Regarding the national budget and the funding of oncological medications for the treatment of common tumours

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To:

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AN OPEN LETTER

Regarding the national budget and the funding of oncological medications for the treatment of common tumours

At a time when the world's leading media (*The Guardian*, *CNN*, *The Telegraph*, *The Daily Mail* et al.) and medical journals (*BMJ*, *JAMA*, *The Oncologist* et al.) are assessing and analysing the excessive cost, toxicity and questionable effectiveness of oncological medications, our own local media space has oddly enough been inundated with one unmistakable viewpoint – Latvia lacks both the money and the desire to pay for these innovative resources whose efficacy has garnered divided reactions abroad. A diverse group of people have been addressed during the preparation of the national budget, including individual members of Parliament, creating a misleading impression throughout society that only expensive innovative remedies can solve the cancer problem in Latvia. Are we truly so wealthy that we can afford to buy such extravagant medications that have proven to be ineffective and even toxic?

An October 26, 2014 article in the *Journal Sentinel*[i] pointed out that the American Food & Drug Administration (FDA) approves medicines based on surrogate measures (the reduction of tumour masses, length of time without a recurrence) that have no direct correlation to a patient's chances of living longer or enjoying a better quality of life. Since 1992 the FDA implemented an accelerated cancer medication approval process, including surrogates, which potentially forecasted a clinical benefit. In many cases, a prolonged survival rate hadn't been proven even several years after the medication had been released on the market.

In August of 2015, Leonard Saltz of the Memorial Sloan Kettering Cancer Center in New York contended in an article published in *American Health Drug Benefits*[ii] that new, innovative

medicines cost roughly 4,000 times more than gold and make one wonder if there must be a prescribed limit which society can afford to spend for each individual cancer patient.

Recently, unmistakable pressure has been placed on Latvian society to accept the erroneous idea that only the latest (innovative) medications will help. This is illustrated in an interview by journalist Inga Paparde with Gunta Purkalne on the *nra.lv* website in which the doctor stated "*For many years our patients have suffered from incomplete care, which is why I believe that additional funds must be directed toward compensating the costs of oncological medicines*" and with Jānis Eglītis who said "*we are very concerned by the question – if and when new cancer drugs will be available, especially for metastatic intestinal cancer and metastatic breast cancer?*" Such miracle cures for cancer simply don't exist, but this intentionally orchestrated publicity worries cancer patients as well as their family and friends.

An article published on March 8, 2017 in *STAT*[iii] argues that cancer patients not only have to contend with the challenges of the disease's symptoms, the toxic manifestations of the treatments, the financial burden and the expectations of society, but must also navigate an ocean of myths and fallacies. Cancer medications are often presented as miracles, fantastic achievements and game changers, even if they are not. Using US national cancer statistics data and FDA approvals, the authors Nathan Gay and Vinay Prasad determined that 68% of Americans predicted to die from some type of cancer will die from one for which there currently is no approved immunotherapeutic drug (including prostate, ovarian and colon cancer). Furthermore, a reduction in tumour masses is only expected in 26% of patients being treated with innovative immunotherapy drugs. If check-point inhibitor drugs were available to all patients (both financially and in reality), then any type of response can be expected in only 26% of patients with tumours and 8% of all tumours in general. On the other hand, there would be no response to therapy in 74% of patients whose tumour treatment check-point inhibitors are approved and 92% of all tumours in general.

Therefore, for those whom it helps, we can truly expect a positive result, but what about those for whom it doesn't help? Given our already modest budget, we shouldn't treat some patients suffering from metastatic illnesses with particularly expensive medications (admitting that not all will be effective) and not others.

On April 3, 2017, Andrews Gregory, the political editor of the *Daily Mirror*[iv], responding to sensational news that thousands of patients suffering from non-small cell lung cancer could prolong their lives by using a medication called *nivolumab*, pointed out that only 16 of 129 patients (around 12%) lived for 58 months.

But what of the other 84% of the patients in this study and in real life? Are we prepared to talk about the verified ineffectiveness of this therapy and whether or not we should have to pay for it?

In an article published on April 26, 2017 entitled "*How hype can mislead cancer patients, families*"[v], CNN's health news reporter Liz Szabo reported that cancer patients and their friends and family are constantly bombarded with news that we're winning the battle against cancer and that pharmaceutical companies, to ensure sales of their products,

promise the chance at a longer life. Who wouldn't succumb to this kind of temptation? Doctor Otis Brawley, a member of the American Cancer Society has indicated that "*We have a lot of patients who spend their families into bankruptcy getting a hyped therapy that [many] know is worthless.*"

As we can see from the news in the Latvian media, the sums are staggering. For example: *NRA*, July 14, 2016, Inga Paparde about T.B. – "*The council of doctors decided that from now on she had to be treated with drugs that cost €9,106 per month.*"; website *nra.lv*, October 22, 2016, Inese Blažēviča about A.K. – *"… the only hope is expensive chemotherapy (€54,000). The family doesn't have that kind of money.*"; website *nra.lv*, October 1, 2017, "*The council of doctors decided in favour of the drug Vemurafenib, whose cost isn't compensated by the state. A. has been given a fixed sum of €14,228 which will be compensated by the state, but the remaining sum of €50,507 necessary to cover the year-long treatment will have to be paid by A. herself. Her family doesn't have the resources.*" Are those really our own doctors, who so cold-heartedly exploit a patient's despair encouraging them to contact the charity www.ziedot.lv, knowing full well that the advanced tumour is untreatable? Essentially, doctors, industry specialists, the "Vita" patients' organisation and journalists manipulate public opinion by saying look how evil our country is, not caring for its seriously ill citizens by not buying those expensive, good drugs. The Ziedot.lv database offers information about numerous cases of money donated to specific patients who are now deceased being divided among other cancer patients.

On July 3, 2017, the *National Center for Health Research*[vi] interviewed its president Diana Zuckerman. From 2002 until 2014 the FDA approved 71 medications meant to treat a variety of localised tumours, yet less than half of these were proven to extend the patient's life for 2.5 months on average. But the prices were remarkable – over $10,000 per month, and many were very toxic. Why do so many innovative oncology drugs offer such little results? It's possible that in their zeal to offer "life-saving" drugs as quick as possible, the FDA approves medications before information about their true benefits has been received. Moreover, the organisation of post-registration studies is extremely complicated. If the drug improves progression-free survival, that doesn't mean that the patient will live longer. Dr. Zuckerman invites all patients to be vigilant and when in doubt to contact info@stopcancerfund.org.

On September 11, 2017, *REUTERS*[vii] warned that some doctors used Twitter to promote drugs, for which they receive compensation from the manufacturers. It tums out that pharmaceutical companies regularly pay doctors to recommend their drugs and to speak at conferences and seminars.

On April 11, 2016, Lato Lapsa at *Pietiek.com*[viii] wrote "*Over the course of a year, pharmaceutical companies have "supported" Latvian doctors by paying them over 2,85 million euro in a variety of ways: the largest portion was spent paying doctors and health care professionals to attend industry events abroad and to sponsor various events right here in Latvia, while the rest was donated to various health care organisations.*"

On September 26, 2017, *The Guardian*[ix] wrote that immunotherapy [modern innovative medications – author] is good cause for optimism, but it's not a panacea. Unfortunately, it

doesn't work for a large number of patients (roughly 80%), and for those for whom it is effective it has a variable survival benefit. Moreover, taking into account the side effects, our common mission ought to be "*primum non nocere*" (first, do no harm).

On September 27, 2017 *CNN*[x] noted that although immunotherapy has begun a new era in cancer treatment, it's not all-conquering and only 8% of cancer patients (including all potential localised cancers) benefit from its use. Even if this proportion increases to 12-15-25%, "*the glass is still more than half empty*".

On October 5, 2017, *The Daily Mail*[xi] published medical correspondent Ben Spencer's article in which he notes that the vast majority of cancer treatment drugs licenced in Europe (57% of those registered between 2009 and 2013) don't necessarily prolong a patient's life or improve their quality of life.

On October 16, 2017, *The Times*[xii] notes, already in the title of its article, that expensive cancer drugs could have a detrimental effect on the care of other cancer patients.

On October 23, 2017, *The Business Post*[xiii] wrote that over half of the cancer medications approved in Europe lack convincing evidence that they prolong a patient's survival or improve their quality of life.

However, what have medical and scientific journals published on the subject?

In 2013, *The Oncologist*[xiv]published an article about the financial toxicity of cancer treatments. In a survey of 254 participants with a variety of localised tumours that were undergoing an active course of therapy, the authors concluded that, due to financial considerations, 68% had to stop or limit their free time activities, 46% were forced to limit spending on groceries and clothing, 42% considered their illness a significant or catastrophic financial burden. To save money, 20% used less medication than was prescribed, 19% only partially followed their doctor's instructions, 24% refused to purchase drugs prescribed by their doctor.

In 2015, *JAMA Internal Medicine*[xv] concluded, after having carried out a systematic review of meta-analyses in clinical studies, that most of the studies' targets had little correlation with survival rates.

In 2015, *JAMA Internal Medicine*[xvi]. After analysing 54 drug approvals from 2008 to 2012, Chul Kim and Vinay Prasad concluded that 67% were approved on the basis of a surrogate. Furthermore, surrogates were the basis of all 15 (100%) medications which received accelerated approval and 21 of 39, which received traditional approval. After a median 4.4-year period of observation, only 5 medications demonstrated a believable improvement in survival, 18 showed no improvement in survival, whereas 13 still lack clear evidence of any impact on survival. Thus, the authors concluded that the FDA may have approved many expensive and toxic medications that have no impact on survival.

Conversely, Romualds Ražuks, a member of the Latvian Parliament, stated in an article in *Diena* on June 30, 2016: "*I completely agree with the representatives of the patient organisations that it should be a priority that additional funding directed toward oncology*

should be used to pay for innovative medications..." In addition, in an interview with Inga Paparde published on July 22, 2016 on the website *nra.lv* Gunta Purkalne stated that "*Latvia is one of the few nations in Europe and even the world, where the use of new generation medications to treat cancer is strictly limited, they're not included in the list of compensated medications and their efficacy in treatment, prolonging of survival and improvement of quality of life is no longer in doubt by oncology specialists the world over.*" As it turns out, there are still many doubts.

In February of 2017, *JAMA Internal Medicine*[xvii] asked how an informed discussion about consent between a doctor and patient is possible, if the FDA approves medications lacking any evidence of clinically significant, positive results. Referencing Kim's and Prasad's study, 18 of all 36 medications approved by the FDA from 2008 - 2012 were approved on the basis of surrogate studies – a reduction in tumour mass and progression-free survival – and postmarketing clinical studies failed to demonstrate a positive effect on survival.

In January of 2017, *ESMO Open*[xviii] published a study that analysed newly approved cancer therapy methods from January of 2009 to April of 2016. Evaluating different surrogates, the authors concluded that in the majority of cases survival benefit is less than 3 months, moreover in 37 indications (27%) no data was provided for PFS (progression-free survival) or OS (overall survival). A prolonging of overall survival was found in 76 of the licenced indications (55.5%), of which only 22 (16%) were longer than 3 months.

In October of 2017, the *British Medical Journal*[xix] concluded, after systematically analysing EMA (European Medicines Agency) approvals from 2009 to 2013, that the majority of medications were approved for sale without convincing evidence of their positive impact on survival or quality of life. Even if an extension of survival was observed, when compared to existing therapy methods or a placebo, the effects were often marginal. Of the 48 cancer drugs approved for 68 indications, 8 indications (12%) were approved on the basis of a single arm study. At the time of market approval, prolongation of survival was observed in 24 of the 68 (35%), ranging from 1 to 5.8 months (2.7 months on average). There was an improvement in quality of life in 7 of 68 indications (10%). Of the 68 cancer indications with EMA approval, and with an average of 5.4 years of post-approval follow-up (from 3.3 to 8.1 years), only 35 (51%) had shown a significant improvement in survival or quality of life. However, of 23 indications associated with a survival benefit, less than half (11/23, 48%) were judged to be clinically meaningful.

When promoting national priorities in oncology, resources must be distributed in a balanced manner to ensure the availability of diagnostic tests (PET/CT), to modernise radiation therapy (including stereotactic radiotherapy) and to fund palliative care, rehabilitation and the development of human resources. Our needs should not be narrowed down to the procurement of a few particularly expensive innovative medications for a limited circle of patients that will, at best, produce an unpredictable result.

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[i] http://archive.jsonline.com/watchdog/watchdogreports/fda-approves-cancer-drugs-without-proof-theyre-extending-lives-b99348000z1-280437692.html/

[ii] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4570079/

[iii] https://www.statnews.com/2017/03/08/immunotherapy-cancer-breakthrough/

[iv] http://www.mirror.co.uk/science/hope-thousands-cancer-sufferers-revolutionary-10152592

[v] http://edition.cnn.com/2017/04/26/health/hope-vs-hype-cancer-treatment-partner/index.html

[vi] http://www.center4research.org/special-report-many-expensive-new-cancer-drugs-useless-worse/

[vii] https://www.reuters.com/article/us-health-twitter-medical-ethics/doctors-who-take-pharmaceutical-money-use-twitter-to-hype-drugs-idUSKCN1BM2EU

[viii]https://www.pietiek.com/raksti/farmacijas_kompanijas_pasutijusas_kampanu_pareizajam_viedoklim_par_maksajumiem_arstiem

[ix] https://www.theguardian.com/commentisfree/2017/sep/26/immunotherapy-has-changed-cancer-medicine-but-its-no-miracle-cure

[x] http://edition.cnn.com/2017/06/02/health/immunotherapy-cancer-debate-explainer/index.html

[xi] http://www.dailymail.co.uk/health/article-4950018/The-costly-cancer-drugs-DON-T-help-patients.html

[xii] https://www.thetimes.co.uk/article/expensive-cancer-drugs-harm-care-for-other-patients-mltl7gp80

[xiii] https://www.businesspost.ie/health-social/watchdog-expensive-cancer-drugs-not-delivering-400391

[xiv] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3639525/

[xv] https://www.ncbi.nlm.nih.gov/pubmed/26098871

[xvi] https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2463590

[xvii] https://www.ncbi.nlm.nih.gov/pubmed/27898978

[xviii] https://www.ncbi.nlm.nih.gov/pubmed/28848662

[xix] https://www.ncbi.nlm.nih.gov/pubmed/28978555