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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