Conference Report

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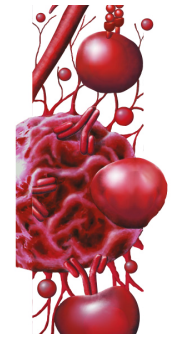
Immunotherapy



# Updates and new perspectives in nonmelanoma skin cancer therapy: highlights from 'Immunotherapy Bridge'

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**Over the last few years, extensive research has improved our understanding of tumor immunology and has enabled the development of novel treatments. The state of the art of immunotherapy in various types of malignancies was exhaustively discussed in the 'Immunotherapy Bridge' meeting, which was held in Naples on 4–5 December 2019. Highlights related to the immunological treatment of nonmelanoma skin cancer are the content of this article.**

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Over the last few years, extensive research has improved our understanding of tumor immunology and has enabled the development of novel treatments, which can harness the patient's immune system and prevent immune escape. The state of the art of immunotherapy in various types of malignancies was exhaustively discussed in the 'Immunotherapy Bridge' meeting, which was held in Naples on 4–5 December 2019. Within Congress, available evidence and new perspectives on the immunological treatment of nonmelanoma skin cancer (NMSC) were presented. This heterogeneous group of malignancies includes basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (cSCC) and Merkel cell carcinoma (MCC), and ranges from easily cured diseases to adverse outcomes [1,2]. Highlights related to this latter subject are the content of this article.

## Merkel cell carcinoma

MCC is rare and highly aggressive skin cancer, and, in many cases, it is caused by the Merkel cell polyomavirus or in countries with high insolation also by UV-exposure [2]. Treatment is based on surgery and chemotherapy with adjuvant radiotherapy; in unresectable metastatic MCC, mono- or poly-chemotherapy achieves high remission rates but responses are usually short-lived [2]. The PD-1/PD-L1 immunosuppressive pathway is often upregulated in MCC, and advanced metastatic MCC was found to be responsive to PD-1 blockade. Current evidence supports the use of checkpoint inhibitors as the best option to treat patients with advanced MCC [3]. In the Phase I/II CheckMate 358 trial, neoadjuvant nivolumab was administered 4 weeks before surgery to 25 patients with resectable MCC (44% Merkel cell polyomavirus positive, and 30% PD-L1+). Among 17 evaluated resections, 65% had major pathologic response, including eight complete responses (47%) [4]. Recently, in an expanded Phase II trial, durable tumor regression and increased overall survival were obtained in patients with advanced MCC, with pembrolizumab as the first-line treatment [5]. The objective response rate (ORR) was 56% in this study [6].

Part A of the JAVELIN Merkel 200 trial showed that avelumab, an anti-PD-L1 antibody, demonstrated efficacy in second-line or later treatment of patients with metastatic MCC. Recently, part B of the JAVELIN Merkel 200 trial evaluated the efficacy and safety of avelumab as a first-line treatment for patients with distant metastatic MCC. Patients were not selected for PD-L1 expression or Merkel cell polyomavirus status. In a preplanned analysis, efficacy was assessed in 29 patients with at least 3 months of follow-up; the confirmed ORR was 62.1% (95% CI: 42.3–79.3%), with 14/18 responses (77.8%) ongoing at the time of analysis. In responding patients, the estimated

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proportion with a duration of response (DOR) of at least 3 months was 93% (95% CI: 61–99%); and with a DOR of at least 6 months was 83% (95% CI: 46–96%) [7]. The primary analysis for part B of this trial after ≥15 months of follow-up in the full patient population showed that the median OS was 20.3 months (95% CI: 12.4 months–not estimable) and the 12-month OS rate was 60% (95% CI: 50–68%) [8].

Based on this evidence, a new standard of care is now available for MCC. Although the National Comprehensive Cancer Network guidelines used to recommend chemotherapy only for MCC until 2016, checkpoint immunotherapy has been preferred over chemotherapy since 2018 [9].

## Basal cell carcinoma

BCC is the most common NMSC, representing 75–80% of cases [10]. It arises in sun-exposed areas, mainly after the age of 40 years. Although most BCCs are successfully treated surgically, no effective therapy exists for locally advanced or metastatic BCC.

The Hedgehog (Hh) signaling pathway regulates body patterning and organ development during embryogenesis, and is mainly quiescent in the adult life, with the exception of roles in tissue maintenance and repair. Several disparate human cancers have been linked to inappropriate reactivation of Hh signaling, either in an autocrine or in a paracrine manner [11].

Molecular and genetic studies have shown that almost all BCC contain genetic alterations in the Hh signaling pathway, resulting in aberrant pathway activation and uncontrolled proliferation of basal cells. Most commonly, these alterations cause a loss of function of *PTCH1*, which normally acts to inhibit the signaling activity of SMO, a seven-transmembrane protein [12,13]. Vismodegib (GDC-0449, Genentech, CA, USA) is a first-in-class, small-molecule inhibitor of SMO, investigated in the ERIVANCE BCC trial. In 33 patients with metastatic BCC, the response rate to vismodegib was 30% (95% CI: 16–48; $p = 0.001$). In 63 patients with locally advanced BCC, the response rate was 43% (95% CI: 31–56; $p < 0.001$), with complete responses in 13 patients (21%). The median DOR was 7.6 months in both cohorts. Serious adverse events were reported in 25% of patients; seven deaths due to adverse events were noted [14]. 39 months after completion of accrual, investigator-assessed ORR was 48.5% in the metastatic BCC group (all partial responses) and 60.3% in the locally advanced BCC group (20 complete responses and 18 partial responses). The median DOR was 14.8 months (metastatic BCC) and 26.2 months (locally advanced BCC). Median overall survival was 33.4 months in the metastatic BCC cohort and not estimable in the locally advanced BCC cohort. Adverse events remained consistent with clinical experience. A total of 33 deaths (31.7%) were reported; none were related to vismodegib [15].

The Hh signaling inhibitor sonidegib was investigated in a randomized Phase II trial enrolling patients with locally advanced or metastatic BCC. An objective response was observed in 36% of patients receiving 200 mg sonidegib and in 34% of those receiving 800 mg. Serious adverse events occurred in 11 (14%) of 79 patients in the 200-mg group and 45 (30%) of 150 patients in the 800-mg group [16].

## Cutaneous squamous cell carcinoma

cSCC is the second most frequent NMSC, and its incidence is rapidly increasing [1]. It frequently arises from a precancerous lesion; actinic keratoses are common lesions with a risk of progression to cSCC of approximately 1/1000 [17].

More than 90% of cSCC may be cured by early surgery. Nevertheless, a minority of lesions, still representing approximately 5% of patients, progresses to locally advanced or metastatic disease, which has an unfavorable prognosis, and has no established standard therapy [18]. Some criteria may help identify high-risk cSCC: tumor thickness, as indicated by Breslow thickness or Clark level, grade of differentiation, histological subtype, perineural or lymphovascular invasion and locations, such as ear, lip, scars and immunosuppression [19]. A German study in the real-life setting showed unmet issues in the current treatment of advanced cSCC: 59% of patients with locally advanced cSCC received no therapy, while 92% of subjects with metastatic cSCC received systemic therapy but had a mean DOR of only 3 months [18]. In this cohort, 75/152 (49%) of patients died during the study and the median overall survival was 48 months. Therefore, at that time, available therapies lacked a clear therapeutic advantage. It has been recently observed that cSCC has a high tumor mutational burden, which opened new perspectives for treatment targets. PD-L1 expression was documented in cSCC, with a positive correlation between the degree of PD-L1 expression and pathologic findings related to risk factors of metastasis including large diameter, higher histological grade and tumor thickness [20]. Only preliminary experience exists for use of anti-PD-1 antibodies in patients with cSCC. Borradori *et al.* reported that among four patients with cSCC and one patient with

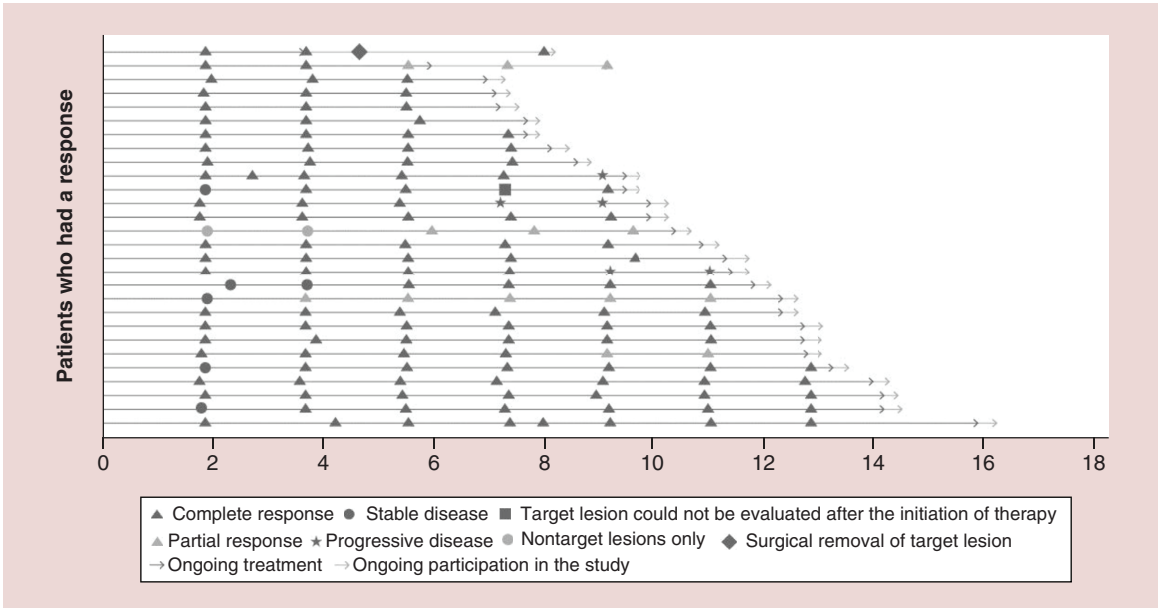


**Figure 1. Time to response and duration of response for the 28 patients in the metastatic-disease cohort of the Phase II study who had a response.** Of the 28 patients, 23 continued to have a response at the time of data cut-off, three had progressive disease, one had surgical removal of the responsive target lesion and thus had censored data after surgery **(top line)**, and one had a confirmed complete response but had censored data after being lost to follow-up **(second line from the top)**. One of the 23 patients who continued to have a response **(14th line from top)** had nontarget lesions only and was deemed by independent central review to have a complete response after the lesions disappeared.
Reproduced with permission from [23] © Massachusetts Medical Society (2018).

baso-squamous cancer, two partial responses and three stabilizations were obtained within 3 months of therapy, and mean DOR was more than 6 months [21]. A pivotal Phase II study is evaluating the anti-PD-1 cemiplimab in metastatic cSCC and in unresectable locally advanced cSCC [22]. Patients receive intravenously 3 mg/kg of body weight every 2 weeks. In the metastatic-disease cohort, including 59 patients, with a median follow-up of 7.9 months, a response was observed in 28 patients (47%; 95% CI: 34–61). Among the 28 responding patients, the DOR exceeded 6 months in 57%, and 82% continued to have a response and to receive cemiplimab at the time of data cut-off (Figure 1). The estimated progression-free survival was 52.5% (95% CI: 37.0–65.8), and the estimated overall survival was 80.6% (95% CI: 67.7–88.8) (Figure 2).Adverse events that occurred in at least 15% of the patients were diarrhea, fatigue, nausea, constipation and rash; 7% of the patients discontinued treatment because of an adverse event [23].

The 12-month follow-up data for the metastatic cohort were presented in 2019: ORR was 49.2% (95% CI: 35.9–62.5; 10 complete responses and 19 partial responses). Median DOR had not been reached and the longest DOR at data cut-off was 21.6 months and was still ongoing. Durable disease control rate (stable disease or response for ≥16 weeks) was 62.7% (95% CI: 49.1–75.0) [24].

In the locally advanced disease cohort, 78 patients were enrolled. With a median follow-up of 9.3 months (range: 0.8–27.9), ORR was 43.6% (95% CI: 32.4–55.3; 10 CRs and 24 PRs). Median DOR had not been reached. The longest DOR at data cut-off was 24.2 months and was still ongoing. The durable disease control rate was 62.8% (95% CI: 51.1–73.5). Median progression-free and overall survival had not been reached. The most common treatment-emergent adverse events were fatigue (42.3%), diarrhea and pruritus (both 26.9%), and nausea (21.8%). One patient died due to an unknown cause that was assessed as treatment related [25].

Aiming at overcoming acquired resistance, an ongoing randomized, double-blind, placebo-controlled study is evaluating adjuvant cemiplimab versus placebo after surgery and radiation therapy in patients with high-risk cSCC. The primary objective is disease-free survival (protocol R2810-ONC-1788, ClinicalTrial.gov).

Neoadjuvant use of cemiplimab prior to surgery is being studied in patients with stage III/IV cSCC of the head and neck in a Phase II trial that enrolled 20 patients. ORR by RECIST was 30%, and pathologic complete

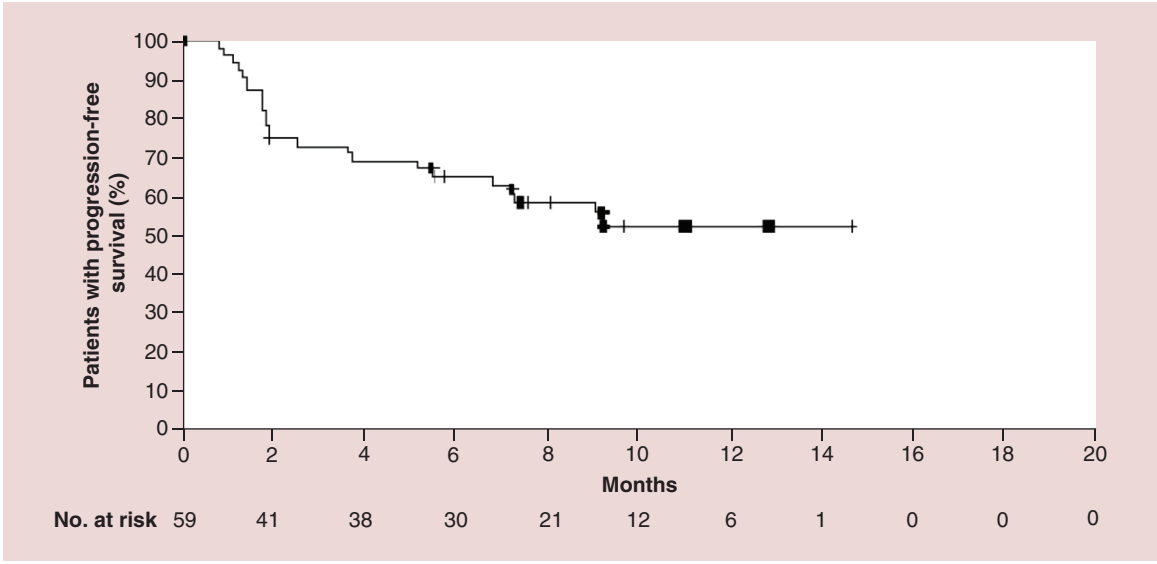


**Figure 2. Progression-free survival in metastatic cutaneous squamous cell carcinoma in the pivotal Phase II study.** Reproduced with permission from [23] © Massachusetts Medical Society (2018).

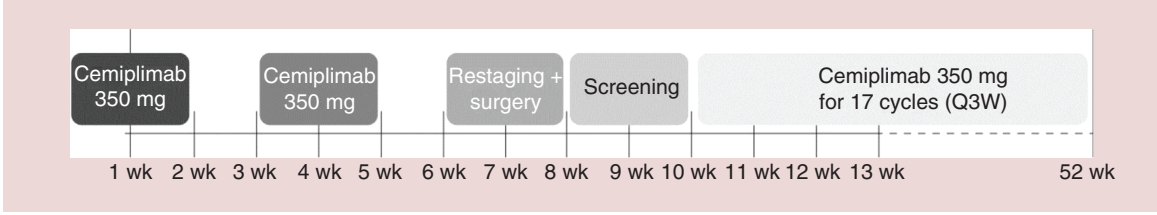


**Figure 3. Study design of the NEOCESQ trial.**

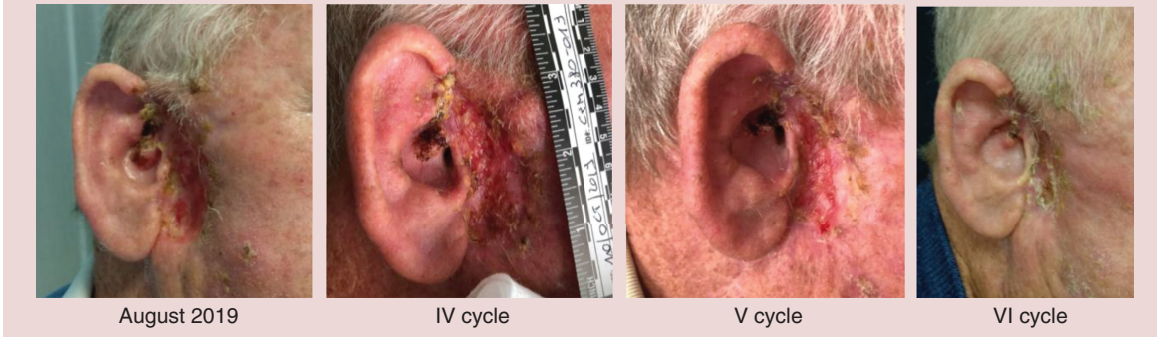


**Figure 4. A male patient with cutaneous squamous cell carcinoma of the preauricular area initiated cemiplimab treatment in August 2019.** After four cycles of treatment, a partial response was observed as lesion diameter was slightly reduced. Therapy continued with progressive further reduction of lesion size.

response (0% viable tumor cells) was 55% [26]. Neoadjuvant with adjuvant use of cemiplimab prior to surgery will be evaluated by NeoCESQ (Neoadjuvant plus adjuvant study with CEmiplimab in SQuamous cell carcinoma) study, designed as a single arm Phase II trial (Figure 3; personal communication by Ascierto P).

The ongoing CARSKIN trial is assessing pembrolizumab in patients with unresectable cSCC. Out of 39 enrolled patients, 27 were evaluable for the primary end point that was tumor response at week 15. The response rate was

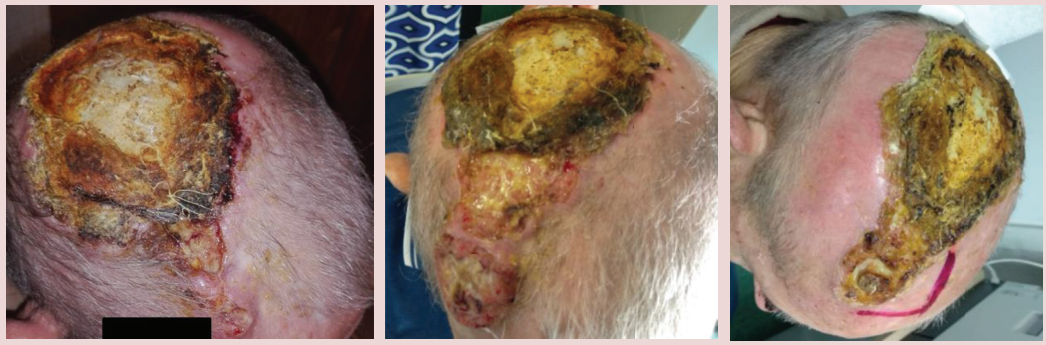


**Figure 5. A male patient affected with locally advanced Cutaneous squamous cell carcinoma located on the scalp received cemiplimab in June 2019.** Disease was stable after four cycles of therapy, in September and later in October 2019. Therapy was continued with further 11 cycles.

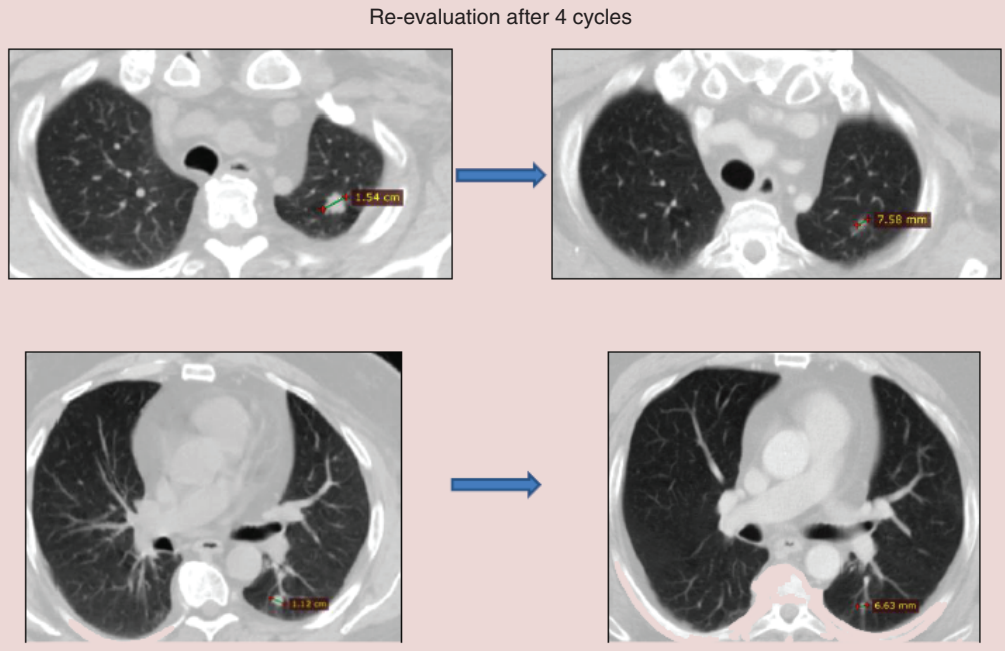


**Figure 6. CT demonstrated two lung metastases in a patient affected by cutaneous squamous cell carcinoma, with a diameter of 1.54 and 1.12 cm, respectively.** The patient initiated treatment with cemiplimab. A scan control after four cycles found a partial response as lesion diameters were diminished to 7.58 and 6.6 mm, respectively.

38.5% (15/39; 95% CI: 24–55%) and median DOR was 12.5 months (Q1–3: 10.60–17.1). The antitumor activity was independent of PD-L1 expression [27].

## Conclusion

Based on available evidence the current standard for the systemic treatment of aggressive forms of NMSCs has recently changed. Knowledge of possible therapeutic targets opened new perspectives toward immunotherapy. Checkpoint immunotherapy is to now be considered the standard of care for MCC, and locally advanced or metastatic nonresectable cSCC, while Hh-signaling inhibitors are being used as first-line treatment for advanced BCC. Cemiplimab was approved for the treatment of nonresectable cSCC in the EU and USA. Clinical experience

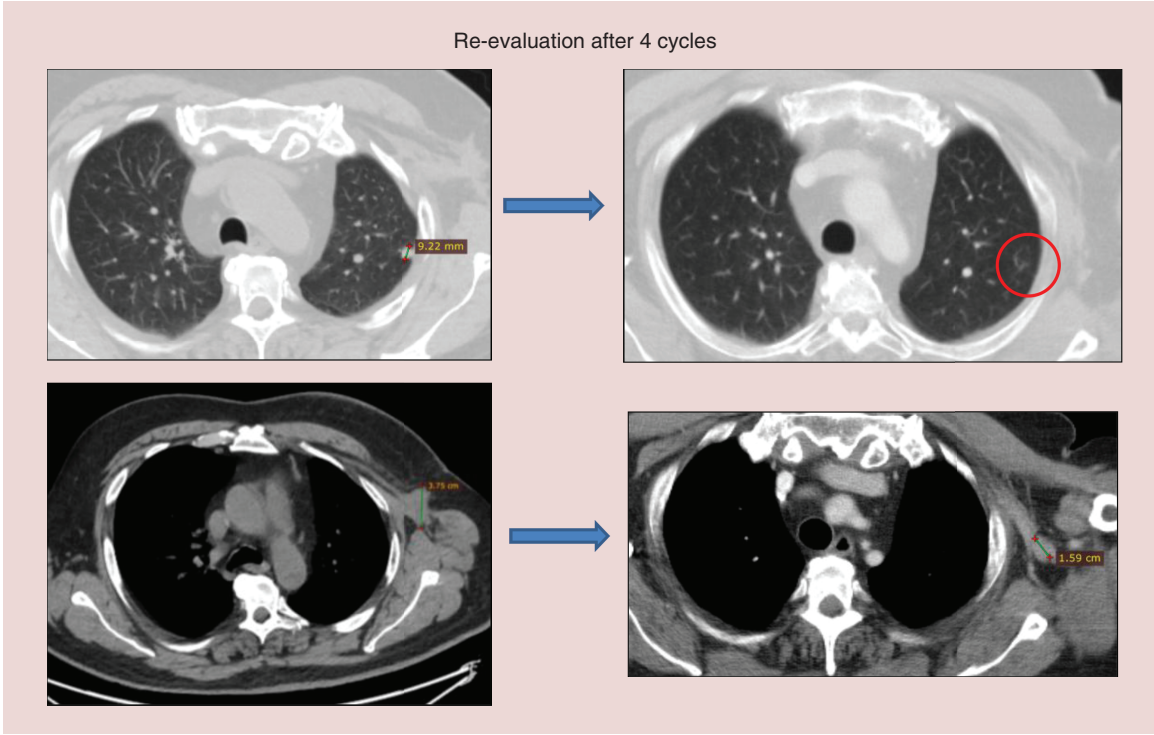


**Figure 7. CT demonstrated cutaneous squamous cell carcinoma metastases of 9.2 and 3.7 cm of diameter, at baseline.** After four cycles of treatment with cemiplimab, the larger lesion was no longer demonstrated in the CT scan, and the small diameter was diminished to 1.6 cm.

in real life is confirming results from clinical studies (Figures 4–7). Combined checkpoint blockade or ipilimumab could provide improved efficacy but experiences are not yet available.

### Financial & competing interests disclosure

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