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A Review Article on the Past, Present, and Future of Vemurafenib in Metastatic Melanoma: From Translational Development to Clinical Implementation in the Republic of Ireland

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Introduction

Melanoma is a malignant skin cancer that arises from melanocytes in the skin. **[**1**]** According to the World Health Organization (WHO), melanoma accounts for approximately 1-2% of all skin cancers and is responsible for the majority of skin cancer-related deaths. **[**2**]**

Melanoma is diagnosed histopathologically by obtaining an excision biopsy of the pigmented lesion.

Gold standard management of melanoma involves performing a wide local excision (WLE) with appropriate margins and sentinel lymph node biopsy +/- clearance if indicated. Chemoradiotherapy is utilized for effective local control of the disease and is widely used in palliation for advanced metastatic cancer. **[**3**]** The clinical problem is that they are often ineffective in therapeutic management of advanced widespread disease. Patients have relatively low response rates, suffer significant side effects, risk damage to healthy tissues and are intolerant due to toxicity. This limits its usefulness in patients with metastatic disease. Hence, more targeted treatment options for advanced metastatic melanoma were needed to counteract this issue.

Target discovery:

Melanoma is a highly heterogeneous disease with high levels of biological complexity and multiple genetic alterations that drive its development and progression. **[**4**]** This makes it a very good candidate for targeted gene therapies. By specifically targeting the genetic drivers of melanoma, this method would offer a more effective and less toxic treatment option for patients. It would be more precise and selective than traditional chemoradiotherapy, which kills both cancerous and healthy cells indiscriminately.

One of the key genetic drivers of melanoma is the presence of activating mutations in the BRAF gene. BRAF is a gene that in normal physiology encodes a protein called BRAF kinase. (See Figure 1) This protein is a member of the RAF family which are important regulators of the MAPK signaling pathway. This pathway is involved in cell proliferation, differentiation, and survival. Its dysregulation plays a vital role in neoplastic transformation and is implicated in the development and progression of melanoma. Mutations in this oncogene result in the activation of the MAPK signaling pathway, which promotes melanoma proliferation, apoptosis inhibition, progression and survival. (See Figure 2) **[**5**]**

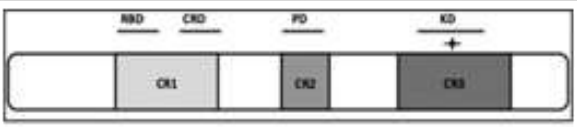

Figure 1: BRAF structure. CR3 contains the kinase domain (KD) and contains the valine 600 residues often mutated in melanoma.

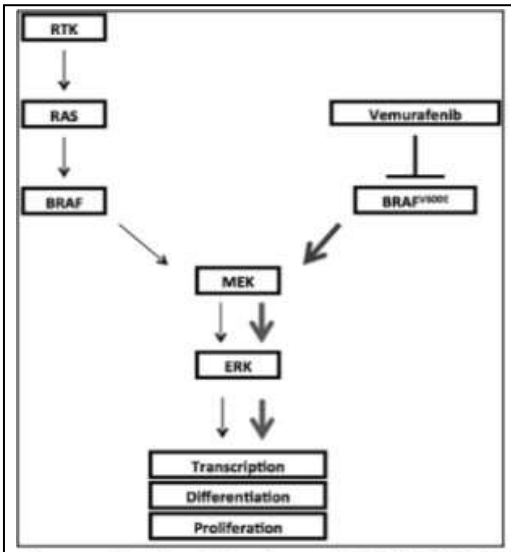

Figure 2: Physiologic and BRAF V600E MAPK pathway activation. Vemurafenib inhibits BRAF V600E to shut down this pathway activation.

It was determined that the BRAF gene would make a good intervention target. Due to improved modern genetics and molecular biology techniques, an oncogene-selective inhibitor targeting BRAF could be developed. This would block the MAPK signaling pathways and help achieve the ultimate goal of producing an agent capable of inducing apopto sis and slowing the growth of melanoma tumors.

BRAF mutations are present in approximately 50% of cases. The most common mutation in melanoma is a valine-to-glutamic acid substitution at position 600 (V600E). This accounts for approximately 80% of all BRAF mutations in this disease. **[**6**]**

The BRAF gene was first identified and cloned in 1991 by a group of researchers in London. They identified the BRAF gene in a study that was aimed at identifying new oncogenes involved in human cancer. **[**7**]** The discovery that mutations within the BRAF gene lead to melanoma is attributed to several groups of researchers who identified the BRAF V600E mutation in melanoma samples.

One of the first studies to report the mutation in melanoma was published in 2002. These findings were subsequently confirmed by multiple groups worldwide in the same year. [8] In 2006, Plexxikon, a biopharmaceutical company based in California, began developing vemurafenib, a highly specific inhibitor of BRAF kinase with selectivity against melanoma cells. The development of vemurafenib involved preclinical studies in cell lines and animal models, as well as clinical trials in patients with melanoma. [9]

Pre-clinical studies:

A multitude of preclinical studies were performed on vemurafenib using both animal models and melanoma cell lines to demonstrate proof of concept.

Three major preclinical trials were performed. These were all in favor of vemurafenib being effective in adequately inhibiting BRAF V600E mutations and ultimately melanoma cell cycle arrest and apoptosis.

A study performed by Tsai et al in February 2008 investigated the efficacy of vemurafenib by implanting melanoma tumor xenografts in female athymic mice. During the 2 week treatment period, 44% of the mice achieved tumor regressions to below palpable levels. In addition, a cell based study performed on synthetic skin yielded similar results. It was revealed that BRAF V600E cells were significantly inhibited in the presence of vemurafenib, as evidenced by the thin melanoma layer and existence of the outer keratinocyte layer of the synthetic skin. [10]

Moreover, another similar study performed in May 2008 by Sala et al saw vemurafenib inducing growth arrest, regression and ultimately apoptosis in melanoma cell lines and in-vivo xenograft mice models. [11]

A 2010 study performed by Yang et al saw vemurafenib potently inhibiting proliferation in a panel of BRAF V600E melanoma cell lines. It also found the drug to cause complete tumor regressions with subsequent improved animal survival, in a dose-dependent manner. [12]

All studies demonstrated the preclinical validation of vemurafenib in displaying antimelanoma activity in both cell and animal-based model systems with no evidence of toxicity or adverse effects on any parameters. With promising preclinical data, vemurafenib was soon approved for use in phase I clinical trials.

Phase I

The BRAF Inhibitor in Melanoma Phase I trial (BRIM1) performed in May 2010 was conducted to assess the role of vemurafenib in metastatic BRAF V600E melanomas. The objectives of the study were to characterize drug pharmacokinetics, pharmacodynamics, safety profile and determine early efficacy of the drug by evaluating tumor response rate. The trial had strict inclusion and exclusion criteria and only involved candidates over 18 with advanced melanoma refractory to standard therapy with no brain metastasis and good ECOG performance status. BRIM 1 enrolled 55 patients. The trial discovered the safety profile of vemurafenib to be grossly positive with the majority of patients complaining of only mild dermatological and non-specific generalized musculoskeletal side effects. This included photosensitivity, arthralgias, fatigue, rash, nausea and pruritus. No specific contraindications were discovered during phase I trials.

In addition, the overall tumor response rate from BRIM1 was extraordinary with over 69% of recipients having a partial or complete response with vemurafenib. Within this group, 81% of candidates experienced a median progression-free survival of more than 7 months. **[**13**]**

Phase II

BRAF inhibitor in Melanoma Phase II trial (BRIM2) performed in January 2011 was a multi-center trial initiated to determine the clinical response rate of vemurafenib in patients with previously treated BRAF positive advanced stage melanoma. The trial enrolled 132 patients. It revealed a complete response and partial response rate of 6% and 47% respectively, resulting in a staggering 53% overall response. Progression of the disease was identified in only 14% of the participants and saw a median progression-free survival of 6.8 months in responders. This trial truly revealed the anti-tumor properties of vemurafenib in those harboring BRAF V600E melanomas. **[**14**]**

Phase III

BRAF Inhibitor in Melanoma Phase III trial (BRIM3) performed in May 2011 was a double-blinded multicenter RCT designed to compare the clinical efficacy of vemurafenib versus a chemotherapeutic agent dacarbazine. The trial included and randomized 680 patients to treatment arms. Patients belonging to the vemurafenib treatment arm boasted a 84% overall survival at 6 months, a median progression-free survival rate of 5.3 months and had a much superior confirmed objective tumor response rate of 48%. Whereas, dacarbazine recipients had a 64% overall 6 monthly survival rate, 1.6

month median progression-free survival and a 5% tumor response rate. Overall, vemurafenib resulted in a relative risk reduction in mortality of 63% and a reduction of 74% in the risk of tumor progression. This study solidified the role of vemurafenib as an efficacious treatment option for metastatic BRAF V600E melanoma. [15]

Clinical implementation:

Vemurafenib received global approval from all major regulatory bodies worldwide. Due to its excellent tolerance, low toxicity profile, rapid tumor response, and improved outcomes determined from clinical trials, vemurafenib was advanced rapidly to receive approval by the FDA, EMA and HPRA in 2011. [16] [17] It is available for use in Ireland for the treatment of BRAF V600E melanomas. Vemurafenib is available under the trade name Zelboraf and requires a high tech prescription from a licensed healthcare provider to be withdrawn in Ireland. [18]

Cost of vemurafenib varies vastly depending on the country, region and healthcare system. Many insurance providers worldwide cover the drug and in some countries with national healthcare systems, the medication is usually covered by the government and public insurance programs. Although very expensive, averaging a cost of approximately

$10,000 for a 30-day supply, or $120,000 per year of treatment, the medication is listed under the High Tech Arrangements (HTA) scheme in the HSE's reimbursement program and eligible patients qualify for complete compensation if prescribed by a consultant oncologist or dermatologist. [19]

The advent of BRAF inhibitors like vemurafenib has not influenced the timing of melanoma intervention. Early stage localized or regional disease is still best treated with wide local excision, sentinel node biopsy, regional nodal clearance and/or chemoradiotherapy. Targeted gene therapies like vemurafenib are only indicated as first line therapies for patients with advanced or unresectable melanoma who have BRAF V600E mutations who never received prior systemic therapies.

In regards to other clinical applications, vemurafenib is also approved for use in management of patients with BRAF positive cutaneous SCCs that are not candidates for surgery or radiation. [20]

Current status:

Vemurafenib reached the T4 stage of development due to the undertaking of multiple studies exploring long-term population based outcomes.

Long-term studies revealed the drug to have an overall improved impact on populations and global health. There was a reported improved progression-free survival and long-term survival benefit of using vemurafenib in treatment of BRAF metastatic melanoma. **[**21**]** However, a myriad of long term studies revealed an increased risk in development of new localized cutaneous SCCs with vemurafenib. One study quoted the development of keratoacanthoma-type SCCs to be found in one third of patients treated at maximum tolerated dose. The median time of treatment to appearance of SCC was 8 weeks with some patients requiring operative resections. The exact mechanism is unknown but it is hypothesized that SCC development results from a paradoxical activation of protein signaling pathways in normal cutaneous cells resulting in a transformation to SCCs. (See Figure 3) **[**22**]**

In addition, long term studies revealed a handful of contraindications to vemurafenib. Majority of these are associated with liver pathology and drug-drug interactions with other hepatic metabolized medications since vemurafenib is metabolized by the liver cytochrome P450 system. Figure 4 depicts the common contraindications of vemurafenib adapted from the HPRA SPC. **[**23**]**

Contraindications of Vemurafenib (Zelboraf)
• Hypersensitivity to the active substance or any of the excipients.
• Strong CYP3A4 inhibitors, such as ketoconazole, itraconazole, clarithromycin
• Strong CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin
• Pregnancy and breastfeeding.
• Severe liver impairment (Child-Pugh Class C).
• Concurrent use of medications that can prolong the QT interval, such asamiodarone and sotalol
• History of retinal vein occlusion

Figure 4: Table adapted from HPRA SPC depicting major contraindications of vemurafenib **[**23**]**

Currently, vemurafenib is widely available and there are very few challenges associated with it. The only potential challenges in the future that could threaten its availability and supply are factors such as manufacturing, distribution and reimbursement policies. The latter is most crucial as the high cost of medication limits access to those who are able to afford it, who possess private insurance or those residing in countries with national health systems. **[**24**]** A previous major challenge that had to be

succumbed, and still an ongoing problem that is subject to many ongoing trials is the development of resistance.

Vemurafenib in some patient cohorts seemed to have a paradoxical activating role on some intrinsic and extrinsic signaling pathways controlling BRAF. This ultimately saw recurrence of cancer and progression of disease within 6-8 months of treatment initiation. (See Figure 3) **[**23**] [**25**]**

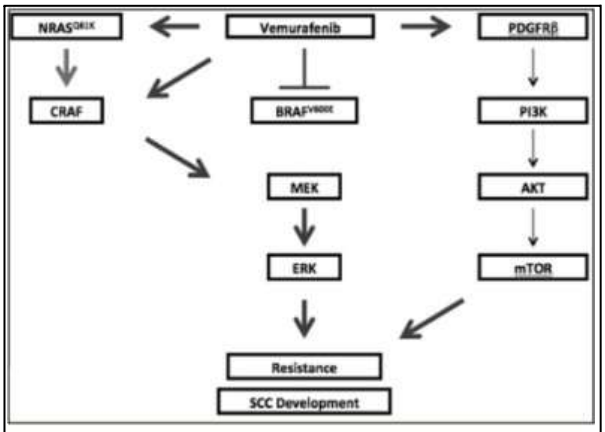

Figure 3: Mechanism of vemurafenib resistance and SCC development

The issue of drug resistance has led to a growing interest in investigating combination therapies that combine vemurafenib with drugs that target other proteins in the BRAF pathway. One such medication that was deemed to be effective in combination with vemurafenib is cobimetinib. This drug is a downstream inhibitor of MEK; another protein within the BRAF intrinsic pathway. coBRIM was a multicenter phase 3 RCT consisting of 495 patients that compared vemurafenib and placebo to vemurafenib and cobimetinib. The double blinded trial demonstrated a significantly higher progression-free survival and overall response rate in dual therapy recipients. In addition, it saw reduced disease progression and reduced rate of grade 3 and 4 adverse events. This revealed a clear advantage of combination therapy over vemurafenib alone which resulted in the FDA approving cobimetinib and vemurafenib as a combination therapy for melanoma in late 2015. **[**26**]** This is now the gold standard for patients declaring resistance to vemurafenib monotherapy.

There are multiple ongoing trials at present being performed concerning vemurafenib within the oncological community. Given the constant battle against ongoing drug resistance, a vast majority of the clinical trials are focused on evaluating other novel drug combination approaches to find new dual therapy regimens capable of being effective against the disease. In addition, recent evidence has debunked the exclusivity of BRAF V600E mutations in melanoma. The same mutation in melanoma

has been identified in non-small cell lung cancer (NSLC), colorectal cancer and papillary thyroid cancer (PTC). [10] There is very limited data available at present for the role of vemurafenib on those pathologies and its usage is wholly investigational. However, there are a multitude of current ongoing trials investigating the role of vemurafenib on other BRAF positive cancers and its effectiveness in combination with other agents.

In conclusion, vemurafenib has revolutionized the treatment of malignant melanoma. The drug has demonstrated significant improvements in all aspects of survival and disease free status with only minor limitations to include resistance and side effects. The discovery and success of vemurafenib portrays an evolution in targeted cancer therapy and will continue to serve as a platform for future translational drug development. The timeline of development of vemurafenib as depicted, highlights the lengthy, complex, costly and risk-laden nature of such endeavor.

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