

# Systemic treatment of advanced basal cell carcinoma: how to critically evaluate value for patient and society?

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Last year, the Food and Drug Administration and European Medicines Agency approved the anti-programmed cell death protein 1 (anti-PD-1) agent cemiplimab for locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma (mBCC) in patients where a hedgehog pathway inhibitor (HHI) is (no longer) an appropriate treatment option. Although we embrace any therapeutic progress in the field of dermatology, we believe it is important to keep assessing the indications critically.

The direct treatment cost of a hedgehog inhibitor (HHI), that is, vismodegib and sonidegib for 1 year in Belgium is around 50,000 EUR from a health-care payer perspective. This does not include costs due to follow-up consultations, side effects, or indirect costs (i.e. transportation or informal care). For HHI, objective response rates (ORRs) reported in the ERIVANCE trial (vismodegib) were 60% for laBCC and 48% for mBCC.<sup>1</sup> The BOLT trial (sonidegib) reported ORR of 56% in laBCC and 8% in mBCC.<sup>2,3</sup> Complete responses were confined to the laBCC subgroup and reported in 28% of vismodegib-treated and 5% of sonidegib-treated patients.<sup>1,3</sup> At the timepoint of, respectively, 39 and 42 months after initiation of the ERIVANCE and the BOLT trial, more than 90% of patients had interrupted treatment. Treatment discontinuation was mostly due to progressive disease, adverse events, patient decision, or doctor decision.<sup>1,3</sup> The frailty of the population presenting with advanced BCC is reflected by the fact that more than one-third of patients in the BOLT trial had Eastern Cooperative Oncology Group

performance status 1 or 2 at study initiation. More than 30% of the included patients in the ERIVANCE study had died at the 39-month evaluation (with no relation to vismodegib).

Davis *et al.* have demonstrated that anti-PD-1 immunotherapy with cemiplimab is a valuable treatment option in patients where HHIs have failed.<sup>4</sup> Considering the limited number of complete responses in HHI and the high number of treatment discontinuation over time, a large part of patients with advanced BCC may be eligible for anti-PD-1 immunotherapy at a certain moment in time. Anti-PD-1 immunotherapy has overall response rates of 31% (25% partial and 6% complete) and a grade 3 or 4 toxicity in half of the patients.<sup>5</sup> This treatment option comes with a yearly direct treatment cost in the order of 100,000 EUR in Belgium. No good biomarkers to predict who is going to respond could be identified in the pivotal trials leading to market authorization.<sup>5</sup> In the end, a considerable part of the initial patient group with advanced BCC will still have incomplete response after two lines of systemic treatment.

The healthcare budgets are more than ever under pressure, and the number of BCC patients is likely to further increase in the next decade.<sup>6</sup> The cost per quality-adjusted life-year or 'QALY' expresses how much society is willing to pay for one year of life in perfect health. The *WHO Choosing Interventions that are Cost-Effective* (WHO-CHOICE) methodology recommends a QALY threshold of less than three times the national

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annual gross domestic product per capita<sup>7</sup> and is estimated around 35,000USD/33,252.45EUR for Europe.<sup>8</sup> In older age groups, the willingness to pay may be lower. An intervention can cause a gain in QALYs either by increasing the patients' life expectancy and/or increasing the patients' quality of life (QoL) by means of reducing symptoms or discomfort.

A median survival of 54 months has been reported in mBCC.<sup>9</sup> It is not clear whether therapy with HHI or anti-PD-1 immunotherapy can improve survival. Metastatic BCC is extremely rare with a cumulative 14-year incidence estimated lower than 4/100,000 in patients with a history of BCC.<sup>10</sup> In laBCC, a gain in QALYs would need to result from improved QoL. However, clear data on QoL and disease-specific symptoms in advanced BCC are lacking.<sup>11,12</sup> On the other hand, treatment may also negatively impact QoL due to toxicity and/or time spent on consultations, day clinic, blood analysis, or imaging. In view of treatment responses and toxicity described above, one can imagine that a delta increase of 1 QALY (at a willingness to pay threshold of 33,252.45EUR) for the treatment of advanced BCC will be difficult to achieve.

Before initiation of systemic treatment in aBCC, it is important to not only inform the patient about treatment response and side effects, but also to clarify the patients' expectations [using Patient-Reported Outcome Measures (PROMS)] and evaluate the patient's frailty and life expectancy. Validated tools and questionnaires such as EORTC PROMS questionnaires, G8 and CCI can assist in this shared decision making process and have demonstrated their usefulness in cancer care. The goal of care should be predefined, and the risks and benefits of systemic treatment should be weighed against patient's expectations. We believe certain frail and elderly patients in this subpopulation could be better off with a watchful waiting/active surveillance approach and a palliative treatment regimen to alleviate symptoms.<sup>13</sup> This process takes time and would benefit from a clinically validated decision-making algorithm that can assist the patient and the doctor to select the most appropriate treatment strategy.

## Declarations

*Ethics approval and consent to participate*  
Not applicable.

## Consent for publication

Not applicable.

## Author contribution(s)

**Isabelle Hoorens:** Conceptualization; Writing – original draft; Writing – review & editing.

**Laura Van Coile:** Conceptualization; Writing – original draft; Writing – review & editing.

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**Evelien Verhaeghe:** Conceptualization; Writing – review & editing.

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## Competing interests

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## Availability of data and materials


Not applicable.

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