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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PAR PHARMACEUTICAL, INC.,

Petitioner,

v.

NOVARTIS AG,

Patent Owner.

Case IPR2016-01479
Patent No. 9,006,224

NOVARTIS'S PATENT OWNER OBSERVATIONS ON CROSS-EXAMINATION OF DR. MARK J. RATAIN

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TABLE OF ABBREVIATIONS

Duran	Ex. 1011, Duran, I., *et al.*, "A Phase II Trial Of Temsirolimus In Metastatic Neuroendocrine Carcinomas (NECs)," *J. Clinical Oncology* 23(16S):215S (2005)
Ex. 2111	Transcript of the August 28, 2017 Deposition of Mark J. Ratain
NETs	neuroendocrine tumors
Öberg 2004	Ex. 1027, Öberg, K., "Treatment Of Neuroendocrine Tumours Of The Gastrointestinal Tract," *Oncología* 27(4):185-89 (2004)
PNETs	pancreatic neuroendocrine tumors
POR __	Novartis's Patent Owner Response in *Par Pharm., Inc. v. Novartis AG*, IPR2016-01479, Paper 17 (filed May 11, 2017)
Reply __	Petitioner's Reply in *Par Pharm., Inc. v. Novartis AG*, IPR2016-01479, Paper 21 (filed Aug. 3, 2017)

I. PNETs And Carcinoids Were Evaluated Separately And Tested With Different Experimental Therapies

In Ex. 2111 at 25:9-11, 28:18-25, and 30:8-15, Dr. Ratain admitted that Ex. 2099 evaluated PNET and carcinoid results separately, and Ex. 2049 only enrolled carcinoid patients. This testimony is relevant to Par's assertion that a POSA would reasonably expect everolimus to effectively treat PNETs based on Öberg 2004 and Duran, which relate to NETs, because prior art clinical trials enrolled both PNETs and carcinoids. Reply 4-6. It is relevant because it shows that therapies were not all administered to both PNETs and carcinoids, and as Par admitted, "PNETs and carcinoids may have different specific responses to a treatment," and thus clinical trials typically evaluated them separately. Reply 6; POR 9-10.

In Ex. 2111 at 254:16-255:10 and 256:19-257:8, Dr. Ratain admitted that a POSA would not rely on Ex. 1096's statement about a possible common origin of different tumors, such as PNETs and carcinoids, and that it was not true in 2005 that the tumors listed in Ex. 1096 had similar treatment programs. This testimony is relevant to Par's assertion based on Ex. 1096 that PNETs and carcinoids could be treated similarly (Reply 5) because the testimony contradicts that assertion.

II. There Is No Evidence That Resistance To Second-Line Therapy In Advanced PNETs Would Be Limited To Cytotoxic Chemotherapies

In Ex. 2111 at 49:7-52:18, Dr. Ratain admitted that Exs. 2015 and 2050 disclose clinical trials enrolling patients (11 of 33 and 41 of 43, respectively) with

prior cytotoxic chemotherapy. This testimony is relevant to Par's assertion that molecularly targeted therapies were effective after prior cytotoxic chemotherapy. Reply 11. It is relevant because, in Exs. 2015 and 2050, temsirolimus failed to effectively treat tumors treated with prior cytotoxic chemotherapy. POR 15-16.

In Ex. 2111 at 52:19-55:17, 57:7-14, 59:2-13, 62:25-63:9, 63:20-64:4, and 66:24-67:8, Dr. Ratain admitted that Ex. 1118 discloses a temsirolimus Phase II trial in lymphoma, which was treated differently from PNETs; that Ex. 1078 discloses an EGFR tyrosine kinase inhibitor Phase II trial in squamous cell carcinoma of the head and neck, which was treated differently from PNETs; and that Ex. 1116 discloses dual EGFR and HER2 inhibitor lapatinib studies focused on breast cancer, not PNETs. This testimony is relevant to Par's assertion that molecularly targeted therapies exhibited antitumor activity after prior cytotoxic chemotherapy. Reply 11. It is relevant because there is no evidence supporting a reasonable expectation for everolimus in PNETs and Dr. Ratain further admitted that he did not suggest that a POSA could make reasonable predictions for everolimus based on another compound (sunitinib). Ex. 2111 at 33:17-34:19.

In Ex. 2111 at 101:13-104:7, Dr. Ratain admitted that Exs. 1092 and 1098 do not concern the efficacy of molecularly targeted therapies. This testimony is relevant to Par's assertion that the mechanism of PNET resistance to molecularly targeted therapies would not be the same as for cytotoxic chemotherapies. Reply

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