dr. Burris will be providing testimony concerning whether there was a reasonable expectation that everolimus would be a safe and effectivetreatment for Afinitor's renal cell carcinoma and breast cancer indications and objective indicia of nonobviousness. And Dr. Burris will also be responding to issues the defendants' expert, Dr. Ratain, raised in his expert report.

... DR. HOWARD A. BURRIS, III, having been duly sworn as a witness, was examined and testified as follows...

MS. JACOBSEN: Your Honor, may I approach the witness?

THE COURT: Yes.

(Ms. Jacobsen handed binders to

DIRECT EXAMINATION

BY MS. JACOBSEN:

Q. Good morning.

A. Good morning.

Q. Please state your name for the record.

A. My name is Dr. Howard A. Burris, III.

Q. What is your current position, Dr. Burris?

A. My current position is I am the president of clinical operations, the chief medical officer, and the executive director of drug development at the Sarah Cannon Research Institute in Nashville, Tennessee, and I'm also an associate with Tennessee Oncology.

Q. What is the Sarah Cannon Research Institute?

A. The Sarah Cannon Research Institute is a private clinical research organization. We conduct all phases of clinical trials for cancer patients, Phase I through Phase III.

Q. Can you turn to PTX-520 in your

binder, Dr. Burris. It's also on the screen if that would help.

A. Yes.

Q. Do you recognize that document?

A. Yes, I do.

Q. What do you recognize it to be?

A. The document is my curriculum vitae, my CV.

MS. JACOBSEN: Thank you, Dr. Burris.

Plaintiffs move into evidence PTX-520, Dr. Burris' CV.

THE COURT: All right. Admitted without objection.

(PTX-520 was admitted into evidence.)

MS. JACOBSEN: And, your Honor, plaintiffs offer Dr. Burris as an expert in medicinal oncology, including the past and current treatment of renal cell carcinoma and breast cancer, and in the clinical development of anticancer and antitumor agents.

THE COURT: All right. You may proceed.

Q. Dr. Burris, what is renal cell carcinoma?
A. Renal cell carcinoma is the most common form of cancer arising from the kidney.
Q. Can we abbreviate renal cell carcinoma to RCC?
A. Yes, we can.
Q. Thank you.
Is everolimus FDA approved for the treatment of RCC?
A. Yes, it is. Everolimus is approved for adults with advanced RCC after failure of treatment with either sunitinib or sorafenib.
Q. And what is sunitinib and sorafenib?
A. Those are two oral agents that work with different mechanisms of action than everolimus that are used for the treatment of RCC.
Q. Is everolimus also FDA approved for the treatment of breast cancer?
A. Yes, it is. Everolimus is also approved for the treatment of breast cancer in

post-menopausal women. That's hormone receptor positive and HER2 negative. It's approved in combination with exemestane, and after these women have failed therapy with either Anastrazole or Letrozole.
Q. And what are anastrozole, letrozole and exemestane?
A. Those three drugs are each oral agents that work through blocking hormonal pathways that are used for the treatment of patients with hormone receptor positive HER2 negative advanced breast cancer.
Q. Are those therapies considered hormonal therapies?
A. Yes, they are.
MS. JACOBSEN: For the record, Dr. Burris referred to JTX-155 on PDX-5002. That's the Afinitor February 2006 label, and plaintiffs move to introduce this exhibit into evidence.
MR. BROWN: No objection.
THE COURT: All right. Admitted without objection.
(JTX-155 was admitted into

MS. JACOBSEN: I'm sorry. I understand I misspoke and said 2006. It should be 2016.
BY MS. JACOBSEN:
Q. Dr. Burris, is it significant that everolimus is FDA approved in RCC and breast cancer after failure of other therapies?
A. Yes, it is. Patients and their cancers who have been treated with other therapies have more resistant disease, more aggressive disease, and have a greater need for control of their disease, so this is a more difficult group of cancer patients to treat.
Q. Dr. Burris, will you please summarize the conclusions on the validity of the '772 patent that you reached in this case?
A. Yes. Based on the little evidence we had for rapamycin, that there was no reasonable expectation for the clinical efficacy seen with everolimus.
With regard to evidence for nonobviousness, there was a long and unfelt need -- a long-felt and unmet need, I should say, for the treatment of both advanced RCC and

advanced breast cancer.
There were also many others who had tried and failed, attempting to develop therapies for this disease, that there was, these results that we saw for everolimus with the demonstrated effectiveness in RCC and breast cancer was unexpected. That there was widespread industry praise for everolimus' efficacy in these settings, and that there's a clear connection between the clinical efficacy of everolimus and the commercial success that we've seen with Afinitor.
Q. So can I have PDX-5003.
Dr. Burris, does this slide accurately reflect the areas that you'll be testifying on today?
A. Yes, it does.
Q. Thank you.
Now, in reaching these conclusions, what definition of a POSA did you use?
A. I used the definition that a POSA would be a medicinal chemist and that medicinal

with at least several years of experience in treating patients with malignant or benign tumors, or that that POSA, the medicinal chemist would also have access to someone with a Ph.D. in medical oncology or medicinal oncology who had knowledge and expertise in preclinical assays.

Q. As of October 1992, were you a person who would have advised the POSA under this definition?

A. Yes, I would have been.

Q. And can we agree that when we refer to what a POSA would have understood in October 1992, we're including what the medicinal chemist would have learned from somebody who advised them such as yourself?

A. Yes, we can.

Q. Thank you.

So, Dr. Burris, we'll take these opinions out of order and start with the long-felt, unmet medical need in advanced RCC.

As of October 1992, were there any treatments available for advanced RCC?

A. Yes, there were.

Q. And what treatments were available?

A. The treatments that were available in October 1992 included the recently approved drug at that time, a drug known as interleukin-2 or IL-2, and then there was also use of a drug known as interferon alpha.

Q. We'll take those in turn.

Were there any problems associated with IL-2?

A. Yes, there were. The problems with IL-2 could best be described as the difficulties with the toxicity profile of IL-2.

The IL-2 therapy was very toxic and caused severe side effects in the majority of patients. Those side effects actually resulted in a black box warning. That black box warning largely centered on the capillary leak syndrome or fluid overload that these patients would develop that often resulted in admissions to the Intensive Care Unit and frequently resulted in death.

patients who actually benefited from IL-2, and unfortunately, about as many patients benefited from the therapy as actually passed away from complications of the therapy.

An expert summarizes, as shown here, there were severe side effects and only marginal activity.

Q. For the record, Dr. Burris, on PDX-5006 referred to PTX-597, the 1993 PDR for IL-2. PTX-607, Stahl 1992 at page 73. And PTX-618, Wersall 1992 at page 71.

And plaintiffs move to introduce those exhibits into evidence.

MR. BROWN: No objection.

THE COURT: All right. Admitted without objection.

(PDX-597, PDX-607 and PTX-618 were admitted into evidence.)

BY MS. JACOBSEN:

Q. You also mentioned interferon alpha. Were there any problems associated with therapy using that treatment?

A. Yes. Although interferon alpha was not FDA approved, it was a drug that was

known to stimulate the immune system. That was thought to be one mechanism of trying to treat patients with advanced RCC. Only a small set of, subset of patients actually responded to this treatment.

Again, we as clinicians that were treating these patients at the time had difficulty administering the therapy. Patients had significant side effects. They were different side effects than that of IL-2 but were classified more as severe flu-like. These patients had fever, fatigue, headache. And, most importantly, these toxicities actually limited our ability to give the drug at a reasonable dosage.

As experts described at that time, these flulike symptoms were substantial and yet we had an overall a minority of patients that actually benefit from the interferon alpha.

MS. JACOBSEN: For the record, on PDX-5007, Dr. Burris referred to PTX-551, Belldegrun 1992, at page 23. PTX-596, the 1992 PDR for Interferon Alpha, and PTX-607, Stahl

And plaintiffs move to introduce PTX-551 and 596 into evidence.

MR. BROWN: No objection.

THE COURT: All right. Admitted without objection.

(PTX-551 and PTX-596 were admitted into evidence.)

BY MS. JACOBSEN:

Q. Dr. Burris, as of October 1992, was there a recognized need for a safe and effective treatment for patients with advanced RCC?

A. Yes, there was. It was clear at that time that none of the therapies we were delivering offered substantial efficacy for patients, and the toxicity profiles were a problem.

This slide demonstrates some of the conclusions that authors and experts in the field described for the state of treatment of RCC.

Dr. Stahl commented it was unquestionable that none of the available systemic approaches could be recommended as a

standard treatment. There was an urgent need for an effective treatment, and actually, sadly, over the prior 20 years, the prognosis for RCC patients had not substantially changed.

MS. JACOBSEN: For the record, on PDX-5008, Dr. Burris referred to PTX-607, Stahl 1992, at pages 75 to 76 PTX-618, Wersall 1992, at page 71.

BY MS. JACOBSEN:

Q. Was the need that existed limited to drugs that could be used as first line therapies?

A. No. As I've stated, some of the patients were treated, many with both IL-2 and interferon alpha. For those that were able to go on and receive subsequent lines of therapy, there was a large, unmet need. These patients also had growing tumors and more aggressive tumors, so that was clearly an area where we needed new therapies.

Q. So moving on then to your opinions regarding the failure of others, but still in RCC, prior to October 1992, had anyone tried to

A. Yes. Numerous investigators and developers had attempted to find new therapies for advanced RCC. With a little bit of success seen with both IL-2 and interferon alpha, much of the research focused on the immune system. It was felt that the immune system played a critical role in these patients in regulating tumor growth, so we saw a number of immunotherapies in the clinic.

This slide lists several of those. LAK, which stands for lymphocyte activated killers cells; TIL, tumor infiltrating lymphocytes; and TNF, a drug known as tumor necrosis factor were all studied.

As is described here in summary publications, the side effects were severe and life-threatening. There was no evidence for superiority. And we had low response rates with each of these therapies.

MS. JACOBSEN: For the record, on PDX-5010, Dr. Burris referred to PTX-551, the Belldegrun 1992. PTX-605, Skillings 1992 at page 70. PTX-607, Stahl 1992, page 74. And PTX-619, Whiteside 1991.

Plaintiffs move to introduce PTX-605 and 619 into evidence.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

(PTX-605 and PTX-619 were admitted into evidence.)

BY MS. JACOBSEN:

Q. Dr. Burris, had any other therapies been tested by October 1992?

A. Yes. During this time period a number of chemotherapies and hormonal therapies had entered the clinic and been tested in patients.

Dr. Yagoda summarized in a later publication that over 75 chemotherapy and hormonal therapies had been utilized. In summarizing the data for those patients, results were classified as dismal. Only six percent of patients benefiting by having a response or objective tumor shrinkage, and it was clear that advanced RCC showed continued resistance to the available therapies.

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