Response to “An innovative mesothelioma treatment based on mir-16 mimic loaded EGFR targeted minicells (TargomiRs)”

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We thank Drs. Viteri and Rosell for their thoughtful comments on our paper “Safety and activity of microRNA-loaded mini-cells in patients with recurrent malignant pleural mesothelioma: a first-in-man, phase 1, open-label, dose-escalation study” published in the October 2017 issue of Lancet Oncology (1).

After examining our data, the reviewers focussed on two questions: (I) what is the precise mechanism of action of this treatment? and (II) how does this new therapeutic approach fit in the current landscape of treatment strategies for malignant mesothelioma? The reviewers mention the significant hurdles experienced by the many investigators who have endeavoured to apply gene therapy to clinical questions in the past. Their comments are very valid and illustrated by the fact that the excitement about the enormous potential of gene therapy for the treatment of cancer 20–30 years ago, was quickly overshadowed by the realisation that we lacked an efficient and reliable carrier to accurately deliver intact RNA/DNA constructs to a sufficient proportion of cells at the “tumour site” (2).

A major hurdle in interpreting the data of our phase I study is related to the rapid disappearance of TargomiRs from the circulation after infusion. In preclinical studies in mice and dogs, EnGeneIC have shown that rapid accumulation of the EnGeneIC Dream Vectors (EDVs) in xenograft tumours 2 hours after administration is followed by rapid clearance from all sites within 24 hours (3). While the unique sequence of our microRNA mimics should afford the ability to detect their delivery to (xenograft) tumours in vivo, this has not proved possible with existing RT-qPCR platforms (4) and will likely require a sequencing-based approach. As biopsies were not foreseen in the first-in-man TargomiR study, we can only theorize that disease control and “tumour” pain in patients treated with epidermal growth factor receptor (EGFR)-targeted EDVs loaded with microRNA mimic was due to their sequestration via the leaky tumour vasculature and endocytosis by tumour cells, as in preclinical models (5-7).

The reviewers were right to propose that pre- and post treatment biopsies will be the key in the future development of TargomiRs. They also suggested that immune responses may provide an alternate explanation for the anti-tumour effects seen in our study and they pointed to the strong immunogenic response elicited by the LPS-containing surface of EDVs. We are unable to exclude that these immune reactions, occurring shortly after the infusion of TargomiRs, provide an explanation for the anti-tumour activity observed in our study. Noteworthy is that no responses were registered with cytostatic-loaded EDVs (8,9). Indeed, free double-stranded RNA could also have been associated with an (innate) immune response (10), but none of the information collected from our pre-clinical studies and our first clinical study suggests that the EDVs are leaky, nor does our sequence contain known stimulatory motifs (11). In addition, only EDVs loaded with active microRNA mimics or siRNAs inhibit tumour growth in vivo; a variety of scrambled or otherwise inactivated controls have no activity (5-7,12). The reviewers also point to the potential contribution of the targeting EGFR antibody (panitumumab) to anti-tumour activity and we agree that with TargomiRs, a combination of gene therapy, immunotherapy and targeting therapy might have been
The unmet need of mesothelioma patients is very high. On the basis of our preclinical data combination therapy seems a logical next step in TargomiR development. Carefully planned trials with a smart/clean design and sufficient attention for future (predictive) biomarkers are obviously the way forward. As indicated earlier, optimal attention for the pharmacology of TargomiRs with pre-and post treatment biopsies is needed to maximally explain the mechanism of action of our novel treatment approach, for mesothelioma as well as for other oncology indications.

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Conflicts of Interest: N van Zandwijk and G Reid are inventors of a patent (US patent 9 006 200) that is owned by the Asbestos Diseases Research Foundation. J McDiarmid and H Brahmbhatt are co-inventors of EDV-based patent families owned by EnGeneIC, and shareholders in EnGeneIC.

References


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