



Athenex – Independent Oraxol Review

Independent biotech consultants commissioned to report on Oraxol clinical data of belief Athenex will not receive NDA.



November 13, 2019 – Viceroy commissioned a report from a highly reputable, independent biotech consulting firm into the prospective NDA approval for Oraxol. We have appended the report in its entirety for our readers.

- Consistent with previous expert opinions we have received in relation to Oraxol, this report concludes that **“Oraxol will likely not secure approval following Athenex NDA submission in 1Q 2020.”**
- Experts **refute management claims in Q3 earnings call that “FDA previously provided positive feedback to Athenex that it would accept the results of this one pivotal trial for license application in the U.S. if the primary endpoint is met”**, noting that **there must also be an acceptable benefit/risk profile.**
- Our Experts note that the treatment regimen for the IV Paclitaxel control group is a high-dose, three week regimen. **This regimen has tested as inferior to the low-dose, weekly treatment.** This would have created a much higher threshold for Oraxol’s primary endpoint.
 - It’s noteworthy that oral paclitaxel competitors, such as Daewa Pharmaceutical Co., have not shied away from this low-dose, weekly regimen as a higher threshold control.
- Differing outcomes in safety profile of Oraxol, when compared to IV paclitaxel, **“is likely due to the delivery mechanism and formulation which includes the novel, unapproved PGP inhibitor HM30181A”**. Our consultants believe this may prompt further studies into the Oraxol delivery method, **consistent with our prior reporting about adverse effects.**
- The report **also highlights issues in relation to the rarity of the FDA approving drugs with no USA clinical patient data.** This presents a greater question mark for Athenex, who have already announced plans to commercialize this in the USA.
- Experts have noted Athenex’s absence in providing any detail relating to Oraxol’s adverse effects, in particular those effects which are inconsistent with IV paclitaxel, such as GI complications.
- Viceroy elected to file all our findings to the SEC, FDA and New York Governor due to the highly irregular corporate governance and business practices committed by the company. We note **the company have failed to address or deny one issue, despite repeated requests to identify one single falsity.**

Athenex		
Exchange		NASDAQ
Ticker		ATNX
Shares Outstanding	m	77.3
Share Price	US\$	11.12
Market Cap	US\$m	859.6
Net Cash	US\$m	78.7
NCI	US\$m	11.7
EV	US\$m	769.2
NTA	US\$m	131.6
Licensing Revenue	US\$m	87.2
Revenue Multiple	X	1.0
Viceroy Valuation	US\$m	218.8
Viceroy Price Target	US\$	2.83
Downside	%	-75%
*As at close of market - Oct 28, 2019		
NB: LTM/balance from Jun 30, 2019		

We await Athenex’s San Antonio presentation, which we believe will provide more granular detail.

*Viceroy remain short Athenex and maintain our price target of \$2.83.
Athenex management continue to ignore our reports or address any of the issues we have highlighted.*

GLOSSARY - For ease of reading we have defined several terms that appear in the report.

- NDA – New Drug Application
- IND – Investigational New Drug Application
- GCP – Good Clinical Practice
- ANDA – Abbreviated New Drug Application
- BLA – Biologics License Application
- PGP – P-Glycoprotein
- IV - Intravenous
- HM30181A – the PGP inhibitor in Oraxol, also known as encephalid
- GI – Gastrointestinal
- ORR – Overall Response Rate
- ITT – Intention-To-Treat
- PFS – Progression-Free Survival
- OS – Overall Survival
- mOS – Median Overall Survival
- AE – Adverse Effect(s)



Report 1: <https://viceroyresearch.org/2019/10/22/athenex-too-little-too-late/>

Report 2: <https://viceroyresearch.org/2019/10/23/athenex-where-theres-smoke/>

Report 3: <https://viceroyresearch.org/2019/10/24/athenex-no-integrity/>

Report 4: <https://viceroyresearch.org/2019/10/25/athenex-bonus-round/>

Report 5: <https://viceroyresearch.org/2019/10/28/athenex-rehash/>

Report 6: <https://viceroyresearch.org/2019/10/29/athenex-unpopular-operating-officer/>

Report 7: <https://viceroyresearch.org/2019/11/04/athenex-financial-situation/>

Q3 Brief: <https://viceroyresearch.org/2019/11/07/athenex-2019-q3-financials-brief/>

Other Coverage: <https://seekingalpha.com/instablog/38002746-denniskneale/5369151-cancer-conflicts-interest>

Attention: Whistleblowers

Viceroy encourage any parties with information pertaining to misconduct within Athenex, its affiliates or any other entity to file a report with the appropriate regulatory body. We also understand first-hand the retaliation whistleblowers sometimes face for championing these issues. Where possible, Viceroy is happy act as intermediaries in providing information to regulators and reporting information in the public interest in order to protect the identities of whistleblowers. You can contact the Viceroy team via email on viceroy@viceroyresearch.com.

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Athenex Phase 3 Oraxol in Metastatic Breast Cancer Analysis

1. The data announcement¹ from the latest phase 3 trial for Oraxol in metastatic breast cancer patients appears to support an NDA filing as a head to head replacement for IV paclitaxel based on efficacy alone. The efficacy data that have been presented thus far are fairly straightforward, though it is difficult to fully evaluate the data without seeing graphs or all values, which should be presented at a conference in December of 2019. There are, however, several regulatory, safety and clinical trial design concerns (highlighted below) which lead [REDACTED] [Expert] to believe that Oraxol will likely not secure approval following Athenex NDA submission in 1Q 2020.

2. Regulatory concerns / Clinical trial design

a) FDA communication

- i) It is important to note that Athenex has been in constant communication with the FDA regarding the development of Oraxol in metastatic breast cancer. This is important to note because it means that Athenex did not initiate this trial on its own but rather sought FDA guidance prior to initiating the Phase 3 clinical trial.
- ii) In January of 2018, Athenex received positive feedback from the FDA regarding the design of the Phase 3 study that is in question².
 - (1) The FDA at this time also indicated that " if the study meets the primary endpoint **with an acceptable Benefit/Risk profile**, it could be adequate as a single comparative trial to support registration of Oraxol for a metastatic breast cancer indication in the United States."
 - (a) On a recent earnings call³, Athenex stated that the "FDA previously provided positive feedback to Athenex that it would accept the results of this one pivotal trial for license application in the U.S. if the primary endpoint is met."
 - (b) This is inaccurate as the quote in the previous bullet states that qualifications for approval were primary endpoint as well as "**an acceptable benefit/risk profile**"
 - (2) [REDACTED] notes that approval following this single Phase 3 trial was stated to be dependent upon "successful completion" of the trial. [REDACTED] believes that, in spite of Athenex touting that they met their primary endpoint, there are significant red flags regarding dosing schedule, lack of clarity regarding data, IV paclitaxel efficacy, safety and other factors outlined below that point to the trial ultimately being unsuccessful.
- iii) On the latest quarterly earnings call⁴, Athenex indicated that they had been in communication with the FDA regarding the NDA submission and had targeted a submission 1Q 2020.

b) Location

- i) There are several benefits to running trials in Latin America, none of which necessarily translate to increasing the chance a drug will be approved by the FDA, and often times decrease the chances of a drug being approved.
 - (1) One benefit lies in being able to design your trial in such a way that gives you the best opportunity to come out with a positive result. Standard of care outside of the US, and especially in developing countries, is significantly lower quality than inside the US due to decreased regulations.
 - (a) This is due not only to the lack of availability of new treatments, but also the physician's experience/ability to administer these treatments.
 - (b) Additionally, some cancer drugs would not be able to be evaluated head to head as a monotherapy in the US because standard of care utilizes a combination or sequential approach and recruiting patients who could be helped by combination standard of care to a monotherapy trial would be either unethical or extremely difficult. Whereas, in countries without access to current global standard of care, patients could still benefit from being involved in a monotherapy trial.

¹ Press release. Oraxel phase 3 data. 8/7/19. [Link](#)

² Press release. 01/16/19. [Link](#)

³ Athenex 2Q 2019 earnings call transcript. 8/7/19. [Link](#)

⁴ Athenex 3Q 2019 earnings call transcript. 10/8/19. [Link](#)



- (c) Another benefit to running this trial in Latin America is simply the reduced cost associated with the trial.
 - (d) The cost of clinical trials in Argentina, which had the most clinical trial sites listed for this trial, is estimated to be 48% of the cost for a US based trial⁵.
 - (e) Argentina, Chile, and Columbia, which account for almost half of the clinical trial sites in Athenex's Phase 3 study of Oraxol all provide significant economic incentives for R&D activities performed within their country⁶.
- (2) Trials can progress much more rapidly outside of the US, especially in developing countries as:
- (a) Subjects are more readily available which translates to shorter recruitment periods and ultimately shorter clinical trials.
 - (b) Both patients and investigators are motivated to participate. Patients are motivated by availability of treatment they would otherwise not have access to while providers are motivated by helping patients and compensation.
- ii) Despite the benefits to running clinical trials outside the US, these must be weighed with the drawback of increased scrutiny
- (1) Data from clinical trials entirely conducted outside of the US can be used in support of an NDA filing. Sponsors may choose to conduct a foreign study under an IND but are not required to do so⁷. Foreign studies conducted under IND are required to comply with all applicable regulations of IND supported studies in the US. Studies not conducted under INDs are not subject to must be conducted in accordance with Good Clinical Practice (GCP) and the FDA reserves the right to validate data from the study through onsite inspections⁵.
 - (2) However, the most recent data from 2008 stated that only 0.7% of foreign clinical trial sites were inspected by the FDA⁵, highlighting that this right of the FDA is not often exercised simply due to the abundance of clinical trials and lack of resources and manpower to inspect each site.
 - (3) In spite of the apparent lack of oversight and slightly less stringent regulations for trials conducted outside the US, there appears to be increased scrutiny for these trials when the drug is being considered for approval by the FDA.
 - (a) This would be expected if there were adverse events in these foreign clinical trials, as was the case with the Phase 3 study of Oraxol.
 - (b) Experts in certain diseases have expressed the expectation of the FDA for at least a quarter of the patients enrolled in clinical trials to support a regulatory approval (NDA, ANDA, BLA) be in the US.
 - (i) **Oraxol has been evaluated in zero patients with advanced metastatic breast cancer in the US.**
 - (ii) Among FDA approvals through the first 2/3rds of 2017, only one drug had no patients enrolled in the US (Radicava, Mitsubishi Tanabe Pharma), while two had slightly less than 25% (22% and 20%) and the rest had greater than 25%.
 - (iii) "Companies aren't told they must absolutely meet this threshold (25% of enrolled patients be in US) if they want to get their drugs approved, but they know they can expect a lot more scrutiny of their data if they don't reach it."⁸
- iii) [REDACTED] [Expert] notes that the location of the Phase 3 trial for Oraxol does not necessarily indicate approval or rejection of a regulatory filing, but since Oraxol will have no data from patients within the US when filing with the FDA, there will certainly be increased scrutiny of both efficacy and safety data, which point to the likelihood of rejection based on the reasons outlined below.

⁵ Presentation. FDA perspective on International Clinical Trials. [Link](#)

⁶ Worldwide R&D Incentives Reference Guide. 2018. [Link](#)

⁷ FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions. [Link](#)

⁸ Article. 9/10/17. [Link](#)



c) Formulation

- i) Oraxol is an oral formulation of the tubulin-targeting chemotherapy paclitaxel combined with the P-glycoprotein pump (PGP) inhibitor HM30181A⁹.
 - (1) PGP inhibitors prevent the efflux of various absorbed molecules back into the gastrointestinal tract, which would lead to excretion and decreased bioavailability following oral administration.
- ii) Athenex is targeting a 505(b)(2) approval for Oraxol.
 - (1) 505(b)(2) approval is an abbreviated approval pathway which is used for drugs that are similar to other drugs that have already been approved¹⁰.
 - (2) It is incumbent upon the applicant to provide sufficient evidence to support the comparison between approved drug product(s) and the product being proposed in the application (e.g. through bioavailability studies to show similar drug pharmacokinetics).
 - (3) FDA guidance states¹⁰: "to the extent that the [approved] drug and the drug proposed in the 505(b)(2) application differ, the 505(b)(2) application must include sufficient data to support those differences."
 - (4) **[REDACTED] [Expert] notes that the Oraxol formulation differs from other paclitaxel formulations by the PGP inhibitor HM30181A.**
- iii) Notably, HM30181A is a "novel" PGP inhibitor, which means that it has not been approved by the FDA for any indication.
 - (1) Because HM30181A is not FDA approved, there will likely be more scrutiny of the Phase 3 results, especially with reference to the safety outcomes (outlined below).
 - (2) If there had not been any safety issues, or if the safety profile of Oraxol was the same as IV paclitaxel, this novel formulation may have been able to achieve approval based on the FDA's positive feedback prior to the commencement of the trial.
 - (3) However, Athenex press release outlining their topline data revealed that there were **GI adverse events (which do not occur with IV paclitaxel** and have been shown with other PGP inhibitors) and an increase in neutropenia and infection associated with Oraxol.
 - (4) **[REDACTED] [Expert] notes that the disparate safety profile of Oraxol is likely due to the delivery mechanism and formulation which includes the novel, unapproved PGP inhibitor HM30181A. The differing safety outcomes may prompt the FDA to require further studies to understand the relationship between HM30181A and the observed adverse events. The FDA may require a second confirmatory Phase 3 trial or potentially, though less likely, require evaluation of HM30181A in healthy volunteers to determine the contribution of this unapproved molecule to the GI events, neutropenia and infection.**

⁹ Press release. 7/22/2013. [Link](#)

¹⁰ Determining Whether to Submit an ANDA or a 505(b)(2) Application: Guidance for Industry. FDA. 5/2019. [Link](#)



3. Efficacy data

- a) There is nothing out of the ordinary with this preliminary release of data as this is simply a comparison of two different arms with no subpopulation analysis shown yet.
- b) One thing that is potentially odd is the ORR of control IV paclitaxel as it seems a bit low. This may be due to two reasons:
 - i) There has been a wide range of IV paclitaxel monotherapy ORRs in the literature (25%-78%. See Table at end noting some examples). A study in 2005, with the same dosing regimen used in the Oraxol phase 3 study, found similar ORR for IV paclitaxel. This indicates that there may be other factors which effect the ORR of paclitaxel monotherapy and could explain the fairly low ORR for IV paclitaxel in this Oraxol study population as well as the wide range noted in other studies.
 - (1) Of note, the highest ORR recorded for IV paclitaxel (78%) resulted from using a weekly, high-dose treatment regimen, which resulted in serious toxicities requiring dose modification, so that study probably isn't a good comparison for the Oraxol study¹¹.
 - (2) Additionally, the study with the next highest ORR (71%) evaluated the efficacy of weekly low-dose paclitaxel compared to standard high-dose every three weeks¹². The weekly, low-dose from this study may be a better comparison for the 3 day QW dosing regimen of the Oraxol group. However, the standard every three weeks IV paclitaxel group from this study only showed an ORR of 35%, which is closer to the 24% from the IV paclitaxel in the Oraxol study.
 - ii) The second thing which could lower the ORR slightly is the inclusion of non-evaluable patients in their presented ORR. If you remove the non-evaluable patients for analysis, this will increase the ORR as there will be the same number of responses with a slightly smaller population. This appears to be the case for two reasons:
 - (1) They state that their analysis of ORR is based on ITT analysis, which includes all subjects randomized to the arm, regardless of their compliance, withdrawal, or anything else that happens after randomization which would eventually affect an accurate assessment of efficacy in that individual.
 - (2) They state later that they also did "analyses on populations excluding non-evaluable patients (which would give higher response rates)" which apparently also showed statistically significant differences. It is strange that they do not disclose these analyses at this time if they are also statistically significant. Perhaps, though the two groups are statistically different from each other, the difference between the absolute values of the ORR is not as striking as the ITT analysis.
 - (3) The exclusion of non-evaluable patients will likely not drastically increase ORR. Most likely, the ORR will increase by 1-4% in each arm, barring a large number of non-evaluable patients for each arm.
- c) It is difficult to make any inference on the PFS or OS as this time as we are unable to see any graphs of the data.
- d) Additionally, PFS and OS data may not be available in December when Athenex is planning to present a full topline dataset. Athenex said in their recent quarterly earnings call that they were waiting to hear back from the FDA to provide guidance regarding defining a new PFS and OS cut-off for regulatory submission.
 - i) **[REDACTED] [Expert] notes that the initial feedback from the FDA prior to the start of the trial indicated that likelihood of approval was based on primary endpoint (ORR) and acceptable benefit/risk profile rather than the secondary endpoints of PFS and OS. This indicates that even if there is no statistically significant benefit for PFS and OS (which could be the case based on Athenex stating that they are seeing a "strong trend"), these data shouldn't impact the decision by the FDA. It appears that only if Oraxol had a negative impact on PFS and OS, which [REDACTED] [Expert] does not expect to be the case, would these data influence the FDA.**

¹¹ Sikov, W. *et al.* Weekly high-dose paclitaxel (P) demonstrates significant activity in advanced breast cancer (BC). *Proc Am Soc Clin Oncol.* 1998. [Link to review that cites this paper](#)

¹² Halim, I. *et al.* Weekly paclitaxel versus standard 3-week schedule in patients with metastatic breast cancer. *J Clin Oncol.* 2011. [Link](#)



5. Safety data

- a) The lower incidence of neuropathy in the Oraxol group is impressive and is certainly one of the main advantages to the Oraxol formulation as dose limiting neuropathy is a serious side effect of paclitaxel.
- b) It is interesting that Athenex doesn't provide values for the neutropenia or gastro-intestinal side effects.
 - i) On their 2Q19 earnings call they describe the increase in grade 4 neutropenia and infection as "slight". Full data from this trial will not be released until later in 2019 at a breast cancer symposium in San Antonio on Dec 13th.
 - ii) They also did not provide any more indication regarding the gastro-intestinal side effects as they repeated what was said in the press release stating there were "more" in the oral paclitaxel group. **The fact that they don't use any other descriptors for the GI side effects, and their lack of comment on the earnings call seems to indicate that there may be significantly more GI AEs.**
 - iii) Also, there is no mention of the grade of the GI AEs which points to potential for yet undisclosed severe (grade 3/4) GI side effects associated with Oraxol, which are most likely not associated with HM30181A rather than the paclitaxel part of Oraxol.

6. Treatment regimen

- a) The use of paclitaxel monotherapy in this trial is a viable clinical regimen for the following reasons:
 - i) The FDA reviewed their trial design, provided positive feedback and indicated that if the study meets the primary endpoint with an acceptable Benefit/Risk profile, it could be adequate as a single comparative trial to support registration of Oraxol for a metastatic breast cancer indication in the United States.
 - ii) The 2017 National Comprehensive Cancer Network (NCCN): Breast Cancer Guidelines stated that paclitaxel monotherapy was still a "preferred single agent" therapeutic modality in recurrent or metastatic breast cancer¹³. However, there are many other single agents and chemotherapy combinations which are also used. There is also delineation between localized breast cancer and metastatic breast cancer and the suggested therapy regimens differ between the two groups. While AC-T (doxorubicin/cyclophosphamide followed by paclitaxel) is a preferred treatment regimen for localized HER2+/- breast cancer, it is not listed by NCCN as a preferred regimen for metastatic breast cancer. Also, NCCN does not list paclitaxel monotherapy as a treatment for localized breast cancer, which means that metastatic breast cancer is the correct population to test oral vs IV paclitaxel monotherapy.
 - iii) The FDA injection label supports the use of paclitaxel as both an adjuvant (node positive breast cancer^{14,15}) and as a monotherapy (relapsed or metastatic breast cancer after failure of combination chemotherapy)¹⁶. This points to the current viability of paclitaxel monotherapy in the clinic.
 - iv) Paclitaxel is also listed as a single agent chemotherapy for metastatic breast cancer on UpToDate in their entry entitled "Systemic treatment of metastatic breast cancer in women: Chemotherapy" updated on May 16, 2019.
 - v) Other studies also use paclitaxel monotherapy as both a control and a treatment arm
 - (1) Daehwa Pharmaceutical Co. is also developing an oral paclitaxel formulation (LipOraxol® solution) for the treatment of metastatic breast cancer.
 - (2) They are doing a monotherapy Phase 2/3¹⁷ in South Korea with IV monotherapy paclitaxel for their control.

¹³ Rajappa, S. *et al.* Novel formulations of docetaxel, paclitaxel and doxorubicin in the management of metastatic breast cancer. *Oncol Lett.* 2018. [Link](#)

¹⁴ Henderson, C. *et al.* Improved Outcomes From Adding Sequential Paclitaxel but Not From Escalating Doxorubicin Dose in an Adjuvant Chemotherapy Regimen for Patients With Node-Positive Primary Breast Cancer. *J Clin Oncol.* 2003. [Link](#)

¹⁵ Mamounas, E. *et al.* Paclitaxel After Doxorubicin Plus Cyclophosphamide As Adjuvant Chemotherapy for Node-Positive Breast Cancer: Results From NSABP B-28. *J Clin Oncol.* 2005. [Link](#)

¹⁶ Taxol injection label. pg 20. [Link](#)

¹⁷ CT.gov. [Link](#)



- b) It is strange that they chose the high-dose, three-week regimen rather than the low-dose, weekly regimen for paclitaxel, as that would have been a better comparison for 3x weekly oral paclitaxel.
- The low-dose, weekly regimen has been shown to improve overall survival compared with the high-dose, three-week schedule with a hazard ratio of 0.78¹⁸.
 - [REDACTED] [Expert] notes that Athenex likely chose the high-dose, three-week regimen of IV paclitaxel as their comparison arm due to the decreased efficacy compared to the weekly regimen. This selection gave Oraxol the best chance of showing significantly better efficacy than IV paclitaxel.**

7. Application

- a) Oraxol does seem to have potential to become a preferred method of administration of paclitaxel in some settings:
- As a monotherapy for the indication on the injection label (relapsed or metastatic breast cancer)
 - As an adjuvant in sequential treatment regimens (e.g. AC-T) as oral administration will be more convenient for the patient.
 - Again, combination chemotherapy has not been shown to improved OS as compared to sequential administration of single agents.
 - As a monotherapy for individuals with already induced neuropathy in most treatment regimens as Oraxol appears to have reduced neuropathy.
 - However, it looks like there is some potential for trading neuropathy for GI side effects.** This may require a decision regarding which is more tolerable for the patient in the above applications.

8. Comparison to Abraxane (Nab-paclitaxel)

- a) Due to the hydrophobicity of paclitaxel, initial IV formulation preparations required solvents which resulted in serious hypersensitivity reactions¹⁹.
- To combat these reactions, premedication with corticosteroids and antihistamines are often given to the patient prior to infusion²⁰.
- b) Abraxane is an albumin-bound formulation of paclitaxel which takes advantage of albumin's ability to transport hydrophobic molecules within the body¹⁹.
- This formulation does not require the use of toxic solvents, which eliminates the need for steroids or antihistamines prior to infusion.
- c) A large (n=454) phase 3 trial from 2001 comparing IV Abraxane (260 mg/m²) to IV paclitaxel (175 mg/m²) in metastatic breast cancer showed that, Abraxane monotherapy had an ORR of 33% compared to 19% for paclitaxel monotherapy, though there was no difference in the OS between the two groups^{21,22}.
- Importantly, there were significantly lower grade 4 neutropenia toxicities in the Abraxane treated group compared to the IV paclitaxel group (10% vs 21%).
 - Though there was significantly increased grade 3 neuropathy in the Abraxane group compared to IV paclitaxel (10% to 2%), this was easily managed by the attending physicians.
 - This pivotal study showed that Abraxane administration was more effective against metastatic breast cancer and was accompanied by fewer side effects compared to IV paclitaxel.**

¹⁸ Mauri, D. *et al.* Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: A meta-analysis. *Cancer Treat Rev.* 2010. [Link](#)

¹⁹ Miele, E. *et al.* Albumin-bound formulation of paclitaxel (Abraxane® ABI-007) in the treatment of breast cancer. *Int J Nanomedicine.* 2009. [Link](#)

²⁰ Berger, M. *et al.* Stopping paclitaxel premedication after two doses in patients not experiencing a previous infusion hypersensitivity reaction. *Support Care Cancer.* 2015. [Link](#)

²¹ CT.gov. [Link](#)

²² Gradishar, W. Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel Compared With Polyethylated Castor Oil-Based Paclitaxel in Women With Breast Cancer. *J Clin Oncol.* 2005. [Link](#)



- d) However, a more recent study has shown that there IV paclitaxel may actually be slightly more efficacious (though not statistically significant) when combined with bevacizumab²³.
- This is not a perfect comparison as this study used paclitaxel in combination, though this study does indicate that Abraxane is likely not superior to paclitaxel and is actually associated with higher rates of grade 3+ toxicity including neuropathy and hematologic toxicity.
- e) Another recent combination study evaluated IV paclitaxel to IV Abraxane (each followed by epirubicin and cyclophosphamide) in 1,206 patients with primary breast cancer²⁴
- This study showed a slight significant increase in disease free survival of Abraxane compared to paclitaxel.
 - However, this large Phase 3 study did not show any difference in overall survival between the two groups.
- f) Abraxane also recently showed a lower ORR of 22%, an mOS of 10.4mo and an PFS of 6.8mo in a 90 patient retrospective study in metastatic breast cancer²⁵
- g) **[REDACTED] [Expert] notes that numerous trials comparing IV Abraxane vs IV paclitaxel in breast cancer have yielded somewhat inconclusive results. Overall, Abraxane efficacy appears to be at least not inferior to IV paclitaxel with a comparable, or slightly improved, safety profile (reduced grade 4 neutropenia in the pivotal study). Some have highlighted the improved disease-free survival of Abraxane compared to IV paclitaxel when used in combination chemotherapy regimens as an indication that perhaps Abraxane should be considered for standard of care in these patients²⁶. This would indicate that perhaps Athenex should have used Abraxane as their control treatment regimen; however, it is important to remember that the FDA provided positive feedback regarding the design of their Phase 3 trial, so they apparently considered IV paclitaxel as a suitable control treatment.**
- h) Athenex states on their 3Q 2019 earnings call that they have positive feedback on "pricing similar to the original Abraxane pricing."²⁷
- In addition to the efficacy and safety comparability, because Abraxane does not require pre-medication with corticosteroids or antihistamines, it represents an attractive alternative to the original IV paclitaxel formulation.
 - In spite of the apparent contradictory results outlined above, Abraxane is often prescribed in an effort to prevent neuropathy and numbness associated with paclitaxel²⁸.
 - This "improved safety profile" has led to significantly increased pricing for Abraxane compared to standard paclitaxel.
 - Original Abraxane pricing (\$4,200/dose) when it was first approved in 2005 was 25x more than generic paclitaxel²⁹.
 - Sources have stated that Abraxane pricing has risen to as high as \$10,000/dose in 2015²⁸.
 - Celgene reported sales of Abraxane totaling \$1.06B in 2018³⁰
- i) **[REDACTED] [Expert] believes that pricing of Abraxane is a good comparable for an approved Oraxol product as neither product requires premedication with corticosteroids or antihistamines due to their lack of inducing hypersensitivity reactions. Additionally, Oraxol does offer the added benefit of not requiring IV administration, albeit with additional safety issues. If approved, it appears likely that Oraxol could achieve similar pricing to the premium placed on Abraxane, though it is difficult to know if insurance companies would require generic paclitaxel first.**

²³ Rugo, H. *et al.* Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance). *J Clin Oncol.* 2015. [Link](#)

²⁴ Press release. 3/6/2019. [Link](#)

²⁵ De Luca, R. *et al.* Nab-paclitaxel in pretreated metastatic breast cancer: evaluation of activity, safety, and quality of life. *Onco Targets Ther.* 2019. [Link](#)

²⁶ Ross, M. *et al.* Nab-Paclitaxel: A New Standard of Care in Neoadjuvant Therapy of High-Risk Early Breast Cancer?. *ASCO.* 2019. [Link](#)

²⁷ Athenex 3Q 2019 earnings call transcript. 11/8/19. [Link](#)

²⁸ Article. U.S. cancer doctors drop pricey drugs with little or no effect. 10/8/15. [Link](#)

²⁹ Article. Hope, at \$4,200 a Dose. 10/1/06. [Link](#)

³⁰ Press release. Celgene 2018 earnings. 1/31/19. [Link](#)



Table: Various studies examining the efficacy and safety of single-agent paclitaxel in metastatic breast cancer.

Formulation (Source)	Therapy Regimen	Dose	N	OS (mo)	PFS (mo)	ORR (%)	Neuropathy (All)	Neuropathy (Grade 3+)	Year
Oraxol (Link)	Mono	205mg/m ² 3x/wk	265	NS	NS	36.0%	17.0%	1.0%	2019
IV paclitaxel (Link)	Mono	175mg/m ² / 3wks	137	NS	NS	24.0%	57.0%	8.0%	2019
IV paclitaxel (Link)	Mono	175mg/m ² / 3wks	224	12.7	3.6	25.0%			2005
IV paclitaxel (Link)	Mono	175mg/m ² / 3wks	242	22.5		34.0%			2002
IV paclitaxel (Link)	Mono	175mg/m ² / 3wks	70	20	10.5	35.5%	42.0%		2011
IV paclitaxel (Link)	Mono	80mg/m ² / wk	70	28	18.5	71.6%	14.0%		2011

[END]