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A Significant Metabolic and Radiological Response after a Novel Targeted MicroRNA-based Treatment Approach in Malignant Pleural Mesothelioma

To the Editor:

Malignant pleural mesothelioma (MPM) is an incurable cancer affecting the pleura and is associated with previous asbestos exposure. Chemotherapy with cisplatin and pemetrexed/raltitrexed are the only treatment regimens that have shown a survival benefit in clinical trials (1, 2). Despite intensive research efforts over the last decade, effective treatment remains elusive.

Recently, microRNAs (miRs) have been identified as important regulators of cancer progression (3). We previously reported consistent down-regulation of expression of members of the miR-15/16 family in MPM cell lines (two- to fivefold compared with normal mesothelial cell line MeT-5A) and tumor specimens (10-fold compared with normal pleura) (4). Synthetic mimics used to restore miR-15 or miR-16 expression in MPM cell lines led to time- and dose-dependent growth inhibition in a panel of MPM cell lines (4). Further, we showed that there was a dose-dependent inhibition of tumor growth using miR-16-containing EnGeneIC Delivery Vehicle (EDV) nanocells (5) in nude mice bearing xenografts derived from the MSTO-H211 MPM cell line (4). These findings formed the basis of the ongoing phase 1 trial MesomiR 1, examining the optimal dose of intravenously administered epidermal growth factor receptor (EGFR)-targeted EDV-packaged miR-16-based mimics (coined TargomiRs for this trial) in patients with MPM and advanced non-small-cell lung cancer (ClinicalTrials.gov NCT02369198). Thus far, six patients have been recruited to cohort 1, in which a weekly dose of 5×10^9 TargomiRs is given for 8 weeks. All six patients have completed the 8 weeks of treatment, and we now report a dramatic response in one patient.

This patient is a 51-year-old plumber who was diagnosed with a right-sided MPM of the epithelial subtype in May 2013; there was no other relevant past medical history. He had surgical pleurodesis and underwent six cycles of platinum/pemetrexed chemotherapy from June to October 2013. After the first cycle of cisplatin, he developed ototoxicity and was subsequently given five cycles of carboplatin. His best response was stable disease according to the modified RECIST (Response Evaluation Criteria in Solid Tumors)

criteria (6). He developed progressive disease in April 2014 and was recommenced on carboplatin and pemetrexed. A partial response was noted after six cycles. However, after 2 months of observation, reevaluation with computed tomography showed progressive pleural disease.

At this point, he consented to the MesomiR 1 trial. Trial screening revealed weak (1+) membranous EGFR staining in 5% of tumor cells (Clone H11; Dako, Carpinteria, CA). His baseline IL-6 level was 20.2 pg/ml, which is considered to be above the normal range. Hence, he received two adapted doses of TargomiRs before the phase 1 dose to minimize the chances of an inflammatory response. He was treated with 1×10^9 TargomiRs in the first week, 2×10^9 in the second week, and 5×10^9 (phase 1 dose) in the following 6 weeks. He experienced minor toxicities: grade 1 toxicity, including transient chills, low-grade fever, fatigue, and headache. However, at the same time, he noticed improvement of chest pain. At the end of the 8-week period, a “complete” metabolic response was evident on his positron emission tomography–computed tomography scan (Figure 1), and a partial response was noted on the chest computed tomography scan (modified RECIST criteria) and confirmed 4 weeks later (see Figure E1 in the online supplement). The objective imaging response was accompanied by a marked improvement in respiratory function test parameters (Table 1).

MesomiR 1 is not the first clinical trial to use a miR mimic-based drug in the treatment of patients with cancer; a phase 1 trial of the miR-34-based MRX34 from Mirna Therapeutics began in April 2013 in patients with hepatocellular carcinoma or liver metastasis of other solid cancers (ClinicalTrials.gov NCT01829971) (7). However, our case is the first report of an objective treatment response using a miR-based therapeutic strategy. In our patient, who had unequivocal disease progression after second-line chemotherapy, a response was identified after only eight weekly infusions of TargomiRs. In a disease that is characterized by treatment resistance and limited efficacy of commonly used second-line options such as vinorelbine and gemcitabine (8), such a response is a very encouraging observation. Furthermore, it is important to note that this response occurred at the first (lowest) dose level investigated.

To put this case report into the context of the first patient cohort, response assessment according to modified RECIST criteria in the other five patients to date included four stable diseases and one progressive disease. Overall, TargomiR treatment was well tolerated during the treatment period. The majority of patients experienced a period of shivering/rigor 80–90 minutes after the start of the infusion, sometimes associated with burning/painful sensations in the area of disease. Laboratory examination revealed a steep but transitory rise in inflammatory cytokines, neutrophilia, and lymphopenia shortly after TargomiR infusion, sometimes accompanied by mild elevation of liver enzymes (see Table E1).

Although encouraging, the results reported here are very preliminary. We are currently recruiting patients into the second cohort, where patients receive 5×10^9 TargomiRs twice weekly as the full dose. At this stage, we have still to determine the maximum tolerated dose and the full extent of potential off-target effects. Given that our patient had as little as 5% EGFR positivity of cancer cells, such dramatic response with an EGFR-targeted therapeutic suggests that other mechanisms must be at play, inducing this impressive result. In addition to the heterogeneous response to the TargomiR treatments observed so far, we recognize the importance of identifying factors that may predict response to TargomiRs for

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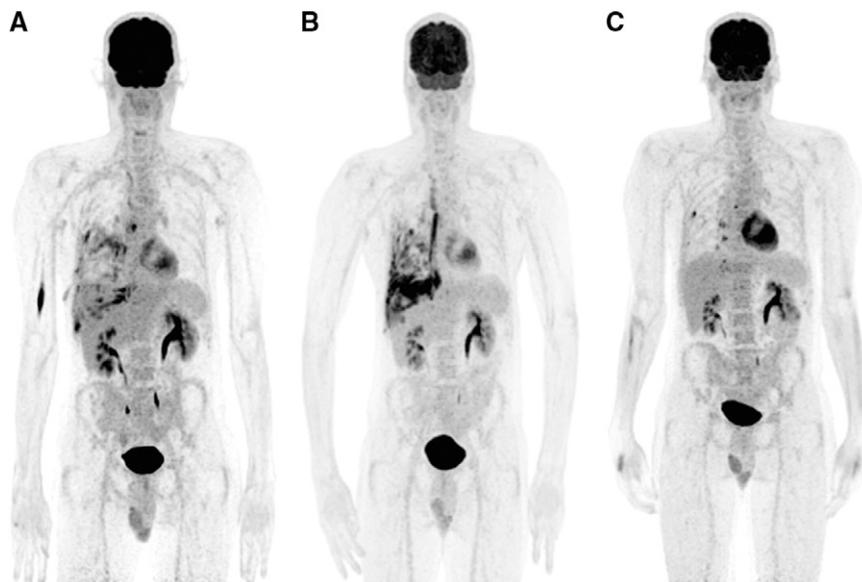


Figure 1. Coronal fluorodeoxyglucose positron emission tomography/computed tomography maximum intensity projection images from serial whole-body scans performed on a Biograph mCT (120-slice device with time-of-flight technology; Siemens Healthcare, Hoffman Estates, IL) with a 60-minute uptake period for all scans performed at (A) baseline (diagnosis), (B) before commencement of MesomiR 1, and (C) after 8 weeks of treatment. In A, there is discontinuous moderate to markedly increased fluorodeoxyglucose uptake throughout the right-sided pleura, and peak standard uptake value laterally in the right lateral costophrenic angle was 7.5. In B, at disease progression there is much more extensive abnormal uptake throughout the pleura, and peak standard uptake value was 17.1. In C, there is a dramatic reduction in the extent and degree of abnormal fluorodeoxyglucose uptake in the right pleura, and peak standard uptake value was 2.7, which reflects an 84% reduction in tracer uptake; the small focal regions of increased fluorodeoxyglucose uptake in the pleura reflect areas of inflammation related to the talc pleurodesis.

better patient stratification, and efforts will be made during planned phase 2 studies.

In conclusion, this proof-of-concept case illustrates the promise of this novel strategy using targeted EDV nanocells to restore the expression of down-regulated miRs in MPM. Such an approach, if supported by further evaluation, has the potential for a paradigm shift in the management of treatment-resistant tumors such as MPM. We are eagerly awaiting the determination of the maximum tolerated dose of TargomiRs and commencement of subsequent phase 2 studies to confirm the efficacy of this novel therapeutic approach. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Table 1. Respiratory Function Parameters at Screening and 8 Weeks after TargomiR Treatments

	Baseline	8 Weeks after Treatment	Change (%)
FEV ₁ , L	2.9	3.7	+28
FVC, L	3.84	5.22	+36
DL _{CO} corr, ml/min/mm Hg	25.7	31.06	+21
TLC, L	6.04	7.88	+30

Definition of abbreviations: DL_{CO}corr = corrected diffusing capacity of the lung for carbon monoxide; TLC = total lung capacity.

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References

- Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C, *et al.* Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003;21:2636–2644.
- van Meerbeeck JP, Gaafar R, Manegold C, Van Klaveren RJ, Van Marck EA, Vincent M, Legrand C, Bottomley A, Debruyne C, Giaccone G; European Organisation for Research and Treatment of Cancer Lung Cancer Group; National Cancer Institute of Canada. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005; 23:6881–6889.
- Reid G, Kirschner MB, van Zandwijk N. Circulating microRNAs: association with disease and potential use as biomarkers. *Crit Rev Oncol Hematol* 2011;80:193–208.
- Reid G, Pel ME, Kirschner MB, Cheng YY, Mugridge N, Weiss J, Williams M, Wright C, Edelman JJ, Vallely MP, *et al.* Restoring expression of miR-16: a novel approach to therapy for malignant pleural mesothelioma. *Ann Oncol* 2013;24:3128–3135.
- MacDiarmid JA, Mugridge NB, Weiss JC, Phillips L, Burn AL, Paulin RP, Haasdyk JE, Dickson KA, Brahmabhatt VN, Pattison ST, *et al.* Bacterially derived 400 nm particles for encapsulation and cancer cell targeting of chemotherapeutics. *Cancer Cell* 2007;11: 431–445.
- Tsao AS, Garland L, Redman M, Kernstine K, Gandara D, Marom EM. A practical guide of the Southwest Oncology Group to measure malignant pleural mesothelioma tumors by RECIST and modified RECIST criteria. *J Thorac Oncol* 2011;6:598–601.
- Bader A. miR-24: a microRNA replacement therapy is headed to the clinic. *Front Genet* 2012;3:120.
- Zauderer MG, Kass SL, Woo K, Sima CS, Ginsberg MS, Krug LM. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. *Lung Cancer* 2014;84:271–274.

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Is Endobronchial Ultrasound Influenced by Sedation Strategy? Comparing Apples to Apples

To the Editor:

We read with great interest the recently published article by Casal and colleagues (1) on the differences in yield, complications, and tolerance of endobronchial ultrasound (EBUS) when performed under moderate sedation versus general anesthesia. Randomized controlled trials are all too rare in the evolving field of interventional pulmonology, and we commend the authors for their efforts in driving the specialty forward. However, we believe the results and conclusions of this trial are not generalizable to most providers. We base our opinion on the following premises: First, the trial is not powered to show either noninferiority or equivalence between moderate sedation and general anesthesia (2). The authors' conclusion that "EBUS-[transbronchial needle aspiration] performed under moderate sedation results in comparable diagnostic yield, rate of major complications and patients' tolerance as [general anesthesia]" implies the performance of an equivalence analysis, which was not the design of this study. To show that moderate sedation is not unacceptably worse than general anesthesia for EBUS procedures, an equivalence study powered to show equivalence within 5% (given a yield of 71%) would in fact require 267 patients per group. Within 2%, the number required would be 1,623 per group.

Second, the patient population appears to differ from the general population, perhaps in part because the patient population served by the Veterans Health Administration is substantially different from the general public. The diagnostic yield of EBUS in this population was 70%, which is much higher than that reported in other studies (3, 4). With rapid on-site evaluation available, this high proportion of EBUS cases with diagnostic material identified during the procedure could have obscured a benefit of deeper anesthesia for more complex procedures, such as, for instance, the systematic mediastinal staging of a radiologically normal mediastinum before lung cancer resection.

In conclusion, although we support and agree with a practice of EBUS under moderate sedation for most directed biopsies, we remain unconvinced that moderate sedation and general anesthesia are, in general, equivalent modalities for EBUS procedures. Although there is no question that targeted EBUS biopsies may be performed under minimal sedation, lengthy and more technically challenging EBUS procedures such as complete mediastinal staging or small intrapulmonary node sampling may still benefit from deeper sedation, particularly when less experienced providers or pulmonary trainees are performing the procedure. ■