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RE: Prospective Grant of Exclusive Patent License: Radiotherapy for Metastatic Castration-Resistant Prostate Cancer, 83 FR 35667 (www.federalregister.gov/d/2018-16066)

Dear Michael Shmilovich:

Knowledge Ecology International (KEI) and the Union for Affordable Cancer Treatment (UACT) are writing to provide comments on the prospective grant of an exclusive patent license for the commercialization of radiotherapeutics for metastatic castration-resistant prostate cancer to Sinotau Pharmaceutical Group, headquartered in Beijing, China, as noticed in the Federal Register notice 83 FR 35667 (www.federalregister.gov/d/2018-16066).

According to the Surveillance, Epidemiology, and End Results (SEER) program in the National Cancer Institute (NCI) Division of Cancer Control and Population Sciences (DCCPS), prostate cancer is the second leading cause of death from cancer for men.[1] In 2015, 3.1 million men were estimated to be living with prostate cancer. The estimated number of deaths from prostate cancer for 2018 is 29,430, and is estimated to account for 4.8 percent of all deaths from cancer. [2]

African-Americans are more than twice as likely to die from prostate cancer than men of other racial and ethnic groups. [3]

[1] https://web.archive.org/web/20180816015209/https://seer.cancer.gov/statfacts/html/prost.html
[2] *Ibid.*
[3] In African American men, the incidence of prostate cancer is almost 60 % higher and the mortality rate is two to three times greater than in Caucasians. Shenoy, Divya et al. “Do African-American Men Need Separate Prostate Cancer Screening Guidelines?” BMC Urology 16 (2016): 19. PMC. Web. 27 Aug. 2018. ""https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4862049/; NIH and Prostate Cancer Foundation launch large study on aggressive prostate cancer in African-American men. July 17, 2018. https://www.nih.gov/news-events/news-releases/nih-prostate-cancer-foundation-launch-large-study-aggressive-prostate-cancer-african-american-men; Ina Wu and Charles S. Modlin, Disparities in prostate cancer in African American men: What primary care physicians can do
Cleveland Clinic Journal of Medicine. 2012 May;79(5):313-320..

In the past, federally-funded inventions for the treatment of cancer have been available in the United States at prices significantly higher than the prices of the same treatment in other high income countries. For example, the current GoodRx price for one year of the prostate cancer drug enzalutamide, when sold by Astellas under the brand name of Xtandi, is $151,037 ($103.46 per 40 mg capsule) retail, or $136,035 ($93.17 per 40 mg capsule), using the GoodRx coupon. By contrast, the price of Xtandi outside the US in another typical high income country is far lower. For example, in Australia, Xtandi is 33.07AUD per capsule[4], equal to $24.29 per 40 mg capsule, or $35,463 per year.

Prices for the drug are generally unaffordable in developing countries and are sometimes even higher in developing countries than in Europe.[5] As a consequence, access to this drug which is easy to administer is often severely limited in the developing world, leading to unnecessary premature deaths and suffering, an outcome that should be problematic for at least some government officials.

According to the notice in the Federal Register, the prospective exclusive license "would be granted worldwide" and for a field of use "not broader than radiotherapeutics for metastatic castration-resistant prostate cancer," the same indication as Xtandi.

Sinotau Pharmaceutical Group was founded in 2004.[6] The Sinotau Pharmaceutical Group has several subsidiaries, including one called Sinotau Radiopharmaceutical which, according to the Sinotau Group's website, "is focused on development of a neurologic precision diagnostics pipeline with a focus on neurodegenerative diseases, oncology and other relevant afflictions."[7] According to the Sinotau Group's website, in 2016, "Sinotau Group and Enigma Biomedical Group, a Canadian company, formed Cerveau Technologies, Inc., in Boston (USA), to help the global development of Sinotau's Radiopharmaceutical pipeline."[8] Cerveau has signed exclusive license agreements for the development and commercialization of medical technologies with other pharmaceutical companies, including Merck and FluoroPharma Medical Imaging, Inc.[9]

The Federal Register notice 83 FR 35667 describes the invention as follows:

> "The invention covered by the patents and patent applications pertaining to HHS Ref. No. E-054-2018-0 pertain to a therapeutic agent that includes a chemically conjugated residue derived from (((R-)-1-carboxy-2-mercaptoethyl)carbamoyl)-L-glutamic acid that is further bound to an Evans blue analog (EB). The EB analog reversibly binds to circulating serum albumin to provide a radiopharmaceutical that retains affinity and

[4] https://web.archive.org/web/20180827191518/http://www.pbs.gov.au/medicine/item/10174L
[5] Additional price comparisons here. https://docs.google.com/spreadsheets/d/1pNGEybsksMVZ_hZnVKVjS2lrjC2aAnwIyNw5ghSg_us/edit#gid=1908943673
[6] https://web.archive.org/web/20180827151941/http://www.sinotau.com/english/about.html
[7] https://web.archive.org/web/20180827151941/http://www.sinotau.com/english/about.html
[8] https://web.archive.org/web/20180827151941/http://www.sinotau.com/english/about.html
[9] https://web.archive.org/web/20180827153520/http://www.sinotau.com/english/news.html

> specificity to prostate specific membrane antigen (PSMA; in this case PSMA-617). PSMA is a surface molecule shown to be specifically expressed by prostate tumor cells. PSMA expression levels correlate with disease stage and with hormone refractory cancers. Although most PSMA expression appears to be restricted to the prostate cancer, low levels of expression can also be detected in the brain, kidneys, salivary glands, and small intestine. The antigen is also shown to be expressed by neovascular tumor vessels of multiple other cancers. Inclusion of the Evans blue analog promotes high internalization and retention rates of the conjugated target ligand, and therefore, higher accumulation in PSMA positive tumors. Labeling EB-PSMA-617 derivatives with the therapeutic beta emitters, e.g.,90 Y,86 Y, and 177 Lu gives rise to improved tumor response and survival rates."

A Clinicaltrials.gov search for "PSMA-617" reflects that there are at least 8 clinical trial studies recruiting or recently launched related to PSMA-617 for the treatment of prostate cancer.[10]

At least one of those studies, NCT03403595[11], received funding from NIH project 1ZIAEB000073-08.[12] NCT03403595 is a Phase 1 study that started on December 1, 2017 and its estimated completion date is December 1, 2018. The estimated enrollment is 30 participants. The same NIH funded project also listed 9 other clinical trials as being related.[13]

The Federal Register notice 83 FR 35667 only describes one patent document, U.S. Provisional Patent Application 62/633,648 filed February 22, 2018. This is a very recent application that does not appear in the USPTO or other patent databases and has likely not yet been published pursuant to 35 USC § 122. The lack of public information regarding the actual scope of the invention claimed in the application that the NIH plans to license to Sinotau Pharmaceutical Group undermines the general public's ability to comment on this prospective exclusive license.

Moreover, according to the Federal Register notice 83 FR 35667, in addition to the U.S. Provisional Patent Application 62/633,648 the prospective exclusive license will include "all continuing U.S. and foreign patents/patent applications thereof." Nevertheless, the Federal Register notice does not explain how many additional "continuing U.S. and foreign" applications the NIH has filed or plans to file based on the priority application 62/633,648, nor whether the NIH plans to file applications claiming this invention in developing countries.

In order to analyze whether in this case an exclusive license is a reasonable and adequate incentive consistent with the statutory requirements of 35 USC § 209, and properly respond to the Federal Register notice, it is necessary to have more information on the actual geographical scope of the prospective exclusive license, the role of government agencies in funding research

[10] https://clinicaltrials.gov/ct2/results?cond=PSMA-617+&term=&cntry=&state=&city=&dist=
[11] https://clinicaltrials.gov/ct2/show/NCT03403595
[12] https://projectreporter.nih.gov/project_info_details.cfm?aid=9555654&icde=40913634
[13] https://projectreporter.nih.gov/project_info_ct.cfm?aid=9555654&icde=40913634

related to the invention, and the expected costs of bringing a new treatment to market. The notice 83 FR 35667 does not contain such information, even though this is essential for making the analysis required by § 209.

At this point, KEI and UACT oppose the granting of an exclusive license, on the grounds that the NIH have not provided sufficient information to evaluate a request for an exclusive license.

However, in the event that the NIH does issue an exclusive license, we propose several conditions on the exclusive license to ensure that the benefits of the invention are available to the public on reasonable terms[14], and that the scope of the exclusive rights are "not greater than reasonably necessary to provide the incentive for bringing the invention to practical application."[15]

1. No discrimination against US residents in pricing

We ask that the NIH include language in the proposed exclusive license to ensure that the prices in the U.S. for any drug, vaccine, medical device or other health technology using the inventions are not higher than the median price charged in the seven countries with the largest gross domestic product (GDP), that also have a per capita income of at least 50 percent of the United States, as measured by the World Bank Atlas Method.

We consider this a modest request to protect U.S. residents, who paid for the R&D that created the licensed inventions.

2. Reduce term of exclusivity when revenues are large

In addition to an external reference pricing test, we propose that the exclusivity of the license in the U.S. should be reduced when the global cumulative sales from products or services using the inventions exceed certain benchmarks.

Given the modest cost of acquiring an NIH patented invention, the amount of money the developer needs in sales to justify additional investments in R&D is reduced, as compared to cases where a company develops or acquires the technology from non government sources.

This request is consistent with the statutory requirements of 35 USC § 209, which demands that "the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application."

One possible implementation of revenue benchmarks is as follows: exclusivity will be reduced by one year for every $500 million in revenue equivalents, earned after the first $1 billion, where revenue equivalent is defined as global cumulative sales plus market entry rewards as well as government grants or tax credits, for the product or products using the invention. However, the

[14] Required by 35 USC § 201(f).
[15] 35 USC § 209.

NIH could choose different benchmarks, so long as the limits on exclusivity address the requirements of 35 USC § 209, in that the incentive is “not greater than reasonably necessary.”

3. Developing countries

We are concerned that several NIH-funded inventions are not accessible in developing countries, due to prices that are high and not affordable in markets where per capita incomes are significantly lower than the United States. For this reason, we ask the NIH to limit the exclusivity in the license to countries that have per capita incomes that are at least 30 percent of the United States.

We also ask the NIH to reach out to the Medicines Patent Pool (MPP), in order to enter into an agreement that gives the MPP an option to negotiate non-exclusive open licenses for the inventions in developing countries.

4. Transparency

The licensee should be required to file an annual report to the NIH, available to the public, on the research and development (R&D) costs associated with the development of any product that uses the inventions, including reporting separately and individually the outlays on each clinical trial. We will note that this is not a request to see a company business plan or license application. We are asking that going forward the company be required to report on actual R&D outlays to develop the subject inventions. Reporting on actual R&D outlays is important for determining if the NIH is meeting the requirements of 35 USC § 209, that “the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application.” Specifically, having data on actual R&D outlays on each clinical trial used to obtain FDA approval provides evidence that is highly relevant to estimating the risk adjusted costs of bringing NIH licensed inventions to market.

Sincerely,

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