

## Targeted Molecular Therapies for Non-Melanoma Skin Cancer

Nataliya Lutay\*

*ImaGene-iT AB, Medicon Village, Lund, Sweden*

## Article Information

Received date: Nov 02, 2015

Accepted date: Nov 04, 2015

Published date: Dec 01, 2015

## \*Corresponding author

Nataliya Lutay, ImaGene-iT AB, Medicon Village, Lund, Sweden, Tel: +46 736 49 33 44; Email: nataliya@imagene-it.se

Distributed under Creative Commons  
CC-BY 4.0

Non-melanoma skin cancer (NMSC) is the most common cancer among Caucasian populations worldwide. More than 1 million new NMSCs are diagnosed each year, making it the most common cancer in the United States. Basal cell carcinomas (BCCs) account for about 80% of NMSCs, and most of the remainder are squamous cell carcinomas (SCCs) [1].

The treatment of advanced-stage NMSCs is challenging as surgical excision becomes impossible. Recent advances in the treatment of these tumors include targeted molecular therapies against epidermal growth factor receptor (EGFR) and hedgehog signaling pathway.

EGFR is a transmembrane tyrosine kinase receptor of signaling pathway that regulates proliferation, differentiation and apoptosis of cells and is involved in the pathogenesis and progression of different carcinoma types. The receptor may be targeted extracellularly by anti-EGFR monoclonal antibodies such as cetuximab against the part of ligand-binding ectodomain or intracellularly by tyrosine kinase inhibitors such as gefitinib. After binding to EGFR cetuximab induced an internalization of the ligand-receptor complex and subsequent down-regulation of intracellular signals [2]. Gefitinib inhibits EGFR tyrosine kinase activity by binding to the adenosine triphosphate (ATP)-binding site of the enzyme resulting in prevention of the anti-apoptotic Ras signal transduction cascade activation, thus inhibiting Ras promoted malignant cells progression and uncontrolled cellular proliferation. The low frequency of Ras mutations in SCCs makes these tumors attractive for EGFR inhibition [3].

Cetuximab (erbitux) is formulated for intravenous administration and has been trialed extensively in a variety of cancer types. The drug was approved by the Food and Drug Administration (FDA) for head and neck SCC treatment in conjunction with radiotherapy. Current evidence of cetuximab's efficacy in NMSC was mainly obtained in cutaneous SCCs and to a lesser extent in BCCs. There are now numerous case reports of its use in advanced and metastatic or recurrent cutaneous SCCs, either on its own or in combination with radiotherapy or another drug. Patient selection is often limited to those who have either failed or have a contraindication to conventional first-line treatments [4]. First-line treatment of 36 patients with unresectable SCC of the skin with single-agent cetuximab showed promising results. At 6 weeks of cetuximab administration, there were one complete response (CR), three partial responses (PR) and 21 patients with stable diseases while over the duration of the 48-week trial - two CR and eight PR [3].

Gefitinib, an inhibitor of EGFR tyrosine kinase activity, is currently licensed for treatment of non-small cell lung cancer. The oral formulation of gefitinib may make them more favorable than monoclonal antibodies to both patient and physician. The results of a phase II trial for gefitinib in in cutaneous SCC has recently been reported. Patients received neoadjuvant gefitinib as induction therapy given prior to standard treatment with surgery and/or radiotherapy. Four patients (18% of the 22 evaluable participants) achieved clinical CR to induction therapy. An additional 27% achieved a PR while 23 percent had stable disease. Further clinical trials are underway including one investigating the combination of gefitinib and PEG-interferon- $\alpha$ -2a in metastatic SCC [4].

Vismodegib (the trade name Erivedge) is a hedgehog inhibitor approved for the treatment of advanced BCCs.

The role of hedgehog ligands and pathway stimulation in BCC is theorized to lie in the activation of a 12-transmembrane domain protein (Patched1, abbreviated PCTH1) that is usually present during the telophase of the cell cycle. This protein normally regulates cell entry activity of smoothen (SMO), a protein receptor, by inhibiting its entry. When hedgehog ligands bind to PCTH1, it causes the loss of inhibition of smoothen, which allows it to enter the cell. This leads to smoothen activation, which further stimulates downstream pathways, resulting in increased cell proliferation.

Vismodegib antagonizes smoothen by binding to and inhibiting its movement inside the cell while also preventing transmission of signals. By antagonizing smoothen, vismodegib is capable of preventing cell proliferation caused by either a genetic mutation or an environmentally induced factor.

The phase II trial entitled ERIVANCE BCC enrolled 104 patients with either locally advanced or metastatic BCC. Vismodegib proved to decrease cancerous lesions by 30% in the participants suffering from metastatic BCC (95% confidence interval [CI] = 16%-48%;  $p = 0.001$ ). An even greater response was seen in patients suffering from advanced BCC: 43% (95% CI = 31%-56%;  $p < .001$ ) with 13 CR [5]. These results were first presented at the 7<sup>th</sup> European Association of Dermato-Oncology Congress in Nantes in June 2011. In January 2012, vismodegib was approved by the FDA for monotherapy in the treatment of unresectable/malignant and advanced BCC.

In the case of advanced and metastatic NMSC, molecularly targeted therapy represents a reasonably promising alternative to classical cytotoxic chemotherapy. The remarkable responses documented in several case reports and trials suggest that EGFR and hedgehog pathway inhibitors can play a major role and may one day become first-line agents for selected patients with aggressive or unresectable NMSC.

## Reference

1. Wu PA, Stern RS. Topical tretinoin, another failure in the pursuit of practical chemoprevention for non-melanoma skin cancer. *J Invest Dermatol.* 2012; 132: 1532-1535.
2. Conen KL, Fischer N, Hofbauer GF, Shafaeddin-Schreve B, Winterhalder R, Rochlitz c et al. Cetuximab in metastatic squamous cell cancer of the skin: a Swiss case series. *Dermatology.* 2014; 229: 97-101.
3. Maubec E, Petrow P, Scheer-Senyarich I, Duvillard P, Lacroix L, Gelly J, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. *J Clin Oncol.* 2011; 29: 3419-3426.
4. Gaffney DC, Soyer HP, Simpson F. The epidermal growth factor receptor in squamous cell carcinoma: An emerging drug target. *Australas J Dermatol.* 2014; 55: 24-34.
5. Nix NM, Burdine O, Walker M. Vismodegib: First-in-Class Hedgehog Pathway Inhibitor for Metastatic or Locally Advanced Basal Cell Carcinoma. *J Adv Pract Oncol.* 2014; 5: 294-296.