UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ROXANE LABORATORIES, INC.,

Petitioner,

v.

NOVARTIS AG,

Patent Owner.

Case IPR2016-01461

Patent No. 9,006,224

EXPERT DECLARATION OF DR. MATTHEW H. KULKE

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I. Introduction

1. Challenged claims 1-2 of U.S. Patent No. 9,006,224 ("the '224 Patent") recite methods of using everolimus monotherapy for the treatment of patients with pancreatic neuroendocrine tumors (PNETs) "wherein the tumors are advanced tumors after failure of cytotoxic chemotherapy."

2. At this preliminary stage of these proceedings, I have been asked by counsel for Novartis AG ("Novartis") to provide my opinion on two issues: (1) whether any of the prior art relied on by Dr. Kenneth Ho-Ming Yu teaches or suggests the claim element "advanced [PNETs] **after failure of cytotoxic chemotherapy**"; and (2) whether a person of ordinary skill in the art would have had a reasonable expectation that everolimus would be effective in a method of treating "advanced [PNETs] **after failure of cytotoxic chemotherapy**."

3. As to the first issue, no cited prior art alone or in combination teaches or suggests the claim element "advanced [PNETs] **after failure of cytotoxic chemotherapy**." Dr. Yu relies only on Tabernero for disclosure of the "after failure of cytotoxic chemotherapy" aspect of this claim element. Tabernero describes a single Phase I everolimus clinical trial in patients with "advanced solid tumors," but no patients were reported to have advanced PNETs and Tabernero does not teach or suggest that all patients enrolled in the Phase I study had previously failed to respond to cytotoxic chemotherapy. Because neither

Tabernero nor any other reference cited by Dr. Yu teaches or suggests the use of everolimus for the treatment of "advanced [PNETs] **after failure of cytotoxic chemotherapy**," this claim element is missing from the cited prior art and therefore, the challenged claims of the '224 Patent would not have been obvious.

4. As to the second issue, no cited prior art alone or in combination teaches or suggests the efficacy of everolimus for the treatment of "advanced [PNETs] **after failure of cytotoxic chemotherapy**." A person of ordinary skill would have known that patients with advanced PNETs who had previously failed treatment with cytotoxic chemotherapy would generally have had a more resistant or aggressive disease, and therefore would have been more difficult to treat than patients who had not undergone and failed cytotoxic chemotherapy. Accordingly, a person of ordinary skill would not have had a reasonable expectation that everolimus would be effective for the treatment of "advanced [PNETs] **after failure of cytotoxic chemotherapy**" and therefore, the challenged claims of the '224 Patent would not have been obvious for this additional reason.

5. In forming these opinions, I have considered the materials referenced in this declaration, including the declaration of Dr. Yu. My opinions are based on those materials and my education, knowledge and experience as a practicing physician and as a professor of medicine.

II. Qualifications

6. I am a board certified oncologist and the Director of the Dana-Farber Cancer Institute ("DFCI")/Brigham and Women's Hospital Program in Neuroendocrine and Carcinoid Tumors in Boston, Massachusetts. The Program evaluates and treats approximately 200 new neuroendocrine tumor patients each year. Through this work, I have played a leading role in advancing the understanding of the biology of and identifying treatments for neuroendocrine tumors. I also am a Professor of Medicine at the Harvard Medical School, where I teach postgraduate courses in both general internal medicine and gastrointestinal malignancies.

7. I obtained my B.A. in molecular biology from Princeton University in 1987, my Doctor of Medicine degree from the University of California, San Francisco School of Medicine in 1992, and my Master of Medical Science (M.M.Sc.) degree from Harvard Medical School in 2007. I completed my postdoctoral training, including an internship and residency in internal medicine at Brigham and Women's Hospital and a fellowship in oncology at DFCI. Since 1997, I have served in active teaching roles in the Harvard Medical School community, including regularly leading conferences at DFCI and providing annual lectures on neuroendocrine tumors in the Cancer Medicine and Hematology course

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