Editorials

Purchasing silence

A version of the Hippocratic oath used by many medical schools includes the statements: 'I will respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow' and 'I will apply, for the benefit of the sick, all measures, which are required' [1]. Fortunately, there are 'hard-won scientific gains' in oncology. Understanding that prostate cancer remains stimulated by androgens in castrate men led to development of abiraterone and enzalutamide, and studies of interactions between T cells and tumour cells led to development of immune checkpoint inhibitors such as pembrolizumab and nivolumab. These drugs and others can improve survival and its quality. Here, we argue that 'to apply, for the benefit of the sick, all measures that are required' requires initiatives to ensure that clinically important drugs be available at affordable prices. The high cost of drugs makes it difficult in developed countries and often impossible in lower and middle-income countries for patients to receive them.

While company scientists make some scientific discoveries that lead to development of new drugs, much preclinical research is funded by grants from agencies supported by governments or charities [2]. For example, initial development of abiraterone took place in the Institute of Cancer Research, UK in the early 1990s, with funds from the Cancer Research Campaign and Medical Research Council [3], while Sawyers et al., funded in part by the Prostate Cancer Foundation and the United States (US) National institutes of Health and Department of Defence, developed enzalutamide [4]. Research showing that inhibition of the PD-1/PD-L1 pathway could lead to antitumour responses was undertaken in several laboratories, but prominently in Kyoto and the Mayo Clinic, supported by publicly funded research grants [5, 6].

Development of the above drugs depended on their being licensed to companies that undertook the necessary clinical trials to bring them to market. Estimates of the cost to companies to develop a new anticancer drug are variable, with a recent median estimate of US$648 million (adjusted for inflation to 2017 and including costs associated with 'failed drugs') [7]. The price of new anticancer drugs in the USA exceeds typically $10 000 per month, and while national health plans can bargain for lower prices in Europe, typically negotiations over months to years are required to reach agreement to make the drugs publically available. The high price of new drugs means that many patients have no or restricted availability, or can afford only a suboptimal schedule of treatment [8, 9].

Price bears no relationship to costs of development and manufacture, the drug's effectiveness, or the extent to which public funds were used in its development; price is set to maximize profit [10–12]. The median revenue gained after marketing approval is high compared with the cost of research and development, and the profit margin of the pharmaceutical industry is substantially higher than for most other industries [13]. Occasional groups of physicians have lobbied successfully against inappropriate pricing [14] but, in general, doctors have failed to mount an effective lobby to ensure that drugs are marketed at a price that renders them available to all patients who might benefit. Possible reasons include lack of doctors' expertise and enthusiasm for lobbying and lack of their professional organizations seeing this as their major purview. For example, the American Society of Clinical oncology (ASCO) position statement addressing the affordability of cancer drugs does not mention public or professional pressure on the pharmaceutical industry as a mechanism to influence prices [15]. Why is this? Herein we suggest that the pharmaceutical industry is highly effective in purchasing the silence of doctors.

Most journals have conflict of interest (COI) guidelines that require authors to disclose financial relationships with pharmaceutical companies. To evaluate the frequency at which this occurs, we reviewed disclosures for the 427 authors of 22 reports of phase III clinical trials published in the *New England Journal of Medicine* in the last 3 months of 2017. Among the 314 authors of these articles, who were not employees of the sponsor, 56% reported personal payments from the sponsor for consulting, lectures, or as members of advisory boards, and a further 16% disclosed other benefits, unrelated to the reported trial, including grants and travel to meetings. Other reports of potential financial COI are in broad agreement [16, 17]. In addition, and more concerning, is the marketing budget of pharmaceutical companies directed at physicians not involved in drug development and authorship, often disguised as payments for 'consulting'. While consultation with a few expert physicians may be helpful to companies, many 'advisory boards' are not set up to seek advice but to 'advertise', to ensure that prescribing physicians become aware of the company's product(s). Thereby, the receipt of personal payments from companies, although relatively small in amount, may provide a de facto barrier to physicians criticizing the company: it becomes difficult for them to 'to apply, for the benefit of the sick, all measures that are required', including advocacy that effective drugs be available to all who might benefit from them at affordable prices.

The development and marketing of new drugs for profit is not likely to change, but the ethical and societal responsibility of large pharmaceutical firms may be more malleable. Unfortunately, patient advocacy groups have been relatively silent about drug prices, lobbying mostly government agencies to ensure drug access regardless of cost. However, doctors can and should have a strong voice in lobbying on behalf of their patients. There is acceptance of restrictions on receipt of gifts and entertainment from industry, and of more transparent relationships between companies

and physicians, including declarations of potential COI as a requirement for publication or presentation. Declaring potential COI does not necessarily prevent or decrease it [18, 19] and further steps are necessary. Some physicians do not accept personal payments from companies, and some institutions mandate that their physicians not receive personal payments from industry; other academic institutions should be challenged to follow suit [18]. Organizations such as ESMO and ASCO should develop schedules that will require both the organizations and their members to move to financial independence; this would enable them to extend their lobbying of both industry and government for availability of effective treatments at affordable prices, as well as developing independent pharmaco-economic analyses for reasonable pricing. A system that seeks to maximize profit to the detriment of the public despite the public origin of many scientific grants is unethical. While doctors, their institutions and their societies must work with pharmaceutical companies to stimulate the conduct of clinical trials that lead to continuing improvements in therapy, it is not easy for them to name and shame a company for extortionate pricing when they are accepting the company's silver.

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References

1. Tyson P. The Hippocratic Oath Today. http://www.pbs.org/wgbh/nova/body/hippocratic-oath-today.html (18 April 2018, date last accessed).
2. Galkina Cleary E, Beierlein JM, Khanuja NS et al. Contribution of NIH funding to new drug approvals 2010-2016. Proc Natl Acad Sci USA 2018; 115(10): 2329–2334.
3. Barrie SE, Potter GA, Goddard PM et al. Pharmacology of novel steroidal inhibitors of cytochrome P450(17) alpha (17 alpha-hydroxylase/C17-20 lyase). J Steroid Biochem Mol Biol 1994; 50(5–6): 267–273.
4. Tran C, Ouk S, Clegg NJ et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009; 324(5928): 787–790.
5. Iwai Y, Ishida M, Tanaka Y et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002; 99(19): 12293–12297.
6. Dong H, Strome SE, Salomao DR et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002; 8(8): 793–800.
7. Prasad V, Mailankody S. Research and development spending to bring a single cancer drug to market and revenues after approval. JAMA Intern Med 2017; 177(11): 1569–1575.
8. Zafar SY, Peppercorn JM, Schrag D et al. The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. Oncologist 2013; 18(4): 381–390.
9. Perrone F, Jommi C, Di Maio M et al. The association of financial difficulties with clinical outcomes in cancer patients: secondary analysis of 16 academic prospective clinical trials conducted in Italy. Ann Oncol 2016; 27(12): 2224–2229.
10. Amir E, Seruga B, Martinez-Lopez J et al. Oncogenic targets, magnitude of benefit, and market pricing of antineoplastic drugs. J Clin Oncol 2011; 29(18): 2543–2549.
11. Prasad V, De Jesús K, Mailankody S. The high price of anticancer drugs: origins, implications, barriers, solutions. Nat Rev Clin Oncol 2017; 14(6): 381–390.
12. Workman P, Draetta GF, Schellens JHM, Bernards R. How much longer will we put up with $100, 000 cancer drugs? Cell 2017; 168(4): 579–583.
13. DeAngelis CD. Big pharma profits and the public loses. Milbank Q 2016; 94(1): 30–33.
14. Maraninchi D, Vernant J-P. L'urgence de maîtriser les prix des nouveaux médicaments contre le cancer. Le Figaro 2016: http://sante.lefigaro.fr/actualite/2016/03/14/24739-lurgence-maitriser-prix-nouveaux-medicaments-contre-cancer (18 April 2018, date last accessed).
15. American Society of Clinical Oncology. American Society of Clinical Oncology position statement on addressing the affordability of cancer drugs. JOP 2018; 14(3): 187–192.
16. Johnston KL, Go RS. Financial conflicts of interest among ASCO annual meeting abstract authors, speakers, and planners. J Natl Cancer Inst 2007; 99(18): 1415–1416.
17. Bariani GM, de Celis Ferrari AC, Hoff PM et al. Self-reported conflicts of interest of authors, trial sponsorship, and the interpretation of editorials and related phase III trials in oncology. J Clin Oncol 2013; 31(18): 2289–2295.
18. Brennan TA, Rothman DJ, Blank L et al. Health industry practices that create conflicts of interest. A Policy Proposal for Academic Medical Centers. JAMA 2006; 295(4): 429–433.
19. Loewenstein G, Sah S, Cain DM. The unintended consequences of conflict of interest disclosure. JAMA 2012; 307(7): 669–670.

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RET-fusions: a novel paradigm in colorectal cancer

The development of deep sequencing assays has allowed the identification of new oncogenic alterations in solid tumours. In the last decades, multiples gene fusions produced by chromosomal rearrangements have been described, although few of them are clinically relevant [1]. Gene fusions resulting in kinase activation lead to an increased activity in downstream signalling pathways promoting tumour growth and cell survival. Moreover, these kinases represent potential targets for drug development. Kinase fusions involving ALK, ROS1, RET, NTRK1/2/3, FGFR1/2/3, BRAF, CRAF and PRKCA/B have been identified in different tumour types, although frequency and distribution differ between them [2].

In colorectal cancer (CRC) gene rearrangements have been described in <1% of cases [2, 3]. As observed in other tumour types [4], these gene alterations define a subtype of CRC characterised