**On the Impossible:**

Why Cardiff Oncology’s onvansertib will fail Phase 2 clinical trials and the stock will trade to $1

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**Executive Summary**

In this work, I will prove that the onvansertib Phase II trial will fail to meet its primary endpoint.

**Introduction**

Med

**History of Onvansertib**

Originally developed by Nerviano Medical Sciences in 2011 (Beria I, 2011)? And licensed by Trovagene (now Cardiff Oncology) in 2017 according to prospectus. Originally developed for Leukemia. Cardiff Oncology did multiple trials in mCRC, Leukemia, and Prostate Cancer.

NMS-P937 -> NMS-1286937 -> PCM-075 -> onvansertib

**Mechanism of Action**

(Smith, 2017).

PLK1 inhibitor ATP competitive (Weiss GJ, 2017) to bind to PLK1 instead of ATP and inducing mitotic arrest and apoptosis at certain thresholds of concentration, however very toxic at high doses and induces thrombocytopenia through apoptosis bone marrow.

KRAS-mut cells are more sensitive to PLK1 inhibition (Ahn, 2024). Phase Ib

A graph of different types of data

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The data suggests PLK1 inhibition to be effective in KRAS-mut cells. However, the high toxicity seen and in-human trial’s failures achieve significance seems to show that the doses at which the drug is effective are too toxic. 37.5% ORR n=7? or 16; PFS and DOR not S.S.

A diagram of cancer cells

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Fabricated explanation for why a bev-exposed tumor would be resistant to onvansertib

Failure of another PLK1 inhibitor BI-2536 in pancreatic cancer (Mross, 2012).

**Preclinical**

Preclinical data showed F=0.23 or 23% bioavailability and significant anti-tumor growth in the 7g compound (60mg/kg). The toxic dose was 17mg/kg^2 and the ones used in the Phase II trials are 15mg/kg^2. In an average human if we use allometric scaling 60kg 1.62m^2 we find a 0.41mg/kg dosing. (Beria I, 2011) Inhibits the hypoxia pathway and shows antitumor activity through angiogenesis. (Ahn DH, 2025)

**A graph of a patient's body

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**Clinical Trials**

**Phase I n=21 NCT01014429**

Before Cardiff bought? the drug from Nerviano Medical Sciences hence the compound name (NMS-P937/ NMS-1286937) they ran a Phase I in 2011 to determine the PK/PD and the MTD and DLTS (Weiss GJ, 2017). This Phase I led to the subsequent discontinuation of development by Nerviano and acquisition by now known as Cardiff.

Open Label metastatic solid tumors first-in-human trial. PLK1 inhibitors are highly sensitive to thrombocytopenia TEAEs and bone marrow. (Weiss GJ, 2017) MTD and RP2D at 24mg/m^2/day. “PLK inhibitors to induce mitotic cell cycle in rapidly proliferating blood cells and have also been observed with BI-2536 and volasertib”

Biomarkers in both pThr199 and pHH3 were not statistically increased, n=2 24mg/m^2 and 36 mg/m^2, and concentrations were below the threshold expected to modulate biomarkers in tumor and skin tissue based on preclinical studies. (Weiss GJ, 2017) Nerviano Medical Sciences.

“In the present study with NMS-1286937, disease stabilization was observed as the best response in 5 out of the 16 evaluable patients (26.3%), while no objective responses were observed.” “3 out of 5 instances of stable disease in our study were observed in patients with KRAS mutant tumors” (Weiss GJ, 2017)

**Phase Ib n=**

Leukemia P.E failed (Zeidan AM, 2020)

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**Phase Ib/II n=**

Acute myeloid leukemia P.E failed (Croucher PJP, 2023) Was expected due to the failure of Volasertib (same MOA) also in acute myeloid leukemia with a 25% ORR p=0.071 OS p=0.757 (Dohner, 2021).

Claimed that because all patients with CR or Cri hadn’t previously been treated with an HMA that could be the group that its effective in. 27% ORR (Croucher PJP, 2023).

**Phase Ib n=23 NCT05593328**

In RAS-mut mCRC (Ahn DH, 2024)

**Phase II n=72 NCT03414034**

In mCRPC Failed P.E

**Phase II n=68 NCT03829410**

1L ORR in NCT03829410 = 10%; 2L = 77%; Even if the drug were to show a response in 2L (bev naiive) patients the population ~9,500 as per press release, it wouldn’t be worth the funding required for further research and Pfizer? would stop working with them ~80m in cash probably down to <60m by now is not enough for further trials and requires heavy dilution or ---. In the overall population however, Failed P.E of ORR>30% ORR was 26.4% n=53 DOR not S.S. Used post-hoc analysis (n=4; wide SD; according to my t-test calculations p=0.8 in entire subgroup, p=0.1 in 30mg, 20mg even worse) to say Bev naïve patients responded better (they should respond better anyways?) Grade ¾ AE in 62%. (Ahn, 2025) In clinical studies you have equal populations in this case of Bev-exposed and Bev-naiive due to the better responses to bev seen in bev-naiive patients so it doesn’t affect the outcome of the trial but I hypothesize that comparing bev naiive to bev naiive populations they will have a higher ORR in both control and active arms but wont be a significant difference.

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Patients not previously exposed to bev are shown to have a better response than bev-exposed and this post-hoc analysis seems uncorrelated to the MOA of PLK1 and how it would be more effective in a bev-naiive only population the ORR of SoC vs SoC+onvansertib should be not a significant difference.

**Phase II n=113 NCT06106308**

**Condition 1**: Bev-naïve patients were responding better due to onvansertib and not because they will naturally respond better to the SoC (bev) anyways even though the n=4 post-hoc wasn’t S.S. The previous failure in whole population of RAS-mut mCRC can be thrown out and previous failures of PLK1 can be thrown out. Probability at most 10%

**Condition 2**: Even though the biomarker data showed no significant effect on PLK1 inhibition through mitosis (the main mechanism of apoptosis of tumors) and the PK showed limited exposure it is still enough to significantly increase the ORR. Probability at most 25%

**Condition 3**:

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Previous drug that tried to claim bev naiive subgroup?

Interim data press release - <https://investors.cardiffoncology.com/news-releases/news-release-details/cardiff-oncology-announces-positive-initial-data-first-line-ras>

In the FORWARD study for paclitaxel, they found Bev-naiive patients with a 59% ORR compared to 35% in BEV pretreated (Husam, 2025); comparatively in the onvansertib study ORR was 77% for bev naiive and 10% for BEV-exposed showing a clear distinction between patients response to bev being a lot higher in naiive than pretreated. So is onvansertib driving some or none of the ORR? It seems likely from previous trials and PK that bev is driving most if not all of the ORR at least enough that it would not achieve significance comparing control to onvansertib.

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