Montreal, January 21st 2019

Dear Cancer Research editors,

I am writing to you regarding the paper recently published in Cancer Research by Alexander *et al*. (*Cancer Res. 2018 Dec 15;78(24):6838-6851*): http://cancerres.aacrjournals.org/content/78/24/6838.long

I am concerned that the abstract of the paper contains potentially misleading and unethical statements. Also, because this paper is currently being aggressively promoted in Canada as part of a lobbying effort to get the government to authorize high-dose vitamin C injections in patients undergoing chemotherapy, I believe that the abstract in its current form may contribute to misguided decisions by non-scientific entities.

My main concern is the following passage in the abstract:

> *We also report on our first-in-human phase I trial that infused P-AscH- during the radiotherapy "beam on." Specifically, treatment with P-AscH- increased median overall survival compared with our institutional average (21.7 vs. 12.7 months, P = 0.08) and the E4201 trial (21.7 vs. 11.1 months). Progression-free survival in P-AscH--treated subjects was also greater than our institutional average (13.7 vs. 4.6 months, P < 0.05) and the E4201 trial (6.0 months). Results indicated that P-AscH- in combination with gemcitabine and radiotherapy for locally advanced pancreatic adenocarcinoma is safe and well tolerated with suggestions of efficacy.*

The rationale for my concerns is as follows:

1. Phase I trials are not designed to support efficacy claims; https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm

2. The authors explicitly state in the paper:

    a. *"Although the trial was not prospectively powered to determine differences in survival (…)";* and
    b. *"(…) this phase I trial was not powered to make any conclusive statements regarding the efficacy (…)"*.

Also, the last sentence of the abstract may also be misleading:

> *"(…) making it an optimal agent for improving treatment of locally advanced pancreatic adenocarcinoma"*

Which, again, is an efficacy claim, and a bold one.

Based on this, I believe that the abstract should not contain any statements about efficacy. Therefore, I am respectfully asking if the journal would consider revising the abstract.

A revised version could be as follows:

> *Chemoradiation therapy is the mainstay for treatment of locally advanced, borderline resectable pancreatic cancer. Pharmacologic ascorbate (P-AscH-, i.e., intravenous infusions of ascorbic acid, vitamin C), but not oral ascorbate, produces high plasma concentrations capable of selective cytotoxicity to tumor cells. In doses achievable in humans, P-AscH- decreases the viability and proliferative capacity of pancreatic cancer via a hydrogen peroxide (H2O2)-mediated mechanism. In this study, we demonstrate that P-AscH- radiosensitizes pancreatic cancer cells but inhibits radiation-induced damage to normal cells. Specifically, radiation-induced decreases in clonogenic survival and double-stranded DNA breaks in tumor cells, but not in normal cells, were enhanced by P-AscH-, while radiation-induced intestinal damage, collagen deposition, and oxidative stress were also reduced with P-AscH- in normal tissue.* ***We also report on our first-in-human phase I trial that infused P-AscH- during the radiotherapy "beam on." Our findings suggest that investigation of P-AscH- efficacy is warranted in a phase II clinical trial.*** *SIGNIFICANCE: These findings demonstrate that pharmacologic ascorbate enhances pancreatic tumor cell radiation cytotoxicity in addition to offering potential protection from radiation damage in normal surrounding tissue,* ***suggesting a potential for*** *improving treatment of locally advanced pancreatic adenocarcinoma.*

To be clear, I see no issue with the Phase I data being presented within the paper itself. My concerns are limited to the abstract.

As a pharmacist and science communicator, I am regularly involved with people living with cancer. I have also worked in cancer research in the past. Unfortunately, as you are well aware, high-quality research can be exploited and used in deceptive ways. I believe that the abstract of Alexander *et al*. comprises flaws that make this more likely, and that these flaws can be easily corrected without compromising the validity and relevance of the paper itself.

Sincerely,

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