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EXPERT OPINION

Successes and setbacks of early investigational drugs for melanoma

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Treatment of advanced and metastatic melanoma is a rapidly changing field. Over the past 10 years, there have been six new drugs approved by the FDA for the treatment of metastatic melanoma. These approved drugs include a number of immune checkpoint inhibitors and MAPK-pathway-targeted therapies. The discovery of such agents as ipilimumab, pembrolizumab, nivolumab, vemurafenib, trametininb and dabrafenib have revolutionized the way in which melanoma in managed. While these agents have succeeded in both early and later phase clinical trials, a large number of investigational therapies have not yet been developed or researched past Phase I clinical studies. Furthermore, there are dozens of potential agents in Phase I and Phase II clinical development that appear promising and are currently being explored. The field currently aims to determine the optimal sequence and combination of these therapies to best overcome such setbacks as toxicity and resistance and build upon the successes previously seen.

Keywords: melanoma, Phase I, Phase II, uveal melanoma

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1. Introduction

Malignant melanoma remains the most deadly form of skin cancer in adults, with incidence on the rise over the past 40 years. Historically, response rates and cures in metastatic melanoma were low and infrequent due to resistance to chemotherapy and radiation. However, over the last 10 years, the discovery of novel immunotherapeutic and targeted agents has dramatically altered the treatment and outcome of this disease.

Immune system modulation as a therapeutic approach in melanoma is not novel. Previous attempts to enhance cancer-specific immune responses using autologous melanoma cells had resulted in only minor successes (< 5% response rate). The first successful experience came with the use of bio-response modifiers/cytokines. High-dose IL-2 therapy proved to be effective with the observation that patients achieving complete response (~ 5 – 10%) remained free of disease for an extended period of time [1]. Despite durable clinical response, significant toxicity such as vascular leak syndrome was clearly a significant setback. High-dose IFN-α treatment resulted in prolongation of recurrence-free survival in stage III patients [2]. However, significant toxicity such as liver damage and impaired quality of life has limited the widespread use of this approach. Other cytokines such as IL-12 and TNF-α have not reached large-scale clinical trials due to unacceptable toxicity.

The paradigm of cancer immunotherapy was subsequently shifted when preclinical data demonstrated immune augmentation by an immune checkpoint inhibitor, anti-CTLA-4 antibody [3]. Encouraging early Phase I reports on the antitumor activity with ipilimumab followed by subsequent Phase II successes ultimately led to the milestone Phase III studies [4-6]. Response rate was modest (~ 10 – 15%) but durability of response has been reported. In responders to ipilimumab, 60%

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demonstrated long-term responses lasting beyond 2 years and a survival plateau at approximately 3 years. However, when balancing efficacy with toxicity, ipilimumab has brought a significant challenge to clinical investigators. Due to its physiological role in preventing immune system anarchy, blocking the function of CTLA-4 is associated with significant autoimmune consequences. Ipilimumab trials showed grade 3 or 4 immune-related adverse event (irAE) incidences anywhere from 10 to 50% [5,6]. Most commonly seen irAE included dermatitis, diarrhea and pruritus. There were also a number of drug-related deaths from irAE, notably severe colitis and bowel perforation. Balancing infrequent and unpredictable tumor regression with significant systemic autoimmunity has been an undeniable drawback in the implementation of this agent.

Following the success of ipilimumab, other types of checkpoint inhibitors quickly entered the arena. A key mechanism for tumor-induced immune suppression is PD-1/PD-L interaction between cytotoxic T-cells/NK cells and tumor cells. These molecules may be more relevant in the tumoral micro-environment and work on the later effector-stage of the lymphocytes, which may explain the better toxicity profile. Melanoma-specific cytotoxic T cells that concentrate in the tumor largely express PD-1 and their activity is suppressed by PD-L1 expressed on the melanoma cells. There have been multiple anti-PD-1 and anti-PD-L1 antibodies evaluated in early phase clinical trials [7-9]. Two of these molecules, pembrolizumab and nivolumab, were granted accelerated FDA-approval for metastatic melanoma. A pooled analysis of patients who received pembrolizumab in selected early phase trials showed an overall response rate (ORR) of 40% in ipilimumab-naive and 28% in ipilimumab-refractory patients with a median PFS of 24 weeks [10]. Similarly, nivolumab showed a 40% ORR and 73% of 1-year OS (overall survival) in a recently published Phase III study [11]. PD-L1 expression was not a definitive predictor of response, indicating that expressions of PD-1 and PD-L1 are more dynamic processes and might not be predictable by investigating pre-treatment tumor biopsy specimens. Importantly, the anti-PD-1 antibodies appear to have similar side-effect profiles to one another, but have overall fewer side effects than ipilimumab, with irAE incidences of 10 – 15% [7-11]. While toxicity, response rate and time to response of the anti-PD-1 antibodies appear more desirable than ipilimumab, they are currently approved only as second-line after ipilimumab or BRAF inhibitors failure. There remains controversy over the sequence and combination of these agents. There are ongoing studies to answer these questions.

Anti-CTLA-4 and PD-1/PD-L1 antibodies successes have further ignited the immunotherapy renaissance. Other immunomodulatory targets recently investigated include OX40, CD137, TIM-3, LAG-3, B7-H3 and CEACAM1 (CD66a) (**Table 1**) [12]. An early translational study evaluating an anti-OX40-mAb (9B12) demonstrated that it was tolerable, and enhanced both cellular and humoral immunity by increasing peripheral $CD4^+$ and $CD8^+$ cells [13]. Unfortunately, two Phase II trials evaluating anti-OX40 alone or with ipilimumab have been withdrawn prior to accrual. Further investigation of this drug as a target is unknown. Urelumab, an anti-CD137 receptor agonist (BMS-663513) is a promising drug leading the next generation of immunotherapeutic agents. Early trials have noted that drug is tolerable, and there have been partial responses and stabilization of disease across a number of dosing cohorts [14]. Furthermore, one study noted that when added to the rapid expansion protocol prior to adoptive T-cell therapy, there was a significantly increased presence, function and survival of infiltrating T cells [15]. Urelumab's placement as a single agent in the algorithm or in combination with other agents is being investigated.

Another mechanism of potential immune system enhancement, currently being explored, is the inhibition of indoleamine 2,3-dioxygenase (IDO). IDO is an enzyme involved in tryptophan degradation, and reduction in levels of tryptophan has been implicated in the suppression of cytotoxic T-cell activity and an increase in regulatory T cells [16]. An IDO inhibitor, Indoximod, is currently being investigated in combination with ipilimumab in a Phase I/II study in patients with metastatic melanoma.

The last decade has also erupted with a wealth of new knowledge regarding tumor cell signaling and molecular pathogenesis. A greater understanding of the MAPK pathway led to the discovery of the BRAF mutation. Initial Phase I-II investigations of vemurafenib opened a new era of treatment for metastatic melanoma [17,18]. Ultimately, a landmark Phase III trial was conducted randomizing untreated patients to receive vemurafenib or DTIC [19]. Results concluded an improved 6-month OS favoring vemurafenib (84 vs 64%). The response rates and time to response seen throughout the Phase I-III trials were touted as triumph; however, most patients who initially respond progressed with a median of 6 – 9 months.

There has been a great deal of research dedicated to investigating the mechanisms of resistance to BRAF inhibition. Ongoing understanding of the MAPK pathway notes intricate feedback pathways and cross-talk complexity among various associated signaling targets. MEK has been identified as a likely downstream contributor to BRAF resistance. An additional BRAF inhibitor, dabrafenib, has now been FDA approved when used in combination with MEK inhibitor trametinib. Early Phase I and II studies using these agents showed benefit in BRAF-mutated melanomas. A Phase III clinical trial evaluating dabrafenib plus trametinib versus vemurafenib alone exhibited an overall survival benefit [20]. Despite the tolerable side-effect profile published in the literature, combination regimens are likely more toxic. Even with this combination, aside from toxicities, a major setback continues to be development of resistance. The majority of patients who initially achieved dramatic regression subsequently develop recurrence with rapid progression of disease.

Table 1. Summary of agents explored in melanoma.

Targeted therapies	
RAS	MEK
BMS-214662	CI-1040 (PD184352)
L-778123	PD0325901
RAF	Selumetinib (AZD6244)
Sorafenib	Trametinib
Dabrafenib	MEK 162
Vemurafenib	AKT
RAF265	MK2206
XL281	GSK2141795
LGX818	CDK4/6
ARQ-736	Palbociclib
Pi3K/mTOR	LEE011
SAR245409	
BKM120	
Immunotherapies	
CD 40	CTLA4
CP-870,893	Ipilimumab
Dacetuzumab	Tremelimumab
Chi Lob 7/4	PD1
Lucatumumab	Nivolumab
CD137	Pembrolizumab
Urelumab (4-1BB)	PDL1
OX40	MEDI14736
Anti-Ox-40	MPDL3280
GITR	TGF-B
TRX518	Fresolimumab
IDO	LAG3
Indoximod	BMS-986016

CD: Circular dichroism; IDO: 2,3-dioxygenase ; MEK: MAP-kinase kinase; SAR: Systemic acquired resistance.

There are a number of other agents with their targets in the MAPK and associated pathways undergoing investigation (**Table 1**). A number of specific drugs targeting RAS, RAF and MEK have been assessed in early Phase I trials but few have progressed to later stages due to lack of benefit, unexpected toxicities or poor bioavailability [21]. Two other MEK inhibitors not discussed above, selumetinib and MEK162 (ARRY-162), are under evaluation for uveal melanoma and NRAS-mutated melanomas, respectively.

Given the awareness of multiple interconnected cell signaling pathways, there has been an attempt to combine targeted agents within and across the pathways, notably combinations within the MAPK and PI3K pathways. Early clinical trials are ongoing assessing a number of combinations including MEK plus AKT, MEK plus PI3K, MET plus MEK; however, we await results regarding the tolerability of these combinations. It has been anticipated that some of these combinations, while needed to overcome resistance, may be too toxic. Combination of multiple signal blockades is perhaps unrealistic, considering the quality of life of patients and subsequent development of multi-resistance to signal blockades.

One of the challenges for current treatment of metastatic melanoma is the selection of treatments and their order in which they are given. Immune checkpoint blockades show modest but durable response. On the other hand, signal pathway blockades, while they induce a rather dramatic and quick clinical response, there is inevitable development of resistance. While further investigation is required, currently there is rationale to use immune checkpoint blockades as first-line in the treatment of metastatic melanoma, including BRAF-mutated melanoma. However, the selection of signal blockades would be preferred for rapidly progressing BRAF-mutated melanoma. Further, there may be a role for BRAF blockade in the neo-adjuvant setting where they are used to increase rates of resectablity of otherwise unresectable bulky tumors.

2. Conclusions

The way in which advanced and metastatic melanoma is treated has been forever altered by the discovery of such novel agents as immune checkpoint inhibitors and MAPK pathway targeted therapies. Response rates, progression-free survival and overall survival, while at an all-time high, are not high enough. There will be successes, and certainly there will be setbacks, but ongoing exploration into early investigational drugs for melanoma is what is needed to continue this momentum.

3. Expert opinion

Recent discovery of novel approaches in immunologic and targeted therapeutics has demonstrated tremendous advancement in the treatment of melanoma. However, we now are faced with the difficult task of developing an appropriate treatment algorithm that will incorporate all of these agents. The discussion regarding sequence and combination of agents within each class of drugs and across classes is critical. When considering treatment strategies, the balancing of efficacy and toxicity will remain a limiting factor. Further, as we attempt to integrate newly established agents such as checkpoint inhibitors and already approved targeted agents into our daily practice, we must also pay close attention to therapies in early clinical trials that may also offer benefit.

The major setback of current cancer immunotherapy is the inability to reliably shift towards a tumor-specific immune response and away from a general systemic autoimmune response. Cytokines and immune-checkpoint interactions are common mechanisms of general immune response and an induction of inflammatory response to normal tissues is inevitable when using high-dose cytokines or immune-check point blockades. To overcome this limitation, future melanoma immunotherapy needs to identify approaches in which maximize tumor-specific immune response and minimize systemic non-specific immune response. Various approaches combining immune-checkpoint blockades with local or regional treatments such as focused radiotherapy, ablative treatment and immunoembolization of hepatic metastasis are under investigation. Such combination modality strategies may take advantage of local attraction and stimulation of

antigen-presenting cells at the site of the tumor as well as offer improved uptake of tumor antigens by necrosing tumor at the treatment site. An alternative approach would be local administration of newly developed immunotherapeutics that would induce antitumor response while limiting systemic autoimmune toxicity. Large-scale clinical trials evaluating these concepts are being considered.

As evidenced by the extensive list of agents noted in **Table 1**, there are a great number of therapies that remain under investigation, and this list will certainly lengthen. While it is encouraging to know there are dozens of potential drugs in the pipeline, we must have the foresight to design clinical trials that will answer important clinically relevant questions. Rigorous pre-clinical data to support early phase clinical trials is crucial at a time when there are so many promising possibilities. When designing clinical trials, choosing the right patient populations, rationalizing sequence or combinations, selecting appropriate endpoints, biomarkers, and correlative studies are imperative as we attempt to further our understanding of the disease and potential effective therapies.

In the era of precision medicine, we must also consider the personalization of these novel approaches. The selection in types of treatments, their timing, and order should be more customized to achieve the best clinical outcome. In this regard, the establishment of reliable immunological and molecular biomarkers for clinical response is critical.

The future of melanoma therapy is as promising as ever, and hopefully as we better understand the optimal treatment algorithm for patients, we will continue to witness unprecedented responses and unprecedented survival.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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