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VIA EDGAR AND OVERNIGHT DELIVERY

December 12, 2016

U.S. Securities and Exchange Commission
Division of Corporation Finance
100 F Street, N.E.
Washington, D.C. 20549
Mail Stop 4546
Attn: Jim B. Rosenberg

Re: ZIOPHARM Oncology, Inc.
Form 10-K for the Year Ended December 31, 2015
Filed on February 24, 2016
File No. 001-33038

Dear Mr. Rosenberg:

On behalf of our client ZIOPHARM Oncology, Inc. (the "***Company***"), we are submitting this letter in response to comments received from the staff (the "***Staff***") of the U.S. Securities and Exchange Commission (the "***Commission***") by letter dated November 28, 2016 with respect to the Company's Annual Report on Form 10-K for the year ended December 31, 2015, filed with the Commission on February 24, 2016 (the "***2015 10-K***").

Set forth below are the Company's responses to the comments. The numbering of the paragraphs below corresponds to the numbering of the comments in the letter received from the Staff, which for your convenience we have incorporated into this response letter in italics.

Management Discussion and Analysis of Financial Condition and Results of Operations
Financial Overview
Overview of Results of Operations
Research and Development Expenses, page 61

1. *Please tell us why you do not disclose your externally incurred costs by research and development project consistent with your October 15, 2010 response to comment 3 from our letter dated September 20, 2010.*

   Response: The Company respectfully acknowledges the Staff's comment and advises the Staff that the Company's externally incurred research and development costs relating to identified clinical stage projects decreased significantly in 2015 as compared to prior years, and therefore the Company believed that such disclosure would no longer materially enhance an investor's understanding of the Company's results of operations. For example, the Company's externally incurred costs relating to its multi-center Phase 1 study in patients with glioblastoma or malignant glioma were $810 thousand; externally incurred costs related to the Company's Phase 1/2 melanoma trial were $376 thousand; externally incurred costs related to the Company's Phase 2 breast cancer trial were $253 thousand; and externally incurred costs related to the Company's Phase 2 breast cancer combo trial were $267 thousand.

Notwithstanding the fact that such externally incurred costs have significantly decreased from prior years, the Company proposes to supplement its future disclosure by including a paragraph describing its externally incurred research and development project costs, substantially similar to the disclosure the Company included in response to comment 3 from the Staff's letter dated September 20, 2010, commencing with the Company's Annual Report on Form 10-K for the year ended December 31, 2016 (the "***2016 10-K***").

The Company expects the supplemental disclosure to read substantially as follows:[1]

For the year ended December 31, 2016, our clinical stage projects included a Phase 1 study with Ad-RTS-IL-12 + veledimex in progressive glioblastoma; a Phase 1b/2 study with Ad-RTS-IL-12 + veledimex in metastatic breast cancer; and an investigator-led Phase 1 study infusing our 2nd generation CD19-specific CAR+ T cells in patients with advanced lymphoid malignancies. The expenses incurred by us to third parties for our Phase 1 study with Ad-RTS-IL-12 + veledimex in progressive glioblastoma were $1.0 million for the year ended December 31, 2016, and $1.8 million from the project's inception in June 2015 through December 31, 2016. The expenses incurred by us to third parties for our Phase 1b/2 study with Ad-RTS-IL-12 + veledimex in metastatic breast cancer were $0.2 million for the year ended December 31, 2016, and $0.6 million from the project's inception in April 2015 through December 31, 2016. The expenses incurred by us to third parties for our investigator-led Phase 1 study infusing our 2nd generation CD19-specific CAR+ T cells in patients with advanced lymphoid malignancies were $0.8 million for the year ended December 31, 2016 and from the project's inception in December 2015 through December 31, 2016.

Note to Financial Statements
Note 3: Summary of Significant Accounting Policies
Revenue Recognition from Collaboration Agreements, page F-12

2. *Please tell us your consideration for disclosing how you determine whether collaboration agreements with multiple deliverables can be separated into individual units of accounting. In this regard, we note your discussion of standalone value associated with your Ares Trading Agreement as disclosed in Note 8 on page F-24 but there is no specific reference in your policy disclosure or in any other agreement-specific disclosure.*

[1] Although the Company's financial statements as of and for the year ended December 31, 2016 are not yet available, the following information reflects the Company's results based on currently available information through September 30, 2016. These results are unaudited, represent the Company's estimates, and are for illustrative purposes only. The Company's actual results may differ materially and adversely from those set forth in this letter as a result of various factors, some of which are listed in the "Risk Factors" sections of the Company's SEC filings, including, without limitation, its 2015 10-K.

Response: The Company respectfully acknowledges the Staff's comment and proposes to revise its disclosure regarding its revenue recognition policy, commencing with the 2016 10-K, substantially as set forth in **Exhibit I**.

3. *Please tell us how your policy to recognize milestone consideration upon achievement of the associated milestone complies with the guidance in ASC 605-28-25-1 and 25-2.*

Response: The Company respectfully acknowledges the Staff's comment and advises the Staff that the Company recognizes milestone consideration using the milestone method of revenue recognition in accordance with the requirements of ASC No. 605-28, *Revenue Recognition-Milestone Method* (ASC 605-28). Accordingly, at the inception of an arrangement that includes milestone payments, the Company evaluates whether each milestone is substantive and at risk to both parties on the basis of the contingent nature of the milestone. Pursuant to the guidance in ASC 605-28-25-2, this evaluation includes an assessment of whether: (i) the consideration is commensurate with either the Company's performance to achieve the milestone or the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the Company's performance to achieve the milestone, (ii) the consideration relates solely to past performance and (iii) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. In accordance with ASC 605-28-25-1, revenue from substantive milestone payments is recognized in its entirety in the period in which the milestone is achieved, assuming all other revenue recognition criteria are met. Milestones that are not considered substantive are recognized as revenue over the remaining period of performance, assuming all other revenue recognition criteria are met. Revenue from commercial milestone payments are accounted for as royalties and recorded as revenue upon achievement of the milestone, assuming all other revenue recognition criteria are met as such payments do not qualify as a milestone as defined in ASC 605-28-20.

Commencing with the 2016 10-K, the Company proposes to revise its disclosure regarding its policy for recognizing milestone consideration substantially as set forth in **Exhibit I**.

Note 8: Commitments and Contingencies
License Agreements
Ares Trading License and Collaboration Agreement, page F-23

4. *Please tell us your consideration for disclosing a description and the related contingent consideration for each milestone, a determination of whether each milestone is considered substantive, and the factors considered in determining whether milestones are substantive as required by ASC 605-28-50-2b, 50-2c, and 50-2d, respectively.*

Response: The Company respectfully acknowledges the Staff's comment regarding the disclosure of a description of each individual milestone and its related contingent consideration as required by ASC 605-28-50-2b. The Company has considered which individual milestones, if any, would be material from a disclosure perspective. As a result, the Company has concluded that the aggregation of milestones in its disclosure to be more meaningful to investors than disclosing individual milestones. The Company's current disclosure aggregated all potential development, regulatory and commercial milestone payments under the arrangement totaling $413.0 million and aggregated all potential technical milestone payments under the arrangement totaling $50.0 million.

The Company believes that disclosure of the individual milestones and the related contingent consideration may be misleading to investors because achievement of such milestones is subject to the successful discovery, development and commercialization of product candidates, which is subject to numerous risks and uncertainties, including uncertainties relating to:

- the successful identification, discovery and development of product candidates;
- the progress and results of clinical trials;
- the timing and outcome of regulatory reviews;
- the Company's ability to maintain the strategic alliance and the success of the strategic alliance;
- the emergence of competing technologies and products and other adverse market developments; and
- the Company's ability to maintain, enforce and defend intellectual property-related claims.

These risks and uncertainties make it difficult to predict if any of the milestones will be achieved by the Company and when such milestones might be achieved. In addition, given the contingent nature of milestone payments, many milestones address contingencies the achievement of which is uncertain at this time. Providing a description of each potential milestone and the related contingent consideration could potentially mislead investors as the inclusion of such detailed information may imply that the Company has a substantial likelihood of achieving some or many of such milestones and receiving the related payments, while the actual prospects for achievement of such milestones is inherently uncertain and certain of the milestones may never ultimately be achieved.

Additionally, the Company believes that the individual milestones and payment amounts are not material to investors unless there is a high likelihood of achieving a particular milestone. After review and consideration, the Company has determined that its

prospects for achieving any of the milestones included in the Ares Trading License and Collaboration Agreement are both uncertain and difficult to determine. The Company also believes that the expected timeframe in which a milestone may be achieved is a relevant factor in determining whether disclosure of individual milestones and payment amounts are material to investors. The Company is in the early stages of discovery and development in the collaboration with Ares Trading S.A. ("***Ares Trading***"). Currently, there have not been any product candidate(s) discovered or developed under the collaboration with Ares Trading. Accordingly, a substantial amount of time is anticipated to pass between the up-front payment and any potential milestone payments. For example, the first milestone that could be received occurs upon the initiation of a Phase I clinical trial for a product candidate. Therefore, the Company believes the disclosure of individual milestones that are both highly uncertain and many years from being achieved, if at all, is not material to investors.

For the reasons discussed above, the Company does not consider any of the individual milestones in its arrangement with Ares Trading to be significant. The Company acknowledges that: (i) separate disclosure of the immediately succeeding milestone payment that could be received, (ii) the aggregate milestones by category (i.e., technical, development, regulatory and commercial) and (iii) a description of the nature of the milestones in each category to be more meaningful and useful to investors. Such disclosure places appropriate emphasis on the contingent consideration that will have potential impact to the Company's financial results in the nearer term. As a result, the Company proposes to revise its disclosure in its 2016 10-K substantially as set forth in **Exhibit II** attached hereto to include additional disclosure regarding the next milestone payment that could be received. The Company has also included additional disclosure of the events that trigger achievement of the milestones. By aggregating the remaining potential future milestones into categories of: (i) technical milestones, (ii) development milestones, (iii) regulatory milestones and (iv) commercial milestones, and providing further information with respect to the related milestone triggering events, the Company believes it is providing investors with all material relevant information as well as with an understanding of the possible scope of its collaboration with Ares Trading. Such categorization of milestone payments allows investors to differentiate amounts that are at risk at each development phase prior to regulatory approval from amounts that are at risk as to the successful commercialization of the related product candidate.

The Company respectfully acknowledges the Staff's comment regarding the determination of whether each milestone is considered substantive pursuant to ASC 605-28-50-2c and the factors that were considered in determining whether the milestones are substantive pursuant to ASC 605-28-50-2d, and the Company has proposed revised disclosures regarding its revenue recognition policy and the Ares Trading License and Collaboration Agreement as reflected in **Exhibit I** and **Exhibit II**, commencing with the 2016 10-K.

* * *

Please advise us if we can provide any further information or assistance to facilitate your review. Please direct any questions or further comments regarding this response letter to the undersigned at (617) 937-2316 or Courtney Thorne at (617) 937-2318. Thank you.

Sincerely,

Cooley LLP

/s/ Marc A. Recht

Marc A. Recht

cc: **Kevin G. Lafond,** ***ZIOPHARM Oncology, Inc.***
Caesar J. Belbel, ***ZIOPHARM Oncology, Inc.***
Courtney T. Thorne, ***Cooley LLP***

Exhibit I

The Company proposes the revised disclosure substantially as set forth below for revenue recognition in its 2016 10-K, and will then update this disclosure as appropriate in subsequent filings. The changes from the previously filed disclosure are shown below in bold type. New wording is shown in bold and underline and removed language is shown in bold and strikethrough.

Revenue Recognition from Collaboration Agreements

The Company has primarily generated revenue through collaboration arrangements with strategic partners for the development and commercialization of product candidates. The Company recognizes revenue for each unit of accounting when evidence of an arrangement exists, delivery has occurred or services have been rendered, the seller's price to the buyer is fixed or determinable and collectability is reasonably assured**.**

The Company's collaboration agreements may provide for various types of payments, including upfront payments, funding of research and development, milestone payments, licensing fees and product royalties. The specifics of the Company's significant agreements are detailed in Note 8, Commitments and Contingencies.

The Company considers a variety of factors in determining the appropriate method of accounting for its collaboration agreements, including whether multiple deliverables can be separated and accounted for individually as separate units of accounting. **Pursuant to the guidance in FASB Accounting Standards Codification (ASC) 605-25, *Multiple-Element Arrangements* (ASC 605-25), the Company evaluates multiple-element arrangements to determine whether the individual deliverables represent separate units of accounting or whether they must be accounted for as a combined unit of accounting. This evaluation involves subjective determinations and requires management to make judgments about the individual deliverables and whether such deliverables are separable from the other aspects of the contractual relationship. Deliverables are considered separate units of accounting provided that: (i) the delivered item(s) has value to the customer on a standalone basis and (ii) if the arrangement includes a general right of return relative to the delivered item(s), delivery or performance of the undelivered item(s) is considered probable and substantially in the control of the Company. In assessing whether an item has standalone value, the Company considers factors such as the research, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. In addition, the Company considers whether the collaboration partner can use the other deliverable(s) for their intended purpose without the receipt of the remaining element(s), whether the value of the deliverable is dependent on the undelivered item(s) and whether there are other vendors that can provide the undelivered element(s). The Company's collaboration arrangements do not contain a general right of return relative to the delivered item(s).**

Where there are multiple deliverables within a collaboration agreement that cannot be separated and therefore are combined into a single unit of accounting, revenues are deferred and recognized over the estimated period of performance, which is typically the development term. If the deliverables can be separated, the Company applies the relevant revenue recognition guidance to each individual **unit of accounting** ~~**deliverable**~~. The specific methodology for the recognition of the underlying revenue is determined on a case-by-case basis according to the facts and circumstances applicable to each agreement. Generally, the Company has accounted for its collaboration agreements as a single unit of accounting.

At the inception of an arrangement that includes milestone payments, the Company evaluates whether each milestone is substantive and at risk to both parties on the basis of the contingent nature of the milestone. This evaluation includes an assessment of whether: (i) the consideration is commensurate with either the Company's performance to achieve the milestone or the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the Company's performance to achieve the milestone, (ii) the consideration relates solely to past performance and (iii) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. The Company evaluates factors such as the scientific, clinical, regulatory, commercial and other risks that must be overcome to achieve the respective milestone and the level of effort and investment required to achieve the respective milestone in making this assessment. There is considerable judgement involved in determining whether a milestone satisfies all of the criteria required to conclude that a milestone is substantive. In accordance with FASB ASC 605-28, *Milestone Method* (ASC 605-28), revenue from substantive milestone payments is recognized in its entirety in the period in which the milestone is achieved, assuming all other revenue recognition criteria are met. Payments from milestones that are not considered substantive are ~~**Milestone payments are recognized as revenue upon achievement of the milestone only if (1) the milestone payment is non-refundable, (2) substantive effort is involved in achieving the milestone and (3) the amount of the milestone is reasonable in relation to the effort expended or the risk associated with achievement of the milestone. If any of these conditions are not met, the milestone payment is**~~ deferred and recognized as revenue over the estimated remaining period of performance under the contract as the Company completes its performance obligations**, assuming all other revenue recognition criteria are met. Revenue from commercial milestone payments is accounted for as royalties and recorded as revenue upon achievement of the milestone, assuming all other revenue recognition criteria are met.** Royalties are recognized as earned in accordance with the terms of various research and collaboration agreements.

Exhibit II

The Company proposes the revised disclosure substantially as set forth below for the Ares Trading License and Collaboration Agreement in its 2016 10-K and will then update this disclosure as appropriate in subsequent filings. The changes from the previously filed disclosure are shown below in bold type. New wording is shown in bold and underline and removed language is shown in bold and strikethrough.

Ares Trading License and Collaboration Agreement

On March 27, 2015, the Company and Intrexon signed a worldwide License and Collaboration Agreement, or the Ares Trading Agreement, with Ares Trading S.A. or "Ares Trading", a subsidiary of the biopharmaceutical business of Merck KGaA, Darmstadt, Germany, through which the parties established a collaboration for the research and development and commercialization of certain products for the prophylactic, therapeutic, palliative or diagnostic use for cancer in humans.

Under the collaboration, Ares Trading will elect CAR-T targets, of which two have been selected during 2015, and for which Ares Trading will provide certain research funding. The Company is responsible for certain research and development expenditures. Once these candidates reach investigational new drug (IND) stage, the programs will be transferred to Ares Trading for clinical development and commercialization. The Company expects to perform multiple preclinical development programs, each consisting of the development of one product candidate, pursuant to the agreement. The Company and Intrexon will also independently conduct research and development on other CAR-T candidates, with Ares Trading having the opportunity during clinical development to opt-in.

Intrexon is entitled to receive $5.0 million payable in equal quarterly installments over two years for each identified product candidate, which will be used to fund discovery work. The Company will be responsible for costs exceeding the quarterly installments and all other costs of the preclinical research and development.

Ares Trading paid a non-refundable upfront fee of $115.0 million to Intrexon as consideration for entry into the Ares Trading Agreement. Pursuant to the ECP Amendment, the Company was entitled to receive 50% of the upfront fee, or $57.5 million, which we received from Intrexon in July 2015.

The Ares Trading Agreement provides for up to ~~**$413.0 million of potential payments for certain development and commercial milestones for each product candidate, and**~~ **$60.0 million in development milestone payments, up to $148.0 million in regulatory milestone payments and up to $205.0 million in commercial milestone payments for each product candidate. Development milestone payments are triggered upon initiation of a defined phase of clinical research for a product candidate. Regulatory milestone payments are triggered upon approval to market a product candidate by the U.S. Food and Drug Administration (FDA) or other global regulatory authorities. Commercial milestone**

payments are triggered when an approved pharmaceutical product reaches certain defined levels of net sales by the licensee. The Ares Trading Agreement also provides for up to $50.0 million of **one-time** payments upon the achievement of certain technical milestones **evidenced by the initiation of a defined phase of clinical research. All development, regulatory and technical milestones are considered substantive on the basis of the contingent nature of the milestone, specifically reviewing factors such as the scientific, clinical, regulatory, commercial and other risks that must be overcome to achieve the milestone as well as the level of effort and investment required. Accordingly, such amounts will be recognized as revenue in full in the period in which the associated milestone is achieved, assuming all other revenue recognition criteria are met. All commercial milestones will be accounted for in the same manner as royalties and recorded as revenue upon achievement of the milestone, assuming all other revenue recognition criteria are met. The next potential milestone payment that Intrexon could be entitled to receive under the Ares Trading Agreement is a $15.0 million substantive milestone for the initiation of a Phase I clinical trial. In addition, to the extent any of the product candidates licensed by Ares Trading are commercialized, Intrexon would be entitled to receive** royalties ranging from the lower-single digits to the low-teens of net sales derived from the sale of products developed under agreement. Intrexon will pay 50% of all milestone and royalty payments that it receives under the Ares Trading Agreement to the Company pursuant to the ECP Amendment.

The term of the Ares Trading Agreement commenced in May 2015 and may be terminated by either party in the event of a material breach as defined in the agreement and may be terminated voluntarily by Ares Trading upon 90 days written notice to the Company.

The Company considered FASB Accounting Standards Codification 605-25, *Multiple-Element Arrangements*, in evaluating the appropriate accounting for the Ares Trading Agreement. In accordance with this guidance, the Company identified the license and research and development services as the Company's deliverables in the arrangement. The Company concluded that the license does not have standalone value from the research and development services. Accordingly, the Ares Trading Agreement is accounted for by the Company as a single unit of accounting. The $57.5 million upfront payment received by the Company was recorded as deferred revenue and is being recognized over the estimated period of performance of the research and development services currently estimated to be 9 years, beginning with the commencement of the research and development services. During the twelve months ended December 31, **2016 and** 2015, the Company recognized **$6.4** and $3.2 million**, respectively,** of revenue related to the Ares Trading Agreement. **As of December 31, 2016, the remaining balance of deferred revenue associated with the upfront payment is 47.9 million, of which 6.4 million is current and 41.5 million is classified as long-term. As of December 31, 2015, t**~~T~~he remaining balance of deferred revenue associated with the upfront payment was $54.3 million, of which $6.4 million ~~i~~**wa**s current and $47.9 million ~~i~~**wa**s classified as long term ~~**at December 31, 2015**~~.