TG4010 immunotherapy: a novel weapon against advanced non-small cell lung cancer?

Ramon Andrade de Mello[1,2,3]

[1]Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal; [2]School of Medicine, University of Porto, Porto, Portugal; [3]Head of the Clinical Research Center (Medical Oncology/Hematology), Hospital Haroldo Juaçaba, Instituto do Câncer do Ceará (ICC), Fortaleza, Ceará, Brazil

Correspondence to: Ramon Andrade de Mello, MD, PhD. Department of Biomedical Sciences and Medicine, University of Algarve, Campus de Gambelas, Edifício 7, ala nascente, 3o. andar, 8005-139, Faro, Portugal. Email: ramondemello@gmail.com.

Submitted Apr 10, 2016. Accepted for publication Apr 13, 2016.
doi: 10.21037/atm.2016.04.16
View this article at: http://dx.doi.org/10.21037/atm.2016.04.16

Over 1.5 million new cases of non-small cell lung cancer (NSCLC), a highly aggressive disease, are registered worldwide every year (1). Until the 1980s, treatment generally yielded poor outcomes (2), and prognosis was only good for early stages of operable disease. However, advances in targeted molecular therapy since 2005 have brought new hope to patients with advanced NSCLC, especially those harboring the *epidermal growth factor receptor* (*EGFR*) mutation in exons 18, 19 and 21 (3). As a result, the median overall survival (OS) of a small group of patients with advanced NSCLC increased from 10 to 18–36 months (2). The fusion of the *EML4* gene (echinoderm microtubule-associated protein-like 4) and the *ALK* gene (anaplastic lymphoma kinase) affects the outcome of almost 5% of patients with this phenotype (2,4). Indeed, patients with this profile presented a very good overall response rate (74%) when submitted to treatment with crizotinib (an ALK-inhibitor) in the clinical trial PROFILE 1014 (5). More recently, resistance mechanisms to EGFR and ALK inhibitors have raised concerns regarding disease progression. However, the use of checkpoint inhibitors targeting the mechanisms of CTLA4 (cytotoxic T-lymphocyte-associated protein 4) and PD1/PDL1 (programmed cell death protein 1 and ligand) has become a cornerstone in the treatment of NSCLC (6,7). Several drugs (e.g., ipilimumab, pembrolizumab and nivolumab) have been shown to be efficient and safe in the treatment of advanced NSCLC, though their mechanisms are still not fully understood (7,8). Quoix *et al.* recently published promising results from phase 2b/3 TIME trial (9). TG4010 is a modified vaccinia Ankara expressing MUC1 and interleukin 2. In addition, baseline levels of CD16, CD56 and CD69 (triple-positive activated lymphocytes; TrPAL) were measured to evaluate their potential as predictive biomarkers. The authors recruited 222 previously untreated stage IV NSCLC patients without a known activating EGFR mutation and with MUC1 expression in at least 50% of tumor cells, stratified them according to baseline TrPAL levels and allocated them to two groups (TG4010 + chemotherapy *vs.* placebo + chemotherapy) of 111 patients each. Progression-free survival (PFS) was longer in the former than in the latter (5.9 *vs.* 5.1 months, P=0.019), but overall survival (OS) was statistically similar in the two groups (12.7 *vs.* 10.6 months, respectively; P=0.055). In patients with non-squamous histology and TrPAL levels below the upper limit of normal (ULN), survival was longer when TG4010 was administered (PFS: 6.0 *vs.* 4.9 months, P=0.0033; OS: 15.1 *vs.* 10.3 months, P=0.0072). No significant difference was observed between the groups with regard to PDL1 levels, but patients in the TG4010 group experienced more grade 1 and 2 adverse events (fatigue: 51% *vs.* 47%; nausea: 46% *vs.* 40%; injection site reaction: 33% *vs.* 4%; dyspnea: 23% *vs.* 8%). Thus, in clinical practice premedication should be combined with appropriate anti-emetics, anti-histaminics and steroids to minimize adverse reactions and increase tolerability.

Considering the good results of this trial for patients with non-squamous histology and TrPAL levels below ULN, TG4010 appears to be a promising alternative to extend OS in the first-line setting for patients without the *EGFR* mutation or *ALK* fusion. In addition, nivolumab and pembrolizumab showed activity against advanced NSCLC in a second line setting; however a strong biomarker (PDL1 expression) unfortunately was not validated to this setting, providing a lack of efficacy information for those approaches. As for toxicity, the potential adverse effects of these new drugs require further study to ensure tolerability and quality of life. The validation of TrPAL levels as a new biomarker is urgently needed to tailor therapy for NSCLC patients and may represent the beginning of a new era in immunotherapy for NSCLC.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Commentary commissioned by Section Editor Jianrong Zhang, MD (Department of Thoracic Surgery, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease, Guangzhou, China).
Conflicts of Interest: RA de Mello received advisory board honoraria from Pfizer, support from the National Science Center in Krakow (Poland), and educational grants from Pierre Fabre, Merck and Amgem. RAM is an *ad hoc* consultant for the Brazilian Ministry of Health in Brasília.

Cite this article as: de Mello RA. TG4010 immunotherapy: a novel weapon against advanced non-small cell lung cancer? Ann Transl Med 2016;4(9):185. doi: 10.21037/atm.2016.04.16

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
2. de Mello RA, Madureira P, Carvalho LS, et al. EGFR and KRAS mutations, and ALK fusions: current developments and personalized therapies for patients with advanced non-small-cell lung cancer. Pharmacogenomics 2013;14:1765-77.
3. de Mello RA, Pires FS, Marques DS, et al. EGFR exon mutation distribution and outcome in non-small-cell lung cancer: a Portuguese retrospective study. Tumour Biol 2012;33:2061-8.
4. D'Arcangelo M, Hirsch FR. Clinical and comparative utility of afatinib in non-small cell lung cancer. Biologics 2014;8:183-92.
5. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167-77.
6. de Mello RA, Pousa I, Pereira D. Nivolumab for advanced squamous cell lung cancer: what are the next steps? Lancet Oncol 2015;16:234-5.
7. Domingues D, Turner A, Silva MD, et al. Immunotherapy and lung cancer: current developments and novel targeted therapies. Immunotherapy 2014;6:1221-35.
8. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-28.
9. Quoix E, Lena H, Losonczy G, et al. TG4010 immunotherapy and first-line chemotherapy for advanced non-small-cell lung cancer (TIME): results from the phase 2b part of a randomised, double-blind, placebo-controlled, phase 2b/3 trial. Lancet Oncol 2016;17:212-23.

