Our group has recently published the results of the multicenter phase II study exploring panobinostat, a potent HDAC inhibitor in combination with bortezomib in patients with relapsed/refractory PTCL. Overall, the study regimen showed activity across different PTCL subtypes with objective response rate of 43%. Two patients with ENKTL were enrolled. One patient rapidly attained a partial response with reduction in EBV PCR titres (Figure 1), while the other had stable disease [5]. No reactivation of EBV was evident in both cases and their progression-free survivals were 2 and 9 months, respectively. As panobinostat is still not FDA-approved for use in lymphoma, we had recently treated another ENKTL patient who had no further treatment options with romidepsin/bortezomib combination outside the context of a clinical trial. The patient responded favourably with a rapid reduction in his peripheral blood EBV PCR titres after 2 cycles of treatment.

Although the traditional approach to drug development has been geared at assessing a single drug at a time, the FDA had recently issued guidance on the feasibility of co-development of two or more investigational drugs in combination if the combination is intended to treat a serious condition, comes with a strong biological rationale, has substantial activity or is able to provide a better toxicity profile than the individual agents.

Hence, based on our clinical observations, we feel that proteasome inhibition may mitigate the adverse effects of romidepsin-induced EBV reactivation and HDAC inhibitors should be further explored as part of novel combinations in ENKTL.

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**Challenging the soaring price of cancer medicines: a call for equity and transparency**

As expressed by US cancer specialists in a recent petition paper [1], the exponential increase in drug price threatens equal access to cancer care, and the resulting financial distress in patients may impair survival outcome. In Europe, public systems of health insurance still protect most patients, but high prices have resulted in delays or limitations in reimbursement of effective medical innovations and might challenge the sustainability of this social protection model. Why are these drugs so expensive? According to the pharmaceutical industry, it is primarily due to the increasing level of R&D investments required. However, whereas most ‘old-generation’ compounds were derived from time-consuming and costly screening approaches, ‘new-generation’ therapies are mainly specific drugs directed to a priori designed targets, most frequently identified from publicly funded academic research. Furthermore, duration of clinical development and time to regulatory approval have been dramatically reduced. For example, crizotinib was FDA-approved for patients with ALK-rearranged lung cancer in 2011, based on data from phase I/II trials involving a few hundreds of patients, 4 years only after identification of the target [2]. Moreover, conditional or accelerated approvals may also allow early access to the market, based on surrogate end points rather than mature survival data [3]. Another point alleged by the industrials is the need for rewarding innovation and efficacy. However, a recent
US survey failed to demonstrate any significant relationship between novelty or clinical benefit and price of recently registered anticancer drugs [4]. Finally, it has also been argued that high prices are needed to compensate the decrease in market size, inherent to the genomic segmentation of cancers. Yet, the concept of precision medicine, in which treatments are administered according to molecular alterations rather than tumor location, could also lead to an unexpected market expansion, when rare molecular targets in a given malignancy are repeatedly found in a large panel of distinct diseases. In addition, whereas the successful story of immune checkpoint regulators seems to broadly diffuse across many tumor primaries, their prices have reached record highs. Thus, accumulating data indicate that industrials determine the price of novel drugs essentially according to what the local market can tolerate. This explains the significant price differences across different countries for a same drug, as well as the relative opacity in the pricing process itself [5]. Recently, a hundred of French leaders in Oncology and Hematology have launched a national call (http://sante.lefigaro.fr/actualite/2016/03/14/24739-lurgence-maitriser-prix-nouveaux-medicaments-contre-cancer), supporting the following proposals:

- to define a fair price for cancer drugs, based on real investments in R&D (and taking into account the contribution of academic research), allowing a reasonable financial reward;
- to make the process of price determination more democratic and transparent by involving patient and physician representatives;
- to refuse patent extensions for novel drugs when accelerated clinical development does not justify it;
- to authorize the use of compulsory licensing in developing countries, allowing the production and use of generic drugs before patent expiration (as already possible with AIDS drugs).

We believe that these measures should also be debated by cancer specialists at the European level and worldwide.

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