

Editorial

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Recent breakthroughs in metastatic uveal melanoma: a cause for optimism?

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“In summary, several promising new agents are in development for UM. Together with a better understanding of the biology of the disease and the recent delivery of relatively large studies, this holds hope that new and more effective treatment options will become available for UM patients with metastatic disease in the near future.”

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Uveal melanoma (UM), a rare subtype of melanoma with a propensity for liver metastasis, remains one of very few malignancies for which there are no proven, effective therapies for metastatic disease. While treatment of primary UM is almost invariably successful, metastatic UM has proven resistant to most therapies assessed thus far; this being compounded by its rarity and consequently a historical lack of well-powered trials. In addition, there has been a tendency to transpose clinical results from cutaneous melanoma (CM) to UM, although it has become clear that while these malignancies share a melanocyte lineage, their biological behavior is very different. However, as we outline below, promising early clinical results for novel drugs and approaches, and an evolving understanding of the basic biology of UM, suggest a more optimistic future for the management of metastatic UM.

Immunotherapy is currently the most exciting area of drug development for cancer, holding out the prospect of durable remissions and even cure for metastatic disease. Unfortunately, although widely used, immunotherapy with established agents (monoclonal antibodies against the immune checkpoints CTLA4 and PD-1) has been disappointing to date in UM. In contrast to CM where response rates to single-agent anti-CTLA4 (ipilimumab) and anti-PD-1 (nivolumab or pembrolizumab) are in the order of 10–20 and 40%, respectively, in UM response to single-agent therapy with these monoclonal antibodies is generally reported to be in the region of 5% or less [1,2]. The median overall survival in most UM series is less than a year, and there is little evidence to suggest significant disease control, although studies have all been small single-arm and nonrandomized, thus making it difficult to fully assess efficacy. While there has been some enthusiasm for combination CTLA4 and PD-1 blockade (ipilimumab and nivolumab), there remains very little evidence for meaningful clinical activity in UM. A recent study reported a response rate of approximately 17% in evaluable patients; however the study was limited to 15 patients and median progression-free survival (PFS) was just 2.8 months [2]. Moreover, in a report of a separate expanded access program, which included six patients, none responded and median PFS was similarly 2.8 months [3]. Combined with the considerable morbidity associated with combination immunotherapy, it remains unclear whether this approach is of benefit, and results from ongoing trials are awaited.

The difference in checkpoint inhibitor efficacy between UM and CM is likely to at least partly relate to differences in mutational load and thus cancer cell immunogenicity. A recent study by The Cancer Genome Atlas (TCGA), and others, showed markedly lower mutation rates in UM in comparison to CM or other cancer types [4]. Phenotypically, there is also evidence to suggest that UM is an immunologically ‘cold’ tumor, and is therefore perhaps not ‘primed’

to respond to checkpoint inhibitors. This is supported by the predominantly peritumoral localization of CD3⁺ and CD8⁺ T-cell infiltrates in UM metastases, which appear to be excluded from the tumor mass interiors [5], while expression of the PD-1 ligand (PD-L1) is also significantly lower in UM than in CM [6,7].

However, data from the TCGA suggest that this may be an oversimplification. In a proportion of tumors, PD-L1, and more frequently other checkpoint molecules such as IDO1 and TIGIT, are upregulated [4]. In addition, a recent study of adoptive transfer of tumor infiltrating lymphocytes provides direct evidence that tumor specific T cells are present in UM metastases and that these may be stimulated to engender clinically meaningful responses [8]. This Phase II study involved removal of the metastases, followed by *ex vivo* expansion of tumor infiltrating lymphocytes, which were infused back into the patient after lymphodepleting conditioning chemotherapy. Results from 21 patients have been reported with seven (35%) responding, including one complete response that was ongoing at the time of report 21 months after treatment. While this is clearly very early data that will require confirmation (expansion phase ongoing), it does at the very least indicate that UM is not wholly unresponsive to immunotherapy.

An alternative approach to immunotherapy using a novel bispecific molecule, IMCgp100, has similarly generated much interest. One end of IMCgp100 is a soluble affinity enhanced T-cell receptor targeting the melanocyte lineage protein gp100 bound to HLA A201, while the other end is an anti-CD3 scFv. This allows IMCgp100 to redirect T-cells into UM tumors, leading ultimately to T-cell activation and tumor cell killing. Two Phase I trials have reported initial results in UM; a first in-human dose escalation study that included both UM and CM patients (NCT01211262), and a subsequent study that used an inpatient dose escalation approach and was limited to UM (NCT2570308). The latter strategy was predicated on an observed amelioration in toxicity after the first few doses and achieved an approximately 50% increase in the tolerable dose. A pooled analysis of these two studies was presented at SITC in 2017 [9]. While response rates were relatively low (3/15 and 2/19 patients respectively), initial results suggest prolonged disease stabilization in a significant proportion of patients, and most importantly, a 1 year overall survival of 73% was observed in both studies, which is significantly higher than expected for this population of patients.

Intriguingly, biopsies taken after three doses of IMCgp100 (on day 16) showed an influx of PD-1⁺/CD8⁺ lymphocytes, and an increase in PD-L1 expression in the tumor [9]. In essence, this suggests that IMCgp100 treatment can change a UM tumor from being immunologically 'cold' to 'hot', and in turn that either sequential or combinatorial use of IMCgp100 and checkpoint inhibitors may ultimately improve activity. However, the clinical and biological signals from these two studies will clearly need confirmation in further trials. To this end, both an expansion cohort of the inpatient dose escalation study (NCT2570308), and a pivotal Phase II study (NCT0307392) randomizing against investigator choice are underway.

While immunotherapy has unsurprisingly been a major focus of attention, there have also been significant advances in our understanding of cell signaling and targeted therapies in UM. Data from the TCGA study and others have confirmed that there are only a limited number of driver mutations in UM [4]. Principle among these are mutations in the genes encoding heterotrimeric G-protein subunits *GNAQ* and *GNA11*, one of which is mutated in almost all cases of UM. Notably, the small number of UM without *GNAQ/GNA11* mutation in fact harbors mutations in other genes that activate the same pathways: *PLCB4* and *CYSLTR2*. A number of signaling pathways are activated downstream of *GNAQ* and *GNA11*, including the MAPK pathway, which has been the principle focus of attention. Preclinical models have shown that UM cell lines are susceptible to inhibition of the MAPK pathway by MEK inhibitors [10], leading in turn to a study of the MEK inhibitor selumetinib in comparison to chemotherapy. This study (NCT01143402) showed improvement in its primary end point of PFS (15.9 vs 7 weeks; $p < 0.001$) and response (14 vs 0%), but not overall survival (11.8 vs 9.1 months; $p = 0.09$), in the selumetinib arm [11]. These results suggest only modest efficacy for selumetinib monotherapy, and subsequent studies have mostly investigated combination with other agents. The SUMIT trial (NCT01974752) was a Phase III study that compared selumetinib or placebo in combination with dacarbazine. This study has not fully reported but did not meet its primary end point of overall survival. However, further trials of MEK inhibitors are underway including a randomized Phase II study (SelPac, ISRCTN 29621851) which is seeking to investigate the activity of selumetinib in combination with the chemotherapy agent paclitaxel in UM, based on evidence that the combination increases induction of apoptosis in preclinical models [12,13]. Investigation of agents targeting other components of signaling pathways downstream of *GNAQ/GNA11* (such as the PKC inhibitor LXS196, NCT02601378) is also under way.

Other approaches include glembatumumab vedotin, a monoclonal antibody–drug conjugate targeting the glycoprotein 'nonmetastatic b', which is commonly overexpressed in cancers including UM [14]. This has been assessed in a single-arm Phase II study (NCT02363283), which recently reported initial results [15]. The study included 31

evaluable patients with a reported response rate of 6%, disease control rate of 61% at 3 months and median overall survival of 11.8 months. While these results suggest the agent may have activity in UM, further investigation is required.

In view of UM's predisposition for metastasis to the liver, and the frequent occurrence of liver only metastases, a number of liver-directed therapies have been investigated over the years. Of these, percutaneous hepatic perfusion with melphalan is perhaps the most studied. An initial randomized Phase III study completed several years ago and showed an improvement in hepatic PFS (7.0 vs 1.6 months; $p < 0.0001$) when compared with investigators' choice, however no improvement in overall survival was observed (10.6 vs 10.0 months; $p = 0.77$), although this may have been partly due to patient cross over [16]. More recently, a case series combining data from two major centers reported a median overall survival of 15 months in 51 patients [17]. These results, while encouraging, require confirmation in a randomized study and an international Phase III (FOCUS, NCT026786572) comparing percutaneous hepatic perfusion with investigator choice is currently enrolling patients.

In summary, several promising new agents are in development for UM. Together with a better understanding of the biology of the disease and the recent delivery of relatively large studies, this holds hope that new and more effective treatment options will become available for UM patients with metastatic disease in the near future.

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