Comment on 'Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines'

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To the Editor,

We thank van Delft et al.[1] for their letter to the Editor related to our published European consensus-based interdisciplinary guidelines on the diagnosis and treatment of basal cell carcinoma (BCC) [2]. They comment on the extensive safety margins for conventional (2D) surgical excision of high-risk BCCs and the proposed frequent follow-up of patients with a history of BCC.

We agree that microscopically controlled surgery (3D) provides tumor removal sparing normal tissue, thus avoiding unnecessary morbidity. In the European BCC guidelines, we stated that microscopically controlled surgery (3D) shall be offered in high-risk BCC, in recurrent BCC and in BCC in critical anatomical sites, with a grade of recommendation A and strength of consensus of 100%. However, this surgical technique is not routinely performed in all European countries, and therefore we advised a broad safety margin ranging from 5 to 15 mm. Since we published the 'European' guidelines, we took into account the availability of surgical modalities and the diversity of access to care in the different European countries. A possible concern of microscopically controlled surgery (3D) is the presence of skip areas in morpheaform BCC, which might be overcome with the use of broad safety margins. In addition, disadvantages of microscopically controlled surgery (3D) include the need of special equipment and training, length of procedure and high costs, which currently limit a wide availability in Europe. Furthermore, van Delft et al. [1] suggest that when expensive targeted therapies become more available in Europe, the implementation of a simple surgical/histopathology technique should not be difficult, and this would improve BCC care enormously. In this regard, we would like to emphasise that several countries in Europe still have significantly restricted access to innovative treatments for advanced melanoma and non-melanoma skin cancers because of drug authorization and reimbursement [3] and neither microscopically controlled surgery (3D) nor novel treatments can be commonly used.

Regarding their comment on the suggested follow-up schedule for patients with a history of BCC, we described two groups of patients who would benefit of a more rigorous follow-up every 6–12 months including patients who are at high risk for recurrence and patients with a history of multiple BCCs. In addition, we specified that in case of difficult-to-treat BCC or metastatic BCC, follow-up should be practiced by a multidisciplinary team at a frequency dictated for each individual. Therefore, in our conclusion, the general follow-up recommendation of every 3, 6 or 12 months according to the risk categories wished to include all these clinical situations. Similar follow-up schedules for multiple BCCs, BCCs with high recurrence risk and advanced BCC were indeed recommended in the S2K German guidelines [4]. On the other hand, we agree that a less intensive follow-up can be performed in patients with low-risk BCC and have indicated this in our guidelines. In line with their suggestions, in our guidelines, we emphasised the importance of counseling patients about sun protection measures and about self-monitoring for possible local recurrence and new skin cancers. The surgical margins we proposed indeed represent only an expert consensus because there is a lack of randomised trials in this context. Whilst we agree with van Delft et al. [1] that both 'more nuanced' yearly follow-up schedule may be appropriate and efforts to optimise treatment may make extensive follow-up schemes redundant, long-term randomised clinical trials will be required to establish the ideal follow-up schedule. We would like to thank the authors for their valuable comments, which will be considered at the next update of this BCC guideline.

Conflict of interest statement

K.P. reports receiving grants and personal fees from Almirall and Abbvie, during the conduct of the study, and personal fees for Advisory Board Meeting from Biogen, Lilly, Celgene, Galderma, LEO Pharma, Novartis, Pierre Fabre, Sanofi, Sandoz, Sun Pharma

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References

[1] van Delft LCJ, van Loo E, Mosterd K, Kelleners-Smeets NWJ. Comment on "Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. Eur J Canc 2020 Jan 10. pii: S0959-8049(19)30853-30856.

[2] Peris K, Fargnoli MC, Garbe C, Kaufmann R, Bastholt L, Seguin NB, et al. European Dermatology Forum (EDF), the European association of dermato-oncology (EADO) and the European organization for research and treatment of cancer (EORTC). Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. Eur J Canc 2019;118:10–34.

[3] Kandolf Sekulovic L, Guo J, Agarwala S, Hauschild A, McArthur G, Cinat G, et al. Access to innovative medicines for metastatic melanoma worldwide: melanoma World Society and European Association of Dermato-oncology survey in 34 countries. Eur J Canc 2018;104:201–9.

[4] Lang BM, Balermpas P, Bauer A, Blum A, Brölsch GF, Dirschka T, et al. S2kguidelines for cutaneous basal cell carcinoma - Part 2: treatment, prevention and follow-up. J Dtsch Dermatol Ges 2019;17:214–30.