Commentary

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Melanoma Management

# Evolving treatments and future therapeutic targets in desmoplastic melanoma

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"Immunotherapies have ushered in a new and promising generation of anticancer therapies providing durable responses across multiple tumor types"

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Desmoplastic melanoma (DM) is a rare and histopathologically distinct type of melanoma that is a subvariant of spindle cell melanoma [1]. It has a strong association with chronic sun exposure and usually occurs later in life. Incidence is reported to be less than four percent of cutaneous melanomas. Early diagnosis can be challenging because DM is predominantly dermal and often amelanotic [2]. The diagnosis can be difficult not only clinically but also histologically, as DM can be mistaken for a variety of benign and malignant nonmelanocytic spindle cell tumors. Histology of DM is divided into pure and mixed types, and this classification plays an important role in prediction of clinical outcomes [3]. Pure DM tends to have less potential for metastasis and as a result has a more favorable prognosis than mixed DM [4]. DM commonly demonstrates local invasion with poor circumscription due to its infiltrative nature which results in a high recurrence rate. It primarily affects patients with fair skin with age distribution of 60–80 years old and male-to-female ratio of two–one [5]. The overall survival for patients with DM is relatively favorable despite its depth at diagnosis with median survival at 5 and 10 years of 84.8 and 79.2 %, respectively [6]. Advanced age of the patient, higher stage of the tumor as well as increased Breslow depth were found to be independent positive factors associated with DM [7]. While established DM treatment options are surgical excision, sentinel lymph node biopsy, systemic chemotherapy and radiation therapy, a number of genetic mutations associated with DM have shown it to be responsive to targeted therapies. This review will focus on the future of DM therapy, which lies in better targeted therapy approaches and better penetration into the tumor core leading to more robust responses to therapeutic agents.

## Targeted therapies

As additional information about genetic structure and mutations associated with DM becomes available, more opportunities for targeted therapies are discovered. DM carries a particularly high mutation burden when compared with other melanomas [8]. A comprehensive genomic profiling on 1240 melanoma cases, 12 of which were DM [9] demonstrated that the average observed tumor mutational burden in DM was 77 mutations/Mb, compared with 35 mutations/Mb identified in other nondesmoplastic melanomas. In the same study 83% of DM cases studied indicated an ultraviolet light related mutational signature with C>T and G>A mutations responsible for more than 80% of the base substitutions. It was concluded that the *TP53* gene was mutated in 75% of DM cases. Other less frequent but prominent mutations observed in DM cases include neurofibromin 1, neurofibromin 2, cyclin-dependent kinase inhibitor 2A and AT-rich interactive domain-containing protein 2 ($ARID_2$). All of the desmoplastic cases that were profiled in this study were *BRAF* wild-type [9]. Other mutational derangements associated with DM have been reported. These mutations include the promoter for the gene *NFKBIE* which is mutated in 15–33% of DM samples. *NFKBIE* governs a complex molecular pathway of both highly implicated in progression of cancer. Its role in both cell cycle progression as well as tumor suppression making it difficult to target

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from a therapeutic standpoint. Additionally, it should be noted that the detection of promoter gene mutations is technically challenging making finding these mutations difficult. There have also been found to be deletion mutations of *TSC1*/*TSC2* found in 41% of cases, and activating *NOTCH1* and *KDR* mutations found in 45 and 40% of cases, respectively [10,11]. These observed mutations present opportunities for targeted therapies. The high frequency of mutations make gene products of both *NFKBIE* and *NOTCH1* desirable in terms of therapeutic targeting.

Recent advances in biotechnology have made a number of mutation-directed therapies possible, many of them still in clinical trials but with some approved for treatment of various malignancies [12]. *TP53* gene replacement therapy has been shown to have promising results in cancer gene therapy through clusters regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (CRISPR-Cas9) technology [13]. This treatment approach was applied to lung adenocarcinoma but could theoretically be applied to DM given DM's prominent *TP53* mutation burden. Others have discussed therapeutic approaches to the genetic disorder neurofibromatosis type I, which shares the same neurofibromin 1 mutation as DM [12]. In addition to the CRISPR-based DNA repair, a number of other techniques that could correct the mutation, such as cDNA replacement, RNA repair, antisense oligonucleotide exon skipping and nonsense suppression have been discussed. While these techniques are promising, they are very early in their development and have a long way to go developmentally before they are incorporated into clinical practice. Another malignancy that shares a mutation with DM is adult T-cell lymphoblastic lymphoma (*T-LBL*) with *NOTCH1* being the more frequently observed mutation [13]. It has been proposed that histone deacetylase inhibitors have the potential to improve outcomes in patients with *T-LBL* and *NOTCH1* mutation [14]. Finally, renal cell carcinoma shares *TSC1* and *TSC2* mutations with DM and it has been demonstrated to have a positive response to mTOR inhibitors [15].

Mutation specific therapies are gaining more attention in oncological practice. As the understanding of the genetic composition of DM expands, new mutation specific therapies will hopefully be investigated. While high mutational burden does present potential for targeted therapies it does present therapeutic challenges. The increased number of mutations noted in DM raises concern for underlying mutational patterns that could harbor resistance to targeted therapies. Given the high mutational burden of these cancers they would likely be more treatable with combination therapies.

## Future directions of immunotherapies

Immunotherapies have ushered in a new and promising generation of anticancer therapies providing durable responses across multiple tumor types [16]. Initial case reports had shown promising results in patients receiving immunotherapies for metastatic DM. This led to a multi-institutional retrospective study of patients with advanced, unresectable DM; these patients received PD-L1 or PD-L1 blockade therapy [17]. Of the patients included in the study, 70% demonstrated objective tumor response with 32% of patients achieving a complete response. While limited, the study offered hope that durable responses may be achieved with PD-L1 monotherapy as opposed to combination immunotherapy regimens that are commonplace in the treatment of other types of cutaneous melanoma. This would be of great benefit, given the high toxicity burden seen with combination immunotherapy [18].

In the same retrospective study it was found that DM had a higher percentage of PD-L1 positive cells as well as CD8 density in the tumor parenchyma. It was noted that several patients had progressed through treatment with the cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor, ipilimumab. As PD-L1 expression is more prominent in DM of mixed type, these patients are likely better candidates for anti-PD-L1 targeted therapy [18]. These findings may help explain the profound response to PD-L1 targeting agents without similar results in monotherapy treatment with CTLA-4 inhibitors. There is currently one Phase II clinical trial evaluating the PD-L1 inhibitor, pembrolizumab, in patients with unresectable DM (NCT02775851).

## Drug delivery advancements

It has been previously shown that the fibroblastic microenvironment that is characteristic of DM has been a barrier to both native immune response to tumor cells as well as exogenous chemotherapeutic agents. In order to achieve better penetration of the active agents into the tumor core, additional treatment modalities are currently being explored including combining novel chemotherapeutic and immunogenic anticancer agents together to treat DM [19]. Recently, a novel approach was described utilizing mitoxantrone and celastrol, two agents with anticancer and antifibrotic properties through a nanocarrier mediated mechanism, to treat DM [20]. The results

from the preclinical study revealed that the combination of mitoxantrone and celastrol remodeled the fibrotic and immunosuppressive tumor microenvironment, arrested cancer progression, inhibited metastasis and induced the tumor into long-term dormancy.

A similar study under preclinical investigation is aimed at targeting tumor-associated fibroblasts (TAFs.) TAFs have been shown to promote local tumor progression as well as metastasis by modulating the local tumor microenvironment [21,22]. A current preclinical study is utilizing a nanoemulsion formulation to deliver a novel antitumor vaccine fraxinella which is antifibrotic in nature and also directly targets TAFs [23]. Furthermore, the same group has combined their tumor penetrating antitumor vaccine with the previously approved tyrosine-kinase inhibitor sunitinib in DM and shown reduced collagen as well as inhibition of TAFs both increasing permeability of therapeutic agents. Additionally, there was observed normalization of blood vessels as well as reduction of immune suppressor cells within the tumor microenvironment. All of these factors contributed to a significant response in the cytotoxic T-cell response to the DM. These advanced delivery mechanisms hold promise for better penetration into the DM tumor microenvironment thus leading to better responses to these therapeutic agents.

## Conclusion

Advanced DM has historically been difficult to treat. Recent advancements in nanotechnology have offered hope that there are better therapeutic delivery mechanisms for patients with DM that allow better penetration of the neoplasm by the therapeutic agent. Additionally, whole exome sequencing has led to the discovery of multiple genetic aberrations that may provide future actionable targets. Finally, retrospective research has shown high response rates to PD-L1 blockade in patients with advanced DM revealing promise that checkpoint inhibitors may be integral in future regimens for the treatment of advanced DM.

### Financial & competing interests disclosure

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