Journal Watch

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Melanoma Management

Journal Watch: our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of melanoma management

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Hauschild A, Dummer R, Schadendorf D *et al*. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected BRAF V600-mutant Stage III melanoma. *J. Clin. Oncol*. 36(35), 3441–3449 (2018)

This publication, an update of the COMBI-AD trial, provides the most mature data with extended follow-up in Stage III metastatic melanoma patients treated with immune checkpoint or targeted therapies in the adjuvant setting. The results of this study of Stage III BRAF V600 mutant metastatic melanoma continue to show relapse-free survival (RFS) benefit at 40 months of dabrafenib plus trametinib therapy over placebo with an absolute difference of almost 20% between the arms. The RFS benefit was also confirmed regardless of stage, clinical and pathological subgroups. For the first time, the somewhat controversial, Weibull mixture cure-rate analysis has been used in metastatic melanoma patients and showed estimated cure rates of 54% (treatment arm) versus 37% (placebo arm). Moving forward it will be interesting to compare these results with the results of immunotherapy and combinations therapy trials in the adjuvant and neoadjuvant setting to ascertain the optimal treatment protocol for BRAF-mutant metastatic melanoma patients.

– Written by Robert V Rawson

Long GV, Atkinson V, Lo S *et al*. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised Phase II study. *Lancet Oncol*. 19, 672–81 (2018)

While immunotherapy with PD-1 or anti-CTLA4 checkpoint inhibitors, or both, improves survival of patients with advanced melanoma, efficacy in active brain metastases is unknown because these patients are largely excluded from clinical trials due to their poor prognosis.

This randomized Phase II study investigated the efficacy and safety of nivolumab alone or in combination with ipilimumab in 79 enrolled patients with active melanoma brain metastases. Two randomized cohorts of asymptomatic untreated (no previous local brain-directed therapy) patients (cohorts A and B) and a third non-randomized cohort with poor prognostic features including those who had failed local therapy, had neurological symptoms or had leptomeningeal disease (cohort C) were included in the study. A total of 46% of cohort A (nivolumab combined with ipilimumab), 20% of cohort B (nivolumab alone) and 6% of cohort C (nivolumab alone) achieved durable intracranial response.

Given the enhanced and sustained intracranial responses observed in this study, the authors propose that patients with asymptomatic untreated brain metastases should be considered candidates for combination nivolumab and ipilimumab as first-line therapy.

– Written by Teresa Bailey

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Mao P, Brown AJ, Esaki S *et al*. ETS transcription factors induce a unique UV damage signature that drives recurrent mutagenesis in melanoma. *Nat. Commun*. 9(1), article number: 2626 (2018)

The increased rate of somatic mutations in ETS transcription factor binding sites (TFBS) in active promoters in melanoma has been noted by several investigators.

These somatic mutations are closely related to ultraviolet irradiation, and are present in cutaneous melanoma and other cutaneous malignancies. In a recent article, Mao *et al*. demonstrate the molecular mechanism behind the increased somatic mutation burden at these sites. Using a single-nucleotide resolution map of cyclopyrimidine dimer lesions in UV-irradiated human cells, they confirm that there is increased cyclopyrimidine dimer formation at these particular sites. Using *in vitro* assays, they generated the same somatic mutations using ultraviolet irradiation of DNA template and purified ETS1 protein. This study establishes ETS-driven conformational changes as leading to increased somatic mutation burden in ETS TFBS from ultraviolet irradiation. It suggests that the increased mutation frequency is a result of local steric effects and not restricted access by DNA repair molecules.

– Written by Andrew Colebatch

Nsengimana J, Laye J, Filia A *et al*. β-Catenin-mediated immune evasion pathway frequently operates in primary cutaneous melanomas. *J. Clin. Invest*. 128(5), 2048–2063 (2018)

Cutaneous melanoma is variable in its clinical behavior and response to systemic immunotherapy. The immune microenvironment of primary melanoma is known to be heterogeneous, but substantial studies with clinical outcomes are lacking. Here the authors characterize the immune landscape of a large cohort of primary cutaneous melanomas (n = 703) through analysis of whole transcriptome data. Using transcripts specific to discrete immune cell types within the tumor microenvironment, melanomas are classified into six distinct subgroups called consensus immunome clusters (CIC). The most prevalent subgroup (CIC4; 25%), shows the worst prognosis, the lowest immune scores and increased β-catenin signaling, consistent with an immunosuppressive microenvironment. A wealth of data is supported by long-term clinical follow-up (median 7.5 years), multivariate analysis for clinicopathological parameters, correlation with oncogenic mutations and verification using The Cancer Genome Atlas. This landmark paper charts the heterogeneity of the primary melanoma immunome, providing insights into how immune stratification of melanoma may improve selection of patients for immunotherapy.

– Written by Peter Ferguson

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