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MELANOCYTIC TUMOUR PATHOLOGY

Targeted therapies and immune checkpoint inhibitors in the treatment of metastatic melanoma patients: a guide and update for pathologists

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Summary

The previously dismal prospects for patients with advanced stage metastatic melanoma have greatly improved in recent years. Enhanced understanding of both the pathogenesis of melanoma and its molecular drivers, as well as the importance and regulation of anti-tumour immune responses, have provided new therapeutic opportunities for melanoma patients. There are two major distinct categories of systemic treatments with activity for patients with metastatic melanoma: (1) targeted therapies, which act to inhibit the oncogenes that drive the aberrant growth and dissemination of the tumour; and (2) immune checkpoint inhibitor therapies, which act to enhance anti-tumour immune responses by blocking negative regulators of immunity. Pathologists play a critical and expanding role in the selection of the most appropriate treatment for individual metastatic melanoma patients in the modern era of personalised/precision medicine. The molecular pathology testing of melanoma tumour tissue for the presence of targetable oncogenic mutations is already part of routine practice in many institutions. In addition, other potential oncogenic therapeutic targets continue to be identified and pathology testing techniques must readily adapt to this rapidly changing field. Recent research findings suggest that pathological assessment of tumour associated immune cells and immunosuppressive ligand expression of the tumour are likely to be important in identifying patients most likely to benefit from immune checkpoint inhibitors. Similarly, pathological and molecular observations of on-treatment tumour tissue biopsies taken from patients on targeted therapies have provided new insights into the mechanisms of action of targeted molecular therapies, have contributed to the identification of resistance mechanisms to these novel therapies and may be of higher value for selecting patients most likely to benefit from therapies. These data have already provided a rational biological basis for the exciting prospect of combining them to further improve survival rates and this is currently being investigated in clinical trials. Ultimately it may be the responsibility of the pathologist to identify which therapy or combination of therapies is most likely to benefit individual patients.

Key words: BRAF; diagnosis; immune blockade; immunochemistry; melanoma; pathology; PD-1; PD-L1; targeted therapy; therapy; TILs; treatment.

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INTRODUCTION

The prevalence of cutaneous melanoma is increasing.[1] Even though it is curable with local excision in the majority of cases if it is detected at an early stage when it remains localised to the skin, metastatic disease carries an extremely poor prognosis.[2] Until recently, systemic therapies were either ineffective, with response rates of less than 10% (e.g., dacarbazine),[3] or only suitable for a highly selective subgroup of patients because they had limited benefit and were associated with high toxicity (e.g., IL-2).[4] Regardless of the treatment regimen, the median overall survival for stage IV melanoma patients was only 6–9 months. In recent years, the rapidly evolving understanding of tumour biology and immunity has provided the basis for the more rational design of effective systemic therapies that have improved outcomes for patients with metastatic melanoma. In particular, the identification of specific driver oncogenes and greater understanding of immune checkpoints and their role in anti-tumour immune responses have underpinned this. Drugs targeting BRAF, MEK, CTLA-4 and PD-1 have entered routine clinical oncological practice. A large number of clinical trials, designed to determine which combinations and sequencing of therapies will further enhance the remarkable benefits of these therapies already achieved, are currently under way. This review highlights the recent exciting advances in the treatment paradigm of advanced stage metastatic melanoma patients and their implications for pathologists. The critical role of pathologists in the selection of the most appropriate treatment for individual patients and ongoing advances in the field are expanded upon.

TARGETED THERAPIES

Targeted therapies act to inhibit specific abnormal proteins, which are encoded by oncogenes with specific mutations,

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causing uncontrolled tumour cell proliferation and inhibition of apoptosis. These include mutations in genes such as *BRAF*, *NRAS*, and *MEK* in the mitogen-activated protein kinase (MAPK) pathway (Fig. 1A) and *PTEN*, *AKT*, and *PIK3CA* in the phosphoinositide 3-kinase (PI3K) pathway. A summary of the most common mutations driving melanoma was recently reported by The Cancer Genome Atlas (TCGA) network.[5] The most common mutation in melanoma affects

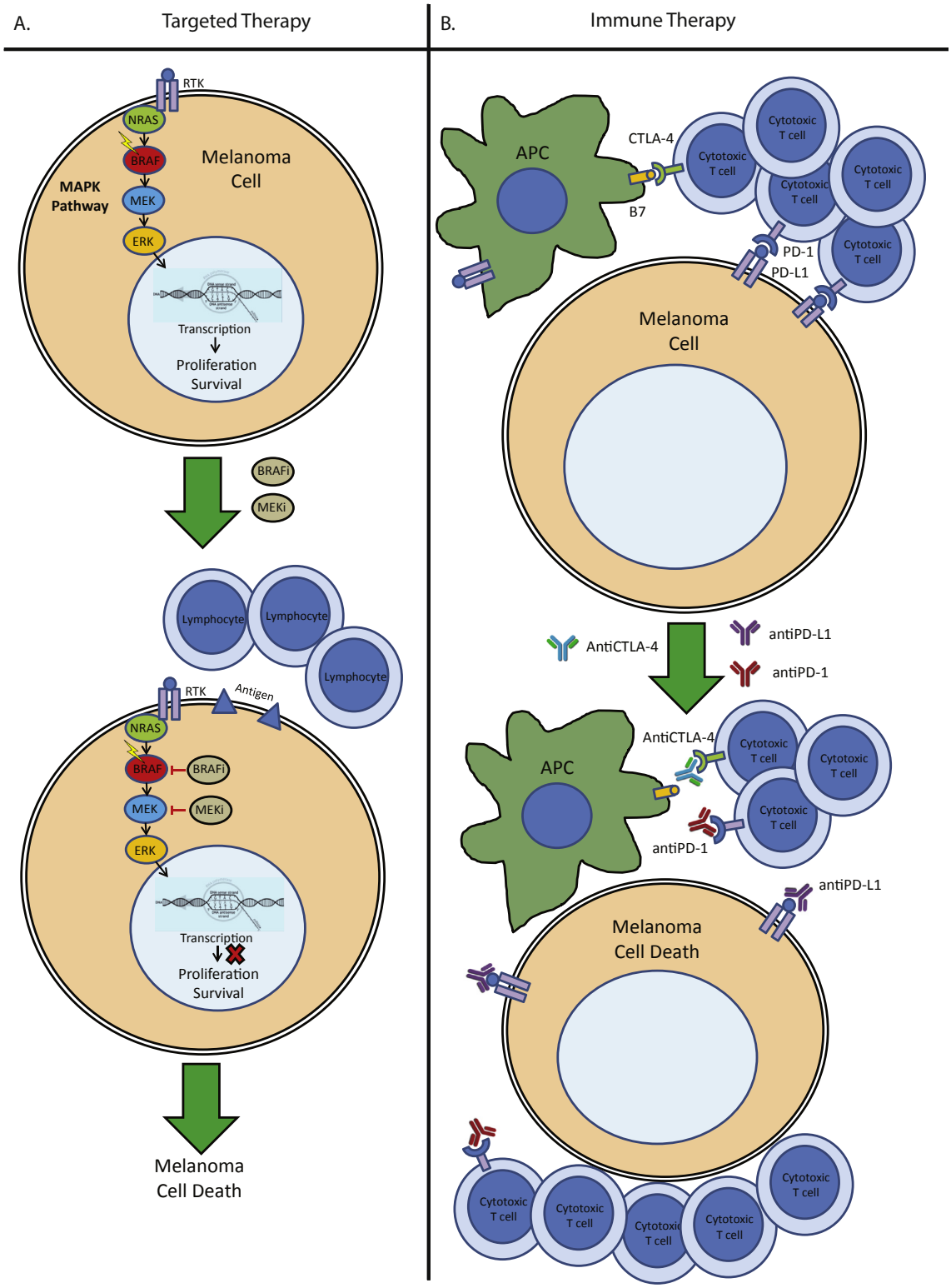

Fig. 1 Schematic diagram of targeted and immune therapies. (A) The treatment of patients with the combination of BRAF and MEK inhibitors to *BRAF* mutant melanoma inhibits signalling through the MAPK pathway, which leads to tumour cell death and an influx of lymphocytes and macrophages early during treatment. (B) The treatment of patients with anti-CTLA-4 and anti-PD-1/PD-L1 inhibitors allows tumour-specific lymphocytes to exert their anti-tumour cytotoxic effects by blocking CTLA-4 on antigen presenting cells, PD-1 on lymphocytes or PD-L1 on tumour cells.