Strategic Use of Patent Opposition Safeguard to Improve Equitable Access to Innovative Health Technologies: A Case Study of CAR T-Cell Therapy Kymriah

Muhammad Zaheer Abbas, PhD*

ABSTRACT

Kymriah is an innovative cancer therapy which works by removing disease fighting T-cells from patients, genetically modifying or reprogramming the immune cells to attack cancer, and re-infusing them back into the patients. It treats childhood blood and bone marrow cancer. The cost of this new hope-giving gene therapy is CHF 450,000 per treatment. This exorbitantly high price set by Novartis, in exercise of its exclusive rights resulting from patent protection, undermines the real-world impact of this revolutionary therapy. On December 16, 2019, Novartis relinquished its European patent on Kymriah as a result of a successful patent opposition lodged by 'Public Eye' and 'Médicins du Monde'. This case study of Kymriah highlights the potential role of civil society in improving equitable and affordable access to innovative health technologies by using the procedural safeguard of patent opposition. This study finds that patent opposition is an important policy option to alleviate some of the financial burdens of health systems, especially in the wake of COVID-19.

KEYWORDS Civil society; gene therapy; Kymriah; patent opposition; public health

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*muhammadzaheer.abbas@connect.qut.edu.au. The author is a Senior Research Assistant at Faculty of Law, Queensland University of Technology (QUT), Brisbane, Australia. This paper benefitted from oral presentation and feedback at the Intellectual Property Scholars Conference 2020, Stanford University, California, USA. Some part of an earlier draft of this paper is derived from the author's PhD thesis entitled 'Community-Based Patent Opposition Model in India: Access to Medicines, Right to Health and Sustainable Development' submitted at QUT, Australia. The author would like to acknowledge his PhD supervisors Professor Matthew Rimmer and Professor Richard Johnstone. The author appreciates Juliana Veras and Théau Brigand, from Médicins du Monde, for their valuable inputs on objectives and potential impact of Kymriah patent opposition. The author would also like to acknowledge with great appreciation his wife Dr. Shamreeza Riaz for her unconditional support and kind cooperation.

Introduction

The emerging technology of personalized gene therapy holds promise for treating different kinds of cancer and other chronic diseases. The discussions and promises about personalized cancer therapy started in 2012 when a CAR-T (Chimeric antigen receptor T-cells) therapy, invented by the University of Pennsylvania researcher Dr. Carl June, cured a 6-year old child patient Emily Whitehead (Monde, 2019). This case benefitted from high media coverage and

stimulated funding in this new line of research. According to Knowledge Ecology International (KEI), up till 2017, the U.S. National Institute for Health (NIH) had invested more than 200 million dollars in CAR-T R&D (Brigand and Muller, 2018).

The ambitious journey of Kymriah began in 2012 when Novartis and the University of Pennsylvania started to collaborate for making this paradigm-changing gene therapy for cancer patients a commercial reality (Upton, 2018). Within five years of launching this successful collaboration, the dream of commercializing Kymriah began to materialize. Kymriah got the United States Food and Drug Administration (US-FDA) approval on August 31, 2017 (Upton, 2018). This approval was achieved in just six months because of spectacular clinical responses in patients. Clinical trials were led by Dr. Stephen Grupp of the Children's Hospital of Philadelphia and the University of Pennsylvania's Perelman School of Medicine (Upton, 2018). In these clinical trials, about 83% of patients who were treated with Kymriah achieved sufficiently durable remission – for five years, if no longer - within three months of treatment (Medline, 2017). Kymriah proved to be an incredibly valuable therapy because alternative treatments do not achieve these types of results (Bach et al., 2017). As noted by Dr. David G. Maloney, 'there is clearly a high initial response rate with CAR T-cell therapy. We are seeing remission rates in patients in whom we did not see any type of remission with conventional therapies' (Cavallo, 2018).

With prominent efficacy results, Kymriah quickly moved forward through health authority approvals and marketing authorizations in other jurisdictions like the EU, UK, Australia, Japan, and Canada (Grupp, 2019). In August 2018, Kymriah became one of the first European Union-approved CAR-T therapies after receiving a positive recommendation from the Committee for Advanced Therapies (CAT) and the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA) (Ali et al., 2020). In February 2019, the UK National Institute for Health and Care Excellence (NICE) recommended Kymriah for diffuse large B-cell lymphoma.

After discussing therapeutic benefits of this hope-giving personalized gene therapy, this paper argues that the unjustifiable cost of Kymriah, resulting from patent exclusivities, undermines the real-world impact of this revolutionary therapy. In 1995, the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property (TRIPS agreement, 1995) provided, under Arts. 27(1) and 33, mandatory patent protection to inventions in all fields of technology, including pharmaceuticals. According to Art. 28, a patent provides the patent owner with the exclusive rights to make, use, sell, offer for sale, import,

license and distribute the protected invention for a period of twenty years (TRIPS Agreement, 1995). These exclusive rights allow supra-competitive pricing and have direct implications for affordable access to innovative health technologies. Patent opposition is one of the legitimate safeguards provided under TRIPS. This paper evaluates Kymriah patent opposition by public health organizations and argues that much less-resourceful civil society organizations can play a crucial role in improving public health by using the TRIPS-compliant procedural safeguard of patent opposition.

Kymriah: A Hope-giving Personalized Gene Therapy

Kymriah treats B-cell acute lymphoblastic leukemia (ALL) in children and young adults up to age 25 (Medline, 2017). It is delivered to a patient just once as it is intended to be a one-time treatment (Huettermann and Partner Patent Attorneys, 2017). Unlike traditional off the shelf one size treats all therapies that are identical from patient to patient, Kymriah is a highly personalized therapy (Hollywood and Denney, 2019). As compared to chemotherapy, which uses drugs (that are generally identical from patient to patient) to stop cancer cells from dividing uncontrollably, Kymriah has a transformative approach to cancer treatment (Hollywood and Denney, 2019). It works by removing disease fighting white blood T-cells from patients through a procedure known as leukapheresis, genetically modifying or reprogramming the immune cells in cell processing facility to produce chimeric antigen receptors (CAR) on their surface, transporting these live cells back to the hospital and re-infusing them back into the patients after a lymphodepleting chemotherapy regimen (Lancet, 2017). These engineered receptors allow reprogrammed T-cells to recognize, attack, and eradicate specific leukemic B cells (lymphoblastic cells that featured target glycoprotein CD19 on their surfaces) with unprecedented efficacy while leaving healthy cells unharmed (Lancet, 2017). This highly technical process typically takes two weeks (Medline, 2017).

Previously, children diagnosed with ALL, having limited options for treatment, had to undergo difficult treatments including bone marrow transplant, stem cell transplant, radiation, and chemotherapy (Shapiro, 2019). Enduring pain and suffering of multiple noncurative or partially curative therapies is hard for patients, especially for children. Kymriah spares patients of a lot of pain and suffering. More importantly, prior to Kymriah, children who had relapsed after conventional therapy had little or no hope. Now they may go on to this transformative CAR T-cell therapy if they relapse after conventional therapy. This new and extremely personalized or customized approach to cancer treatment offers hope to cancer patients with limited options, families of such patients, and health professionals treating such patients. FDA

commissioner Scott Gottlieb noted in a statement that '[w]e're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer' (Mullin, 2017). Dr. Alasdair Rankin, Director of Research and Patient Experience at Bloodwise, commented that:

> CAR T-cell therapy is the most promising breakthrough in blood cancer treatment of the past decade, with the potential to be used much more widely in the future … Ensuring access to CAR T-cell therapies gives these patients the real chance of long-term survival when all other treatments have failed (National Institute for Health and Care Excellence, 2019).

Meindert Boysen, Director of the Centre for Health Technology Evaluation at NICE, said in a statement that '[w]e have seen promising results for CAR-T therapies in early trials and believe there is great potential for tisagenlecleucel-T to help people who have not responded to other forms of therapy' (Homer, 2018). An Evidence Report published by the U.S. Institute for Clinical and Economic Review (ICER, 2018) suggests that Kymriah improved response rates and survival in patients. According to Dr. Dan Ollendorf, Chief Scientific Officer at ICER, the available evidence suggested that Kymriah provided important clinical benefits. Admittedly, Kymriah is a game-changing and revolutionary product as none of the available alternative treatments for the population concerned achieve or claim to achieve these types of results. In addition to its therapeutic value, Kymriah has societal value too because not only many of the patients treated with this therapy will be able to achieve and sustain their health-related quality of life but also their parents and caregivers will be able to return to their normal lives.

Further research in this area may continue to improve outcomes for patients by finding new ways to increase the efficacy of this gene therapy. Kymriah's current target ALL patient population is small as Novartis estimates that each year only around 600 patients will qualify for treatment (Medline, 2017). The success of Kymriah has the potential to revolutionize the field as it has already played a key role in stimulating widespread industry interest in the field of gene therapy (Hollywood and Denney, 2019). Several CAR T-cell therapies for solid tumours are in the pipeline for clinical trials (Karen, 2017). Interest in developing innovative and non-traditional approaches to treating other kinds of cancer and chronic diseases is now booming. As noted by Dr. Carl June that 'the future is not just in the treatment of cancer. Engineering T cells is a way to put the immune system on steroids and boost it to fight not just cancer but other chronic diseases as well, including human immunodeficiency virus

(HIV)/AIDS and potentially hepatitis' (Cavallo, 2018). He further added that 'companies are also investigating CAR T-cell therapy in organ transplantation to eliminate the need for lifelong immunosuppressants' (Cavallo, 2018). The future for CAR T-cell therapy looks bright, but it is important to consider the cost of this transformative therapy because not many patients will be able to benefit if the cost is too high.

Kymriah's Unjustifiable Cost Undermines its Potential Impact

The exorbitantly high cost, predominantly resulting from patent exclusivities, is a significant component and one of the major concerns of this therapy. According to Article 28, a patent provides the patent owner with the exclusive rights to make, use, sell, offer for sale, import, license and distribute the protected invention for a period of twenty years (TRIPS Agreement, 1995). Patent exclusivities have serious implications for affordable access to innovative health technologies because patent holders tend to set exorbitant prices for patented medicines in exercise of these exclusive rights. In case of Kymriah, on July 19, 2017, the European patent (EP 3214091) was granted to the University of Pennsylvania (Huettermann and Partner Patent Attorneys, 2017). Novartis, as a result of a licensing arrangement, acquired the exclusive rights over this patent. Patents protecting Kymriah allow Novartis to set an unreasonably high price for this therapy. The per treatment cost set by Novartis for this new hope-giving gene therapy is CHF 450,000 in Switzerland and $475,000 in the U.S. (Mullin, 2017). On top of this cost, the treatment involves considerable additional costs incurred on hospitalization, (Phrmaletter, 2018) supportive care, follow-up, (Karen, 2017)[i] and supplementary treatments like premedication with acetaminophen, concomitant intravenous infusion of the anti-IL-6-receptor tocilizumab and an H1- antihistamine before infusion (Liu and Holle, 2017). The estimated total cost of the therapy exceeds $1 million per patient (Cavallo, 2018).

The unaffordable cost of Kymriah is a substantial barrier in access to this therapy and it seriously undermines the potential impact of this hope-giving gene therapy. This high cost is particularly questionable given the fact that Kymriah was developed through university research with support from public funding. According to Knowledge Ecology International (KEI), the U.S. National Institute for Health (NIH) invested more than 200 million dollars in CAR-T R&D (Brigand and Muller, 2018). Most of the early work on this technology was done at the University of Pennsylvania where Dr. Carl June was granted $30,335,306 of funding by NIH for 39 projects relating to CAR T between 1993 and 2016 (Singhroy, 2017). Novartis tries to overshadow the role of public funding by making claims of heavy R&D investments. Novartis maintained in 2017 that it had spent more than one billion U.S. dollars on R&D for

Kymriah (Herper, 2017). In 2019, Novartis claimed that the cost of putting Kymriah on the market was 1.6 billion U.S. dollars (Monde, 2019). In any case, Novartis should have considered the substantial role of publicly funded research while deciding Kymriah's price because it is not fair if taxpayers are asked to pay twice. The contribution of public spending is clearly not reflected in the current price of Kymriah.

Novartis is also criticized for not making public the cost of manufacturing Kymriah. Due to lack of transparency, it is hard to estimate production costs of the treatment. Dr. Carl June, one of the principal researchers in CAR-T at Pennsylvania University, told the New York Times in 2012 that production would cost about US$20,000 per patient (Monde, 2019). Five years later, analysts estimated in 2017 that the costs of producing Kymriah would be US$200,000 (Monde, 2019). Experts at Médicins du Monde (Doctors of the World) estimated in 2019 that the actual cost of producing Kymriah is between €20,000 and €60,000 (Monde, 2019). Because of the total lack of transparency, it is not clear which of these vastly different estimates is close to reality.

Instead of responding to this criticism and properly justifying the excessively-high price of Kymriah or trying to make the price understandable, Novartis decided to introduce a new concept of outcomes-based or value-based pricing. This model is based on the rationale that drugs 'should be priced on the value they bring to the healthcare system and insurers and governments should pay based on whether the medicines work' (Herper, 2017). Under this innovative indication-based pricing model, the patent holder adds an outcome-based contract to the cost and payments are due only if the patient responds to the therapy by the end of the stipulated time. Under this scheme, Novartis would charge for only those patients treated with Kymriah who have a response within a month of obtaining the infusion (Brigand and Muller, 2018).

The value-based pricing model suits pharmaceutical industry because it takes R&D cost and manufacturing cost out of equation. As advocated by industry representative Thomas Cueni, 'companies should be paid for the therapeutic value of their drugs to society and patients rather than the cost of research and development' (A Public Eye Report, 2018). This innovation in pricing strategy enjoys support of pharma companies, but it is based on a dangerous approach which raises serious societal concerns. As noted by Marie-Paule Kieny, the WHO Assistant Director-General for Health Systems and Innovation, if you apply this approach to other products 'you can say if an airbag can save my life, why isn't the cost of an airbag what I would be willing to pay for my life? And that would be a lot' (A Public Eye Report, 2018). She added,

'What's the value of life? This structure is good for luxury goods because you have a choice … if I'm sick with cancer, what's the choice? We think value-based pricing is not feasible for products that are indispensable' (Brigand and Muller, 2018).

The current pricing model is a major concern not only for patients and the healthcare system but also for healthcare provider institutions and insurers. After signing contracts with the patent holder, they have to negotiate with insurance companies to cover the costs of the therapy (Cavallo, 2018). Insurance companies are generally hesitant to engage in value-based pricing because they do not want to deal with the complexities of tracking patients' outcomes (CMS, 2017). Provider institutions face higher administrative and financial obstacles because insurers impose intense administrative requirements (Robinson et al., 2018). If the current model of pricing Kymriah concerns all stakeholders (i.e. patients, healthcare providers, and insurers) for one reason or the other, there is clearly a need to replace it with a more responsible, sustainable, and acceptable pricing model.

In addition to the cost of Kymriah, the provider institutions need to incur substantial costs in making the prerequisite technological and logistical arrangements for this new type of technically challenging treatment with Kymriah. Generating this personalized therapy typically takes two weeks and involves several technical steps like 'leukapheresis of a patient's blood, stimulation of the harvested T cells with mitogenic beads, transduction with a viral vector to integrates a CAR construct, culture and expansion of the engineered T cells and subsequent cryopreservation' (Medline, 2017). Because of the complexity of the procedure, Kymriah needs to be administered in specialized treatment centres as safe delivery of this personalized therapy requires a robust clinical infrastructure to handle the complex scheduling logistics and to maintain the chain of custody and chain of identity of the cellular product (Kansagra et al., 2019). The provider institutions need to incur additional costs to enhance their technological capability and clinical competencies in hematopoietic cell transplantation. Cancer centres need to train their staff in the 'Risk Evaluation and Mitigation Strategy' because CAR T-cell therapy can be performed only in skilled treatment facilities that have completed this training (Cavallo, 2018). This certification requirement further adds to the financial burden of cancer centres.

NGOs' Use of Patent Opposition Safeguard to Challenge Kymriah Patent

Patent opposition is one of the legitimate flexibilities provided under the WTO TRIPS Agreement. This multilateral treaty did not provide any specific guidelines on patent opposition proceedings. It only prescribed some general procedural requirements that may be applicable

to opposition procedures (Manu, 2017). Art. 62(2) of the TRIPS Agreement (1995) requires the Member States to make sure that the procedures for grant or registration of intellectual property rights do not cause 'unwarranted curtailment of the period of protection'. General obligations concerning safeguards against the abuse of intellectual property rights have been provided in Art. 62(4) of the TRIPS Agreement. Under Art. 41(2) of the TRIPS Agreement (1995), member countries have been directed to adopt fair and equitable procedures that are 'not unnecessarily complicated or costly' and that do not 'entail unreasonable time-limits or unwarranted delays'. Because of this flexibility provided under TRIPS, WTO Member States enjoy a wide discretion to choose only pre-grant or post-grant opposition procedures or a combination of both or no opposition procedures at all.

The European Union used this flexibility to provide a supra-national post-grant third party opposition procedure in the European Patent Convention (EPC, 1973). The European post-grant opposition system is *inter partes* administrative procedure that allows third parties to file a notice of opposition at the European Patent Office (EPO) within nine months after the grant of a European patent is published. Any natural or legal person, other than the patent owner, may file a patent opposition (EPC, 1973). An opposition can be initiated, after paying the prescribed opposition fee,[ii] on a range of issues like insufficient disclosure and enablement, unpatentable subject matter, a lack of novelty, non-obviousness, a lack of industrial application, and the granted patent's scope exceeds the content of the original application (EPC, 1973). The European patent opposition is a single action before the EPO and all European Union countries, in which the opposed patent has an effect, are bound by the decision of the EPO (EPC, 1973). A patent can be reduced or knocked out for the entire European market as a result of a single successful patent opposition at the EPO.

The Swiss-based public health group 'Public Eye' and the French-based NGO 'Médicins du Monde' (Doctors of the World) used the European post-grant patent opposition system to challenge the Kymriah patent. The NGOs filed a patent opposition against a patent for Kymriah on July 2, 2019. The opponents challenged the novelty of the underlying technology and requested revocation of the patent in its entirety (Charles, 2019a). In order to qualify for patent protection, an invention is required to be novel, non-obvious and useful in the sense of being capable of industrial application (Correa, 2007). This is a universal standard required under the TRIPS Agreement. The key terms prescribing criteria for patentability are not defined in the TRIPS Agreement leaving sufficient latitude for the Member States to define scope and meaning of these terms according to their individual situations and public health

needs (Vawda, 2014). The European Patent Convention (EPC, 1973) defined novelty standard under Art. 54 which reads as: 'An invention shall be considered to be new if it does not form part of the state of the art'. It illustrates that 'the state of the art shall be held to compromise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application' (EPC, 1973).

The opponents contended that the opposed Kymriah patent lacked novelty and appeared to be an attempt at evergreening patent protection of CAR T-cells harbouring such CARs for use in the treatment of cancers (Charles, 2019a). The originator pharmaceutical companies arguably make concerted efforts to acquire undeserving patents by using different tactics. Evergreening of pharmaceutical patents is one such tactic to acquire unjustifiable monopoly rights. The World Health Organization Commission on Intellectual Property, Innovation and Public Health (2006) defined evergreening as 'a term popularly used to describe patenting strategies when, in the absence of any apparent additional therapeutic benefits, patent holders use various strategies to extend the length of their exclusivity beyond the 20-year patent term'. The opponents claimed that the opposed Kymriah patent lacked novelty because the corresponding CAR T-cells had been described and patented at least 6 years before the priority date of the opposed patent (Charles, 2019a). The opponents also quoted three academic articles published in 2011 as prior art documents (Charles, 2019a).[iii] The Kymriah patent owners had allegedly engaged in the strategic utilisation of the patent system to extend their exclusive rights as the opposed patent apparently failed to meet the novelty standard provided under Art. 54 of the EPC 1973.

Surprisingly, on November 29, 2019, the patent holders withdrew the opposed Kymriah patent even before the opposition procedure had in fact begun. The authorised representative for Novartis and the University of Pennsylvania requested the revocation of the controversial patent on the ground that 'the appropriator no longer approved the text upon which the patent was granted, and will not be submitting an amended text' (Charles, 2019a). Patent opposition is a strong mechanism because when a patent is opposed, the patent holders are obliged to respond to the objections raised by the complainant. By relinquishing their patent without providing any reasons to withdraw the patent, Novartis and the University of Pennsylvania avoided a discussion on the merits of their contested patent because a detailed discussion on the novelty of this patent could potentially jeopardise their patent rights in other jurisdictions. It is clear that the patent holders did not want this case to set a dangerous precedent.

In December 2019, EPO revoked the opposed Kymriah patent EP 3214091. Though generic competition will not be possible as Kymriah is still protected under other patents on the CAR T-cell therapy treatment, this successful patent opposition indirectly confirms the abusive nature of the Kymriah patent and it will play an important role in facilitating patient access to health technologies that underpin Kymriah. As noted by 'Public Eye', '[t]his volte-face confirms that the patent should never have been granted in the first place, given that the underlying technology is not novel. It also questions the validity of other patents on Kymriah and weakens the monopoly position of the Swiss giant in future price reviews' (Durisch, 2019). In order to avoid another potential patent validity challenge on similar grounds, on September 26, 2019, the authorised representative for Novartis and the University of Pennsylvania unilaterally withdrew a pending application (European Patent Application No. 17191702.4) for another Kymriah patent without providing any reason (Charles, 2019b).

The successful patent opposition by NGOs sent a strong signal to the pharmaceutical industry and its indirect impact is quite obvious. Despite prospects for potential improvements on access to Kymriah, so far, there has been no actual reduction on price. There is no alternate producer in the market as Kymriah is still protected under other patents. As noted by Juliana Veras, Advocacy Coordinator Drug Pricing and Health Systems at Médicins du Monde, 'other patents are still in force that do not allow production of Kymriah biosimilar versions'.[iv] She added that 'our bet is to make an advocacy argument to influence the government drug prices negotiation, and the medical community. This is something we are still working on'. To secure a price reduction for Kymriah was not the sole objective of patent opponents. As noted by Théau Brigand, who directly led patent opposition work on Kymriah within Médicins du Monde:

> Our main objective was to demonstrate patent abuses on CAR-T therapies, in order to strengthen states and health systems in negotiating lower prices … A second objective of this patent opposition was to raise questions about the public production of CAR-T treatments. We didn't really manage to raise this issue during the procedure, but we plan to exploit the outcome to advocate about public CAR-Ts in France, Switzerland and in Europe. A final goal was to make these activist practices/advocacy strategies, mainly inherited from the fight against AIDS and hepatitis, known in the field of cancerology and within the scientific communities. To do so, we submitted abstracts on international conferences. They have been selected and may enable us to reach and

> inform new audiences, particularly physicians, to mobilize them on the issues of price and access. We consider it to be very important outcome.[v]

In their advocacy campaigns and future patent challenges, Médicins du Monde and Public Eye can focus on the issue of patent eligibility of CAR-T therapies. Kymriah as a legal object is clearly not a pharmaceutical drug. It is more likely to fall in the category of medical procedures or methods of medical treatment that are largely not patent eligible around the world. As noted by Médicins du Monde in its press kit, '[t]oday, these therapies are considered medicines in Europe. Yet the procedure is managed essentially by hospitals and could therefore be considered a medical procedure. These two modifications could have important consequences with regard to the reach of intellectual property rights' (Kimani et al., 2020). Similarly, Abinader and Contreras noted in their 2019 paper that 'CAR-T and other recent gene and cell therapies, which operate based on the extraction of genetic or cellular material from a patient, the alteration of such material, and the reintroduction of such material to the patient's body, should … be considered medical treatments' (Gil Abinader and Contreras, 2019). Civil society organizations need to bring it into public attention that in its FDA application for marketing approval of Kymriah, Novartis deliberately referred to Kymriah as a product (U.S. Food and Drug Association, 2017). In Europe, the documentation published by the EMA referred to Kymriah as a product. Kymriah's description as a product, despite the fact that it is not a manufactured product but a process performed on patient's own T-cells, is questionable and needs to be debated. One can clearly see mischaracterization of the nature of this therapy for commercial gains. As defenders of the public interest, civil society organizations, like Public Eye and Médicins du Monde, need to highlight this questionable approach of brand-name companies which undermines societal interests. Civil society actors should press for classification of CAR-T therapies as medical treatments under the EPC so that they may be clearly excluded from patent eligibility.

Overall, Kymriah patent opposition is a remarkable success of public health groups against Novartis. This success highlights the potential role of much less-resourceful civil society organizations in improving public health by using the legitimate safeguard of patent opposition. It is an encouraging sign if community organizations actively engage with the patent system by acting as watchdogs. Vigilance of civil society actors can be instrumental in requiring the patent offices to impose stricter compliance with patentability criteria. Civil society organizations represent the public interest and the outcome of patent validity challenges brought by them affects the public at large. The low-cost patent invalidation proceedings within

the patent office suit resource-constrained civil society organizations because they may be reluctant to become a party to costly and cumbersome multi-year patent litigation (Correa, 2007). The prescribed fee to initiate the European patent opposition proceedings is €745[vi] whereas the costs of invalidating patents through court litigation are prohibitively high (Gugliuzza, 2017). This study proposes that an even reduced fee should be prescribed for civil society organizations in order to encourage their meaningful engagement with the patent system. Patent litigation is not the best option for civil society organizations because, in addition to unaffordable cost of court litigation, the prolonged trial and appeal processes seriously disincentivize interested community representatives from using court proceedings to invalidate a questionable patent (Shi, 2003).

Kymriah is not the only example of a successful patent invalidation in Europe resulting from a challenge brought by representatives of the public interest. Non-governmental organizations and civil society groups have successfully used the European opposition proceedings to challenge several other questionable patents (European Patent Office, 2013; Douglass, 2018; Plomer, 2015).[vii] This study argues that the EU should have crafted pre-grant opposition procedures as well to provide opportunities to third parties to challenge pending patent applications. Preventing the grant of questionable patents is a superior policy option as compared to revoking the granted patents because questionable patents, even if revoked later, have a substantial negative impact. This is important given the fact that the EPO grants patents for 28 countries and its patenting decisions impact a population of more than 450 million (Gaessler and Harhoff, 2017). The European civil society organizations, like Public Eye and Médicins du Monde (Doctors of the World), could play a much more effective role in warding off the grant of questionable patents if provided with opportunities to challenge pending patent applications.

Conclusion

The CAR T-cell therapy is a hope-giving transformative therapy, but its real-world impact will remain limited unless its costs can be reduced significantly. The Kymriah case draws attention to the abuse of intellectual property and irresponsible pricing of health technologies. It sends a strong health policy signal regarding the potential role of civil society in achieving the goal of equitable and affordable access to innovative health technologies. Community organizations can strategically use the procedural safeguard of patent opposition to challenge abusive use of patent exclusivities which threaten the financial sustainability of health systems by enabling supra-competitive pricing of protected health technologies.

Patent opposition is an important TRIPS flexibility, especially in the wake of current public health crisis, because COVID-19 has burdened health systems across the globe. The European Union used this flexibility to provide a post-grant third party opposition procedure. The EU should have crafted pre-grant opposition procedures as well to provide opportunities to third parties to challenge pending patent applications because preventing the grant of questionable patents is a superior policy option as compared to revoking the granted patents.

The European Patent Office is expected to impose strict compliance with patentability criteria, but the Kymriah case draws attention to serious problems with patent examination. Patent examination failures have adverse social consequences, especially in the case of health-related technologies, because equitable access to these technologies is a matter of life and death for patients. An efficient use of patent opposition safeguard has the potential to fix some of the examination failures as it enables third parties to bring additional information to the notice of the concerned authorities.

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[i] According to the Kymriah medication guide, patients treated with Kymriah need to stay within two hours of the location of their treatment facility for at least four weeks after getting the infusion.
[ii] See Supplement to Official Journal of the European Patent Office, Schedule of Fees and Expenses Applicable as from 1 April 2012.
[iii] First article was published by Parter et al. in the *Journal of Cancer*; second article was published by Kalos et al. in *Science Translational Medicine*; and third article was published by Parter et al. in *The New England Journal of Medicine*.
[iv] The author contacted Juliana Veras via email in late August 2020 to enquire about any actual reduction on price of Kymriah resulting from the successful patent opposition. Her response email is on record with the author.
[v] The author contacted Théau Brigand via email in late August 2020 to enquire about any actual reduction on price of Kymriah resulting from the successful patent opposition. His response email is on record with the author.
[vi] See Supplement to Official Journal of the European Patent Office, Schedule of Fees and Expenses Applicable as from 1 April 2012.
[vii] In April 2013, an opposition division of the EPO revoked the stem cell patent in the 'Brüstle' case. In 2015, civil society organizations from 17 countries successfully challenged Gilead's Sofosbuvir patent. Moreover, civil society organizations in Europe opposed the Myriad Genetics' BRCA1 and BRCA2 patents and succeeded in significantly reducing the negative impacts of these controversial patents. https://www.epo.org/news-issues/news/2013/20130411a.html. Accessed June 20, 2020.