Meta-Review of Melanoma Treatment: Current & Future Strategies

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Executive Summary

This meta-review provides a comprehensive review of melanoma pathogenesis, its diagnoses and current treatment, and investigational therapeutics. It is divided into four sections: Genetic and Molecular Pathogenesis of Melanoma, Current & Emerging Approaches: Meta-Review of Melanoma Diagnosis & Staging, Current Best Practices in Melanoma Treatment Review, and New Landscape in Melanoma Treatment Review.

Genetics & Molecular Pathogenesis of Melanoma: New insight into genetic predisposition to melanoma, the pathogenesis of the disease, and its evasion of the immune system response is described. Considering the literature meta-review, a profile of known genetic risk factors that increase an individual's risk of developing melanoma and summarized the current hypothesis and knowledge-based relating to disruption of key signaling pathways (e.g., RAS/MAPK, RAS/PI3K pathways). Also, the role of immune surveillance defects in understanding melanoma oncogenesis (e.g, melanoma oncogenes-KIT and MITF). The aim is to explore the relationship between the increased understanding melanoma pathogenesis and clinical implications in future progress in improving prognosis and treatment options.

Current and Emerging Approaches Meta-Review of Melanoma Diagnosis & Staging: A meta-review of cutting-edge research for treatment of advanced melanoma, including immunotherapies, antibodies, and chemotherapeutic combinations, including the identification of agents and current clinical development status under investigation in melanoma that target signaling pathways that are dysregulated due to mutations in BRAF, cell-based immunomodulatory therapy approaches and recent data summarizes for enhancing immune response to melanoma, potential approaches for enhancing tumor supressor gene function in melanoma. The aim is to discuss targeted immunologic agents under study in melanoma and potential opportunities predictive modeling opportunities using a pathway/mechanistic approach to identify clinical development product life cycle pathways, treatment options, and future understanding of melanoma pathogenesis as a clinical development tool.

Current Melanoma Treatment: Best Practices Review: A meta-review of current therapeutic options for patients with melanoma across the continuum of progression, from the localized to metastatic, including current recommended clinical practice for localized melanoma excision, patient selection for sentinel lymph mode biopsy, current evidence regarding the interferon alfa adjuvant therapy efficacy in preventing relapse and extending survival in patients with high-risk melanoma. The aim is to summarize the clinical data on the efficacy of chemoimmunotherapy in advance melanoma patients and identification of investigational agents for systemic therapy of melanoma being evaluated in the clinical trial setting.

New Landscape in Melanoma Treatment Review: A meta-review of cutting-edge research for treatment of advanced melanoma, including immunotherapies, antibodies, and chemotherapeutic combinations, including the identification of agents and current clinical development status under investigation in melanoma that target signaling pathways that are dysregulated due to mutations in BRAF, cell-based immunomodulatory therapy approaches and recent data summarizes for enhancing immune response to melanoma, potential approaches for enhancing tumor supressor gene function in melanoma. The aim is to discuss targeted immunologic agents under study in melanoma and potential opportunities predictive modeling opportunities using a pathway/mechanistic approach to identify clinical development product life cycle pathways, treatment options, and future understanding of melanoma pathogenesis as a clinical development tool.

Considering the meta-review, an impact gap analysis was perform to provide future direction for clinical development of agent or combination agents.

IMPACT GAP ANALYSIS

Considering the literature information in the meta-review, the following predictive modeling assessment is recommended to provide increase clarity in clinical development schemes/programs:

- Based on the increased knowledge of pathologic mutations (i.e., KIT, NRAS, BRAF, MITF, MEK, ERK), the effect of aberrant regulations of signal transduction pathways (i.e., RAS/MAPK, PTEN/PI3/AKT)1 & chaperones/supressors (i.e, HSP90, proteasomes), & dysregulation of anti-tumor immunity (i.e, indoleamine 2,3-deoxygenase, CD28, CTLA-4), a preliminary assessment of the molecular target profile of all drugs, biologics, & compounds using the Discovery Alogthrim methodology (e.g., explicit, indirect, & implicit)

- The current approved/investigatory therapies (e.g., decarbazine, INF-alpha, IL-2, oblimersen, sorafenib, temsirolmus, PD0325901, RAF265, tremelimumab, ipilimumab, etc) can be evaluated to determine the molecular target inhibitory profile and can be used to forecast the impact of single agent, optimizing the drug combination regimen options to impact clinical outcomes (e.g., the greater molecular target inhibitory coverage may lead to better outcomes) and can clarify which treatments may be better for the different melanoma subclasses to optimize protocol development

- Identification of known and unknown agents & compounds that may have molecular target inhibitory profile as a single agent and in combination as potential clinical development program

- To maximize the benefit of treatment—and avoid unnecessary risk, a patient's molecular profile can be assess to determine dx prognosis and to determine the potential treatment options to maximize patient outcome. This can be used as a protocol screening tool.

- Exploratory approach to identify less apparent biomarkers in the signal transduction pathways, dendritic cell dysregulation, etc that have not been investigated that may further increase our knowledge based of the molecular pathogenesis of melanoma.

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