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EDITORIAL

Clinical Studies

LXS196 for Metastatic Uveal Melanoma - finally some progress

Metastatic uveal melanoma continues to have a poor prognosis with distinct pathophysiology from cutaneous melanoma and limited effective treatment options. Targeted therapy with darovasertib towards protein kinase C is well tolerated with signals of early efficacy, warranting further exploration and combination strategies.

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Uveal melanoma arises from melanocytes within the iris, choroid and ciliary body. Common local management approaches include brachytherapy, external beam radiotherapy, and enucleation. Generally, plaque brachytherapy is standard for localised disease, with prevention of local recurrence in >95% of cases [1]. Despite these local treatments, up to 50% of patients will develop haematogenous metastasis, particularly those with high-risk genetic profiles [2]. For example, BAP1 (BRCA-1-associated protein) abnormalities have been linked with aggressiveness through incompletely understood pathways [3]. Unfortunately, the prognosis for metastatic disease remains poor with a median 1-year overall survival (OS) of 43% [4] highlighting the need for the development of effective therapeutics.

To date, both prospective and retrospective trials with standard checkpoint inhibitor immunotherapy have failed to demonstrate meaningful efficacy in metastatic uveal melanoma. For example, prospective trials of PD-1/PD-L1 monotherapy reported poor overall response rates (ORR) of 3.6% and PFS of 2.6 months [5] whilst the combination of nivolumab and ipilimumab reported a stable disease rate of 33–52%, but a similar unimpressive PFS of 3–5 months in Phase II trials [6, 7].

More recently, tebentafusp, a bi-specific gp100-CD3 T-cell engager, has gained FDA approval for first-line use in the metastatic setting. A Phase III trial of tebentafusp compared to investigator choice pembrolizumab, ipilimumab or darcarbazine control in HLA-A*02:01-positive patients demonstrated a 1-year overall survival benefit of 73% compared to 59% in the control group [8]. However, given that HLA-A*02:01-positive tumours represent up to 45% of the western population only, there remains a need to broaden therapeutic options targeting other molecular features unique to uveal melanoma.

Unlike cutaneous melanomas that commonly harbour BRAF/NRAS mutations, 83% of uveal melanomas arise from mutations in G-alpha pathway [9]. Early initiating mutations within GNAQ and GNA11 in uveal melanoma cause dysfunction of G-alpha-protein subunits, resulting in disabling of intrinsic GTPase activity [9]. This leads to downstream cleavage of phosphatidylinositol diphosphate (PIP_2) into inositol triphosphate (IP_3) and diacylglyceraol (DAG) resulting in the activation of protein kinase C (PKC) which subsequently activates MAPK and ERK1/2 pathways (Fig. 1). PKC isoforms are subdivided into 3 sub-families; classical (α, βI, βII, γ), novel (δ, ε, θ, η) and atypical (ζ, ι) based on their second messenger requirements for DAG and calcium ions [10]. Of the 5 PKC isoforms (α, δ, ε, ζ, ι) consistently expressed in multiple GNAQ/11 mutant uveal melanoma cell lines, knockdown of isoforms δ and ε resulted in reduced downstream MEK/ERK phosphorylation indicating the critical role of novel isoforms in signal transduction [11].

Targeting PKC has proved elusive to date. A Phase I study of a pan-inhibitor of classical and novel PKC isoforms sotrastaurin (AEB071) showed ORR of 3% despite demonstration of target inhibition [12]. Although the combination of sotrastaurin with upstream phosphatidylinositol 3-kinase (PI3K) inhibition using alpelisib demonstrated DCR of 66%, there were no complete or partial responses [13].

This study by Piperno-Neumann et al. highlights that selective targeting of novel PKC isoforms may be a superior and less toxic approach to pan-PKC inhibition. LXS196, also known as IDE196/darovasertib is a more selective inhibitor of the novel PKC isoforms. The study dose escalated from 100 to 1000 mg daily schedule with dose-limiting toxicity (DLT) reported at doses >500 mg daily. The twice-daily schedule was tested from 200 to 400 mg twice daily with maximum tolerated doses declared at 500 mg daily and 400 mg twice daily. The recommended Phase II dose (RP2D) was 300 mg twice daily based on Baysean Logistical Regression Modeling. The main DLT was hypotension occurring in 6 patients on daily dosing with no grade 3 events in the 18 patients dosed with RP2D schedule. Hypotension was experienced within 1–4 h of the first or second dose and resolved with the administration of intravenous fluids. Although the mechanism of this remains unexplored, the authors propose darovasertib's inhibition of PKCα, known to play a role in vascular tone, may be contributing. Hypotension was predicted from pre-clinical animal toxicology studies and showed reversibility within 4 weeks. The study reports targeting novel PKC isoforms is tolerable and may have better ORR (11%) and DCR (78%) compared to first-generation PKC inhibitor.

The biomarker analyses that accompanied the paper was also informative showing activity against PKCδ with decreased levels of phosphorylated PKCδ and its' substrate pMARKS at day 15 biopsy compared to pre-treatment biopsy. Target inhibition did not correlate with disease response. This is consistent with previous GNAQ/11 mutant cell line work demonstrating the level of PKC inhibitor-induced decreases in pMARKS does not correlate with degree of MAPK inhibition and while able to promote cell cycle inhibition, PKC inhibition alone is insufficient to induce uveal

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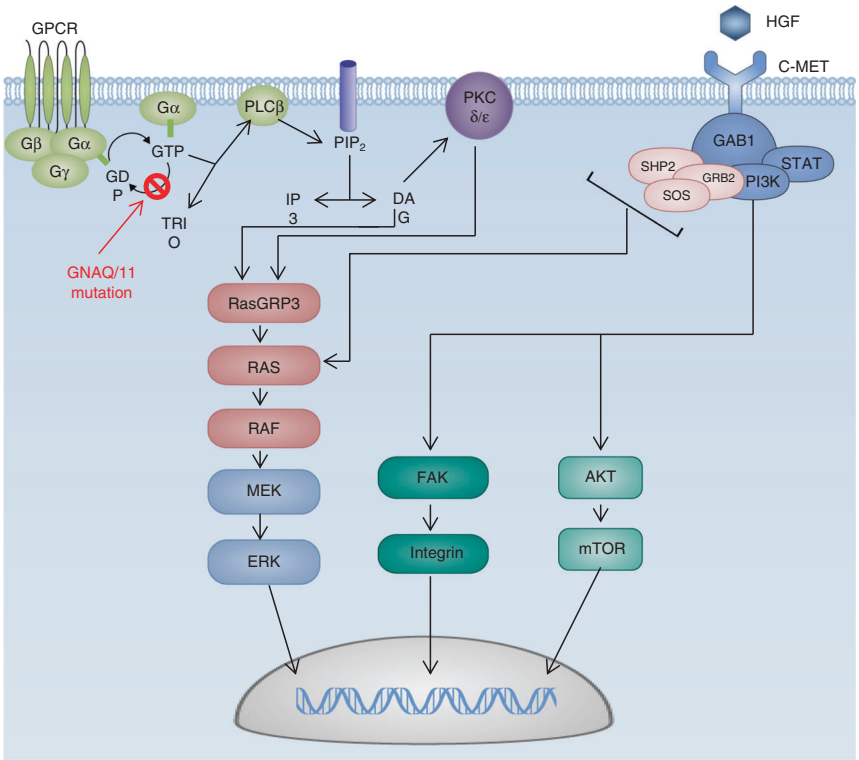

Fig. 1 PKC and MET activation signal growth through MAPK pathway via RAS activation. GPCR G-protein-coupled receptor, GTP guanosine triphosphate, GDP guanosine diphosphate, TRIO guanine nucleoside exchange factor, PLCβ phospholipase C beta, PIP2 phosphatidylinositol diphosphate, IP_3 inositol triphosphate, DAG diacylglyceraol, PKC protein kinase C, RasGRP3 RAS guanyl-releasing protein-3, RAS Rat sarcoma virus, RAF Rapidly accelerated fibrosarcomae, MEK mitogen-activated protein kinase kinase, ERK extracellular signal-regulated kinases, HGF hepatocyte growth factor, c-MET mesenchymal epithelial transition, GAB1 Grb2-associated binder 1, SHP2 Src homology 2 domain-containing, GRB2, growth factor receptor-bound protein 2, SOS son of sevenless, PI3K phosphatidylinositol 3-kinase, STAT signal transducer and activator of transcription, FAK focal adhesion kinase, AKT protein kinase B, mTOR mechanistic target of rapamycin.

melanoma cell death [14]. An alternative biomarker for novel PKC inhibition proposed by the authors is the guanine nucleotide exchange factor RAS guanyl-releasing protein-3 (RasGRP3), which is a demonstrated important module for ERK activation [11] (Fig. 1).

Critical to the further evaluation of darovasertib are combination strategies to MAPK inhibition. High MET receptor expression in uveal melanoma, which is known to signal through MAPK and PI3K pathways [15] (Fig. 1), can be stimulated by elevated hepatocyte growth factor in the liver microenvironment [16]. Interim analysis of a Phase II trial (NCT03947385) exploring darovasertib and c-MET inhibitor crizotinib in metastatic uveal melanoma has shown an impressive ORR 31% in the first line in 35 evaluable patients with PFS not reached but already >5 months (https://media.ideayabio.com/2022-09-11-IDEAYA-Reports-Positive-Interim-Phase-2-Clinical-Results-for-Darovasertib-and-Crizotinib-Synthetic-Lethal-Combination-in-Metastatic-Uveal-Melanoma), which is impressive compared to historical data.

Should this level of activity be maintained and longer-term toxicity found to be manageable, darovasertib alone or in combination may find clinical utility in other disease settings of unmet clinical need. For example, responses have been noted in primary in situ lesions (https://www.ideayabio.com/wp-content/uploads/2023/01/20230110_IDEAYA-Investor-Corporate-Presentation-JP-Morgan-Conf-Jan-2023_vFF.pdf), supporting proof of concept for neoadjuvant/adjuvant therapy, now being tested prospectively with darovasertib monotherapy (NCT05187884).

Given the limited effective therapeutics in metastatic uveal melanoma to date, the authors should be congratulated on the results of this study. Early efficacy signals with an acceptable safety profile certainly warrants further study.

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DATA AVAILABILITY

Not applicable.

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