REVIEW ARTICLE

Progress in the Management of Advanced Thoracic Malignancies in 2017

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ABSTRACT

The treatment paradigm of NSCLC underwent a major revolution during the course of 2017. Immune checkpoint inhibitors (ICIs) brought remarkable improvements in response and overall survival both in unselected pretreated patients and in untreated patients with programmed death ligand 1 expression of 50% or more. Furthermore, compelling preliminary results were reported for new combinations of anti–programmed cell death 1/programmed death ligand 1 agents with chemotherapy or anti–cytotoxic T-lymphocyte associated protein 4 inhibitors. The success of the ICIs appeared to extend to patients with SCLC, mesothelioma, or thymic tumors. Furthermore, in SCLC, encouraging activity was reported for an experimental target therapy (rovalpituzumab teserine) and a new chemotherapeutic agent (lurbinectedin). For oncogene-addicted NSCLC, next-generation tyrosine kinase inhibitors (TKIs) (such as osimertinib or alectinib) have demonstrated increased response rates and progression-free survival compared with first-generation TKIs in patients with both *EGFR*-mutated and ALK receptor tyrosine kinase gene (*ALK*)-rearranged NSCLC. However, because of the lack of mature overall survival data and considering the high efficacy of these drugs in patients with NSCLC previously exposed to first- or second-generation TKIs, definitive conclusions concerning the best treatment sequence cannot yet be drawn. In addition, new oncogenes such as mutant *BRAF*, tyrosine-protein kinase met gene (*MET*) and erb-b2 receptor tyrosine kinase 2 gene (*HER2*), and ret proto-oncogene (*RET*) rearrangements have joined the list of potential targetable drivers. In conclusion, the field of thoracic oncology is on the verge of a breakthrough that will open up many promising new therapeutic options for physicians and patients. The characterization of biomarkers predictive of sensitivity or resistance to immunotherapy and the identification of the optimal therapeutic combinations (for ICIs) and treatment sequence (for oncogene-addicted NSCLC) represent the toughest upcoming challenges in the domain of thoracic oncology.

Keywords: Thoracic oncology; Advances in 2017; Immunotherapy; Target therapy; Thoracic; malignancies

Introduction

The year 2017 was one of the most active regarding the field of thoracic malignancy therapeutics. Immune checkpoint inhibitors (ICIs), in particular, anti–cytotoxic T-lymphocyte associated protein 4 (CTLA4) and anti–programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) agents (Fig. 1*A* and *B*), represent the most important recent developments in the management of thoracic tumors. Their role in patients with previously treated advanced NSCLC was consolidated, and they also emerged as key players in patients with untreated advanced NSCLC as monotherapy or in combination. Additionally, at least five early studies showed promising results for ICIs in patients with previously treated advanced SCLC,[1] thymic epithelial tumors,[2,3] and mesothelioma.[4,5] In the field of precision medicine, besides *EGFR*, ALK receptor tyrosine kinase gene (*ALK*), and *BRAF* molecular alterations (Fig. 2), recently emerged new potentially actionable targets included ret proto-

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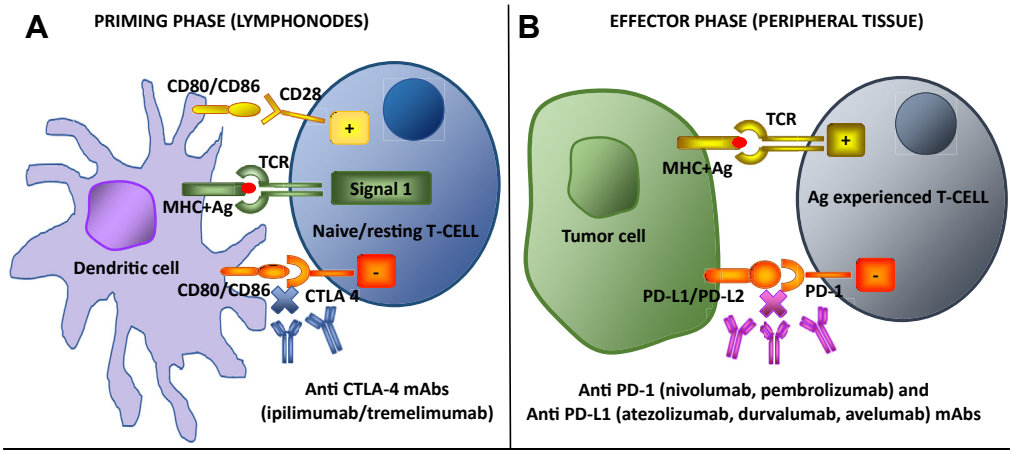

Figure 1. Mechanisms of action of cytotoxic T-lymphocyte associated protein 4 (CTLA4) (*A*) and programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) (*B*) inhibitors in different phases of the anticancer immune response. MHC, major histocompatibility complex; Ag, antigen; mAb, monoclonal antibody; TCR, T-cell receptor; PD-L2, programmed death ligand 2.

oncogene (*RET*) rearrangements and mutations in erb-b2 receptor tyrosine kinase 2 gene (*HER2*) and *EGFR* exon 20. Next-generation tyrosine kinase inhibitors (TKIs) proved to be more active than first-generation drugs in patients with *EGFR*-mutated[6] and *ALK*-rearranged[7,8] NSCLC, although definitive conclusions cannot be drawn about the best treatment sequence able not only to improve progression-free survival (PFS) but also to positively affect overall survival (OS). In this review we cover the main advances regarding immunotherapy, targeted therapy, and chemotherapy in patients with NSCLC, for both pretreated and treatment-naive populations, with a particular focus on targeted therapies. Figure 3 presents current standard therapies and sequences in NSCLC treatment and highlights new options. Studies with targeted therapies and chemotherapy in SCLC, mesothelioma, and thymic tumors are also summarized.

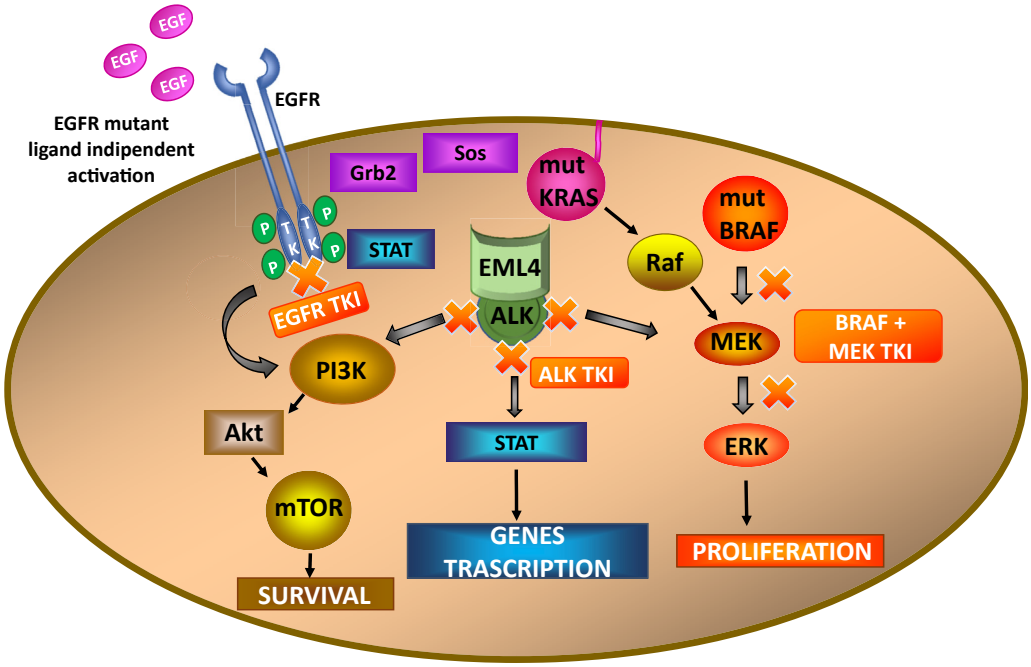

Figure 2. Intracellular signalling pathways activated by *EGFR* mutations, ALK receptor tyrosine kinase gene (*ALK*) rearrangements, and *KRAS*/*BRAF* mutations. EGF, epidermal growth factor; Grb2, growth factor receptor bound protein 2; mut, mutated; STAT, signal transducer and activator of transcription; EML4, echinoderm microtubule associated protein like 4; TKI, tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin.