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# Real-world experience with first- versus second-line cemiplimab for advanced basal cell carcinoma

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ABSTRACT

*Background:* The anti-PD1 antibody (PD1i) cemiplimab is approved as second-line treatment for locally advanced or metastatic basal cell carcinoma (BCC), resulting in an ORR of 20–30 %. This study aimed to investigate the efficacy of cemiplimab as first-line or second-line treatment of BCC in a German real-world patient cohort.
*Methods:* Patients with histologically confirmed locally advanced or metastatic BCC who were treated with cemiplimab were retrospectively identified from the prospective multicenter real-world skin cancer registry ADOREG. Study endpoints were overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). Therapy outcome was compared between patients receiving first-line cemiplimab and patients treated with cemiplimab in second-line.

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*Results:* 37 patients from 17 skin cancer centers were identified who received cemiplimab. The median follow-up after start of any first-line treatment was 37.1 months, and 17.9 months after initiation of any cemiplimab treatment. Patients who received first-line cemiplimab (n = 8) had an ORR of 62.5 %, compared to an ORR of 31.0 % for patients who received second-line cemiplimab (n = 29); Median PFS was 19.8 months for first-line cemiplimab and 5.3 months for second-line cemiplimab. Reinduction with HHIs after progression on second-line cemiplimab resulted in an ORR of 20.0 % and a median PFS of 3.8 months.
*Conclusion:* We demonstrate a comparable outcome for cemiplimab as second-line treatment of BCC in our real-world patient cohort as reported in previous registration studies. Additionally, we found a trend for a more favorable outcome in first-line therapy, suggesting a rationale to further investigate cemiplimab as first-line treatment of advanced BCC.

## 1. Introduction

Basal cell carcinoma (BCC) is the most common malignancy worldwide and its incidence is increasing. A recent cancer registry study of the Swedish population reported an increase in BCC incidence from 308 cases per 100,000 in 2004 to 405 cases per 100,000 in 2017, a relative increase of 1.8 % per year [1]. Even higher rates were reported in the USA and Australia, with incidence rates of 1488 and 1170 cases per 100,000, respectively [2,3]. Almost all BCCs can be treated curatively with surgery [4,5]. Given the high overall incidence of BCC, the occurrence of locally advanced or metastatic BCC, although relatively rare, represents a significant clinical challenge requiring a multidisciplinary approach for management, including surgery, radiation therapy, and systemic therapies such as Hedgehog pathway inhibitors (HHI), which are approved for first-line treatment of advanced BCC. They bind to the transmembrane protein smoothened, which leads to suppression of the downstream signaling cascade and prevents tumor progression. For locally advanced BCC, both vismodegib and sonidegib show an objective response rate (ORR) of 43 % and a median progression-free survival (PFS) of 9.5 months and 22.1 months, respectively. Treatment-related adverse events, including muscle spasms, alopecia, nausea and dysgeusia occur in almost every patient and lead to treatment discontinuation in 12–20 % of patients [6–8]. Cemiplimab, an anti-PD-1 antibody (PD1i), has recently been approved for patients with advanced or metastatic BCC in cases of HHI failure, unacceptable toxicity, or for whom a HHI is inappropriate. In a clinical trial of 84 patients with locally advanced BCC and prior therapy with HHI, treatment with cemiplimab showed an objective response in 31 % and a disease control in 80 % of patients. The median PFS was 19 months and the median overall survival (OS) was not reached even after extended follow-up [9,10]. For the 54 patients with metastatic BCC, treatment with cemiplimab was associated with an objective response in 22 % and a disease control in 63 % of patients with a median PFS and OS of 10 months and 50 months, respectively [11]. In both trials, grade 3–4 treatment-emergent adverse events were observed in 48 % and 39 % with treatment discontinuation due to treatment-related side effects in 11 % and 6 %, respectively.

Treatment data of advanced BCC with immune checkpoint inhibitors outside clinical trials is lacking. Consequently, this study examines efficacy and side effects of PD1i in the real world.

## 2. Patients & methods

Patients with histologically confirmed locally advanced or metastatic BCC who were treated with cemiplimab in any therapy line were retrospectively identified from the prospective multicenter real-world skin cancer registry ADOREG of the German Dermatologic Cooperative Oncology Group (DeCOG). The ADOREG-registry was approved by the Medical Ethics Committee of the University Duisburg-Essen (14–5921-BO), and written informed consent for participation was obtained from all patients.

In total, 37 patients from 17 skin cancer centers in Germany (Bochum, Buxtehude, Dresden, Essen, Gera, Hamburg-Eppendorf, Hannover, Heidelberg, Homburg, Kiel, Leipzig, Lübeck, Minden, Quedlinburg, Regensburg, Tübingen, Würzburg) were included and separated into two cohorts: patients treated with cemiplimab in first-line (group A) and patients who received cemiplimab as second-line treatment after HHI (group B). One patient in group B received pembrolizumab. Due to the same mode of action as cemiplimab, we included this patient in our analyses.

## 3. Statistical analysis

Treatment initiation of the PD1i was defined as index date. PFS was defined as time until first observed progression of BCC or death regardless of cause, whichever occurred first. Follow-up period and OS were calculated from the index date of first-line treatment initiation until death, last contact date, or end of observation period (04/2024), whichever occurred first. Patients without progression or death before data cut-off were censored at the end of the observation period, or at the last contact date, whichever applied first.

Continuous data is presented as median and interquartile ranges; categorical data is presented as percentages. Calculations were performed using Microsoft Excel (Microsoft 365, version 2419, Build 18129.20158 Click-to-Run).

For Kaplan-Meier regression regarding PFS and OS as well as uni- and multivariate analysis (Cox proportional hazards model) the packages survival (version 3.6–4) and survminer (version 0.4.9) in R (version 4.4.1, R Project for Statistical Computing) were used.

P values $< 0.05$ were considered clinically significant.

## 4. Results

### 4.1. Patients' characteristics

A total of 37 patients from 17 skin cancer centers, with locally advanced (n = 33, 89.2 %) or metastatic (n = 4, 10.8 %) BCC who received treatment with a PD1i between 06/2016 and 04/2024 were identified from ADOREG and included in this analysis. Of these, 8 patients (21.6 %) were treated with cemiplimab as first-line therapy (group A), and 29 patients (78.4 %) received cemiplimab following a first-line HHI treatment (group B, Table 1, Fig. 1). Reasons for first-line treatment with cemiplimab in group A were (a) confirmation of the histological subtype of a metatypical BCC after discussion in a multidisciplinary tumor board (n = 1), (b) recommendation of treatment with an PD1i for cancer of unknown primary with the verification of the diagnosis of a BCC after treatment initiation (n = 1), and (c) pretreatment with HHI earlier for unconfirmed locally advanced BCC and actual disease recurrence two years after treatment cessation (n = 1). There was no reason documented in 5 patients.

Patients in group B discontinued first-line HHI treatment due to disease progression in 65.5 % (n = 19), toxicity in 20.7 % (n = 6) or other reasons in 13.8 % (n = 4), the latter including regular end of treatment after complete remission or patient's choice. In 3 patients, complete response was reached following first-line HHI treatment. For these, relapse occurred after a median period of 3.6 months (IQR 3.6–3.6). The median time to next treatment (time between end of HHI

and initiation of cemiplimab) was 11.1 months (IQR 11.1–14.2).

Among the patients from group B, 10 patients were retreated with HHI after BCC progression under cemiplimab.

Patients in group A had a higher median age of 75.5 years (IQR 64.5–87.2) compared to patients in group B (72.2 years, IQR 62.5–79.1). Both groups were well balanced for sex and tumor localization.

At the time of data cut (Aug 1st 2024), 1 patient in group A (12.5 %) and 4 patients in group B (13.8 %) were still on treatment with cemiplimab; 21 patients had discontinued PD1i treatment due to disease progression (group A: n = 3, 62.2 %; group B: n = 14, 48.3 %) or toxicity (group A: n = 1, 12.5 %; group B: n = 3, 10.3 %). The median duration of follow-up was 37.1 months (IQR 22.3–51.4, range 5.8–85.2 months) (Table 2, Fig. 1).

### 4.2. Efficacy and safety

In the PD1i first-line (group A), a response under cemiplimab treatment was observed in 5 of 8 patients (62.5 %), including 2 patients with complete responses (25 %) and 3 patients with partial responses (37.5 %). There were 2 patients with stable disease (50 %), and 1 patient experienced disease progression (12.5 %) as best response. Median treatment duration in this group was 13.5 months (IQR 4.0–24.3) with a median PFS of 19.8 months (IQR 10.8–33.6).

One patient with progressive disease under cemiplimab first-line treatment received a HHI treatment (sonidegib) as second-line therapy, experiencing a complete response for at least 1 year. At data cut-off the patient was still on treatment with sonidegib (data not included statistical analysis).

Among the patients treated with cemiplimab in second-line (group B), 9 of 29 patients (31.0 %) had an objective response: 2 patients had a complete remission (6.9 %), 7 patients had a partial response (24.1 %). In addition, best response was stable disease in 5 patients (17.2 %), mixed response in 1 patient (3.4 %) and progressive disease in 12 patients (41.4 %). Median treatment duration was 5.1 months (IQR 2.9–12.6) and median PFS 5.3 months (IQR 3.1–13.3, Fig. 2).

Patients of group B who stopped prior treatment with HHI after disease progression (n = 20) showed a response rate of 25.0 % (n = 5) when treated with cemiplimab in the second-line, compared to a response rate of 50.0 % (n = 3) for patients who stopped prior HHI therapy due to side effects.

After disease progression, 10 patients in group B were retreated with HHI. There were 2 patients with partial responses (20 %), 3 patients with stable diseases (30 %), and 5 patients with disease progressions (50 %). Median treatment duration was 4.4 months (IQR 3.0–6.4) and median PFS 3.8 months (IQR 2.5–6.4) (Tables 2 and 3).

Until data cut, only 4 deaths (10.8 %) were observed in the total cohort. Due to the high censoring rate, survival analysis, including OS, was not feasible (Supp. Fig. 1).

Uni- and multivariate regression of clinical parameters did not show significant prognostic relevance concerning progression under PD1i treatment, regardless of therapy sequence (Supp. Fig. 2, supp. Table 1).

Side effects under PD1i treatment were documented in 12 patients (27.0 %), of which 3 were ranked as toxicity grade 3 or above according to the version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAE v5.0). In total, toxicity led to PD1i treatment discontinuation in 4 patients (10.8 %, Table 4).

## 5. Discussion

This real-world study investigated the efficacy of cemiplimab in patients with advanced BCC. Patients with prior HHI therapy that were treated with cemiplimab in second-line had an ORR of 31.0 % and disease control in 48.3 % of patients. This response rate is in accordance with the results from the phase 2 trial with an ORR in 31 % of patients [9]. In contrast, the disease control rate in the phase 2 trial was higher, with 80 % of patients experiencing at least stabilization of the disease. In addition, median PFS in our patients was shorter with 5.3 months compared to 19 months in the clinical trial. Reasons may include differences in the patient characteristics: patients from our cohort had a higher median age of 72.2 years compared to 70 years in the phase 2 trial, and a higher rate of BCCs localized outside the head and neck area with 24.1 % versus 10 %, respectively.

Intriguingly, in patients who were treated with cemiplimab first-line without prior HHI therapy, we observed an ORR of 62.5 % and a disease control in 87.5 % of patients. In the first-line group, median PFS was also considerably longer with 19.8 months compared to 5.3 months. These results, however, have to be treated with caution: firstly, due to the small cohort of only 8 patients with cemiplimab as first-line treatment, secondly, as several patients in the second-line cohort had failed first-line therapy with HHI, potentially indicating more aggressive disease.

**Table 1**
patient characteristics according to PD1i treatment line. BCC: basal cell carcinoma; laBCC: locally advanced BCC; metBCC: metastasized BCC; PD1i: PD1-inhibition; HHI: hedgehog inhibition; NA: not available; IQR: interquartile range.

| | | | all patients | group A cemiplimab first-line | group B cemiplimab second-line |
|---|---|---|---|---|---|
| patients | | n(%) | 37 (100.0) | 8 (21.6) | 29 (78.4) |
| sex | female | n(%) | 17 (45.9) | 4 (50.0) | 13 (44.8) |
| | male | n(%) | 20 (54.1) | 4 (50.0) | 16 (55.2) |
| BCC stage (EADO classification) | III (laBCC) | n(%) | 33 (89.2) | 7 (87.5) | 26 (89.7) |
| | IV (metBCC) | n(%) | 4 (10.8) | 1 (12.5) | 3 (10.3) |
| BCC primary localisation | face | n(%) | 15 (40.5) | 1 (12.5) | 14 (48.3) |
| | head | n(%) | 2 (5.4) | 0 (0.0) | 2 (6.9) |
| | ear | n(%) | 6 (16.2) | 3 (37.5) | 3 (10.3) |
| | eye | n(%) | 4 (10.8) | 2 (25.0) | 2 (6.9) |
| | body | n(%) | 9 (24.3) | 2 (25.0) | 7 (24.1) |
| | NA | n(%) | 1 (2.7) | 0 (0.0) | 1 (3.4) |
| histological BCC subtype | superficial BCC | n(%) | 2 (5.4) | 0 (0.0) | 2 (6.9) |
| | solid / nodular BCC | n(%) | 11 (29.7) | 5 (50.0) | 7 (24.1) |
| | basosquamous BCC | n(%) | 8 (21.6) | 3 (37.5) | 5 (17.2) |
| | infiltrative BCC | n(%) | 5 (13.5) | 0 (0.0) | 5 (17.2) |
| | sclerosing BCC | n(%) | 3 (8.1) | 0 (0.0) | 3 (10.3) |
| | NA | n(%) | 8 (21.6) | 1 (12.5) | 7 (24.1) |
| treatment sequence | PD1i | n(%) | 8 (21.6) | 8 (100.0) | 0 (0.0) |
| | HHI – PD1i | n(%) | 19 (51.4) | 0 (0.0) | 19 (65.5) |
| | HHI – PD1i – HHI | n(%) | 10 (27.0) | 0 (0.0) | 10 (34.5) |
| age at first treatment initiation | median, years (range) | | 72.2 (43.8–89.0) | 75.5 (61.5–89.0) | 72.2 (43.8–87.7) |
| | IQR | | 63.2–81.1 | 64.5–87.2 | 62.5–79.1 |

Finally, for most patients a reason for choosing PD1i as first-line treatment was not given.

Nonetheless, our data suggest that cemiplimab may yield a better response in first- compared to second-line treatment. Possible explanations for this remain unclear. Although BCC is the tumor with the highest mutational burden [12,13], various studies on PD-L1 expression in BCC tumor samples revealed contradictory findings: PD-L1 expression was positive in 90 % (124 out of 138), 22 % (9 out of 40), 9 % (3 of 34), and 0 % (0 out of 42) of samples, respectively [14–17]. When comparing treatment-naïve BCCs with pretreated BCCs (including pretreatment with HHI among other treatments), PD-L1 expression was more intense in the latter [14]. In various cancer types, including non-small cell lung cancer and bladder cancer, the degree of PD-L1 expression in tumor cells was positively associated with response to PD1i treatment [18]. However, in the pivotal phase 2 trial, PD-L1 expression was not associated with tumor response to cemiplimab [9]. Therefore, predictive markers may be found beyond expression of checkpoint ligands, such as immunosuppressive chemokine expression by cancer associated fibroblasts or tumor growth promoted by proinflammatory Interleukin-6 signaling in the tumor microenvironment [19,20].

In our cohort, 10 patients who experienced progression after both first-line treatment with HHI and second-line treatment with cemiplimab were retreated with HHI. Of these, 20 % (n = 2) responded, whereas 80 % (n = 8) showed no response. In an earlier retrospective multicenter analysis with 12 patients, a similar response rate of 33 % was observed [21]. Therefore, rechallenge with HHI after progression upon cemiplimab may be considered as a treatment option in selected patients.

Limitations of the study include the sole central monitoring of the data being retrieved from a prospective multicenter registry without local monitoring. Another limitation relates to the small cohort size of patients receiving cemiplimab in first line.

Prospective multicenter phase 2 trials are ongoing in Germany (CEMIfirst study by the German Dermatologic Cooperative Oncology Group (DeCOG)) and the United Kingdom (IMPACT trial, chief investigator Dr. Amarnath Challapalli, Bristol, UK) to investigate the efficacy of cemiplimab in advanced BCC in the first-line setting.

## Author contribution

The author Jessica Hassel is an Editor of the EJC and was not involved in the editorial review or the decision to publish this article.

## CRediT authorship contribution statement

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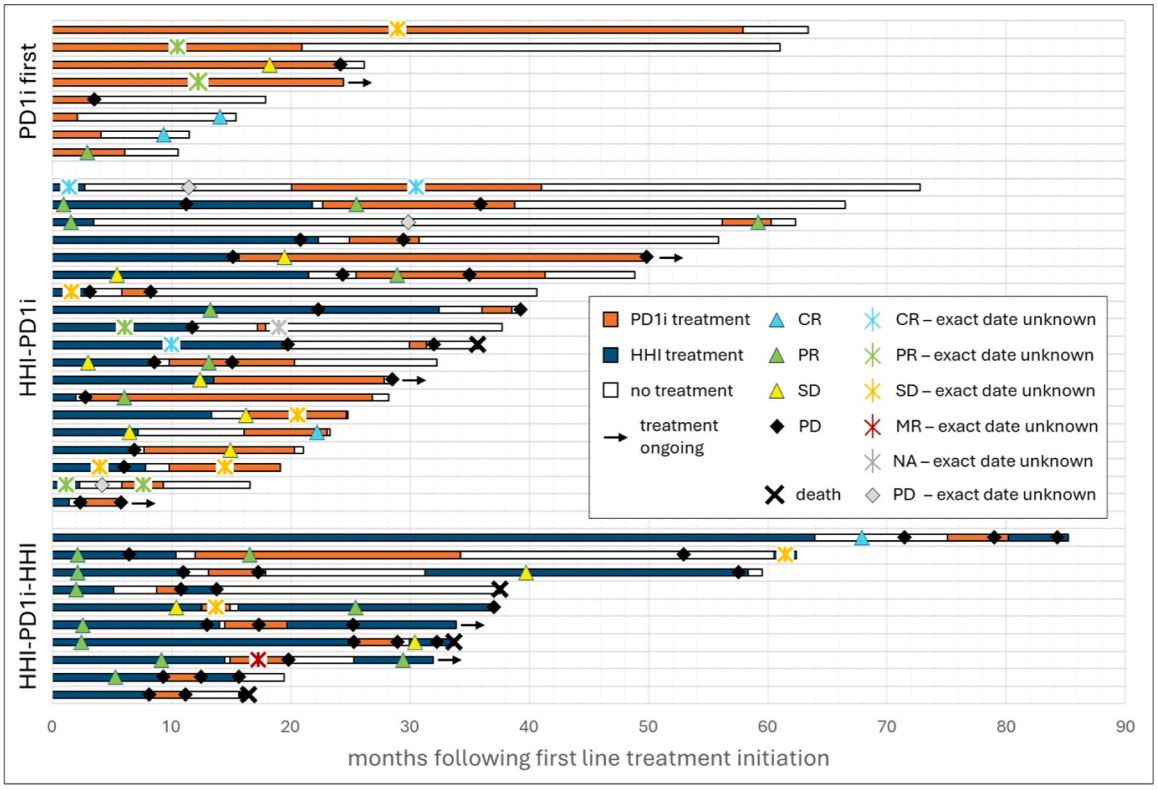


**Fig. 1.** Course of treatment and response across all 37 patients depicted as swimmers plot, separated by treatment group and ordered according to follow-up time.

**Table 2**
Treatment parameters. *includes: planned treatment discontinuation; patient's choice; information not available. PD1i: PD1-inhibition; HHI: hedgehog inhibition; IQR: interquartile range; treatm.: treatment; ORR: overall response rate; R: responder; NR: non-responder; NA: not available; PFS: progression-free survival; DOR: duration of response; CR: complete response; PR: partial response; EOT: end of treatment; progr.: progression; AE: adverse event.

| | | | |
|---|---|---|---|
| n (patients) | | | 37 |
| treatment sequences | group A (cemiplimab 1st line) | n(%) | 8 (10.7) |
| | group B (cemiplimab 2nd line) | n(%) | 29 (78.4) |
| | HHI – PD1i | n(%) | 19 (51.4) |
| | HHI – PD1i – HHI | n(%) | 10 (27.0) |
| response evaluation method | clinical evaluation | n(%) | 32 (86.5) |
| | radiological staging | n(%) | 25 (67.6) |
| | histology | n(%) | 8 (21.6) |
| | more than one method | n(%) | 24 (64.9) |
| follow-up time from first treatment initiation | median, months (range) | | 37.1 (5.8–85.2) |
| | IQR | | 22.3–51.4 |

| treatment parameters – treatment line | | | all | 1st line PD1i | 1st line HHI | 2nd line PD1i | 3rd line HHI |
|---|---|---|---|---|---|---|---|
| treatm. duration | median, months (range) | | 11.5 (1.4–63.9) | 13.5 (2.1–57.9) | 11.5 (1.4–63.9) | 5.1(0.7–34.2) | 4.4 (0.5–27.1) |
| | IQR | | 5.2–20.9 | 4.0–24.3 | 6.8–15.5 | 2.9–12.6 | 3.0–6.4 |
| ORR | R | n(%) | 20 (54.1) | 5 (62.5) | 15 (51.7) | 9 (31.0) | 2 (20.0) |
| | NR | n(%) | 17 (45.9) | 3 (37.5) | 14 (48.3) | 18 (62.1) | 8 (80.0) |
| | NA | n(%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (6.9) | 0 (0.0) |
| PFS | median, months (range) | | 12.9 (2.3–75.1) | 19.8 (3.5–63.4) | 12.5 (2.3–75.1) | 5.3 (2.0–41.1) | 3.8 (0.5–26.4) |
| | IQR | | 8.5–20.8 | 10.8–33.6 | 8.1–19.7 | 3.1–13.3 | 2.5–6.4 |
| DOR | median, months (range) | | 5.0 (0.0–54.7) | 1.6 (0.0–7.8) | 5.6 (0.0–54.7) | 0.0 (0.0–36.5) | 0.2 (0.0–17.9) |
| | IQR | | 0.2–9.0 | 1.4–6.0 | 0.1–9.4 | 0.0–6.2 | 0.0–2.5 |
| | NA | n(%) | 9 (24.3) | 3 (8.1) | 6 (16.2) | 6 (20.0) | 1 (10.0) |
| progr. | yes | n(%) | 21 (56.8) | 2 (25.0) | 19 (65.5) | 19 (65.5) | 8 (80.0) |
| | no | n(%) | 16 (43.2) | 6 (75.0) | 10 (34.0) | 10 (34.5) | 2 (20.0) |
| EOT reason | progr. | n(%) | 22 (59.5) | 3 (37.5) | 19 (65.5) | 14 (48.3) | 4 (40.0) |
| | toxicity | n(%) | 7 (18.9) | 1 (12.5) | 6 (20.7) | 3 (10.3) | 0 (0.0) |
| | other* | n(%) | 7 (18.9) | 3 (37.5) | 4 (13.8) | 8 (27.6) | 4 (40.0) |
| | ongoing | n(%) | 1 (2.7) | 1 (12.5) | 0 (0.0) | 4 (13.8) | 2 (20.0) |
| AE | yes | n(%) | 21 (56.8) | 4 (50.0) | 17 (58.6) | 8 (27.6) | 1 (10.0) |
| | no | n(%) | 14 (37.8) | 4 (50.0) | 10 (34.5) | 21 (72.4) | 8 (80.0) |
| | NA | n(%) | 2 (5.4) | 0 (0.0) | 2 (6.9) | 0 (0.0) | 1 (10.0) |
| AE treatm. related | yes | n(%) | 13 (61.9) | 1 (25.0) | 12 (70.6) | 7 (87.5) | 1 (100.0) |
| | no | n(%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (12.5) | 0 (0.0) |
| | NA | n(%) | 8 (38.1) | 3 (75.0) | 5 (29.4) | 0 (0.0) | 0 (0.0) |

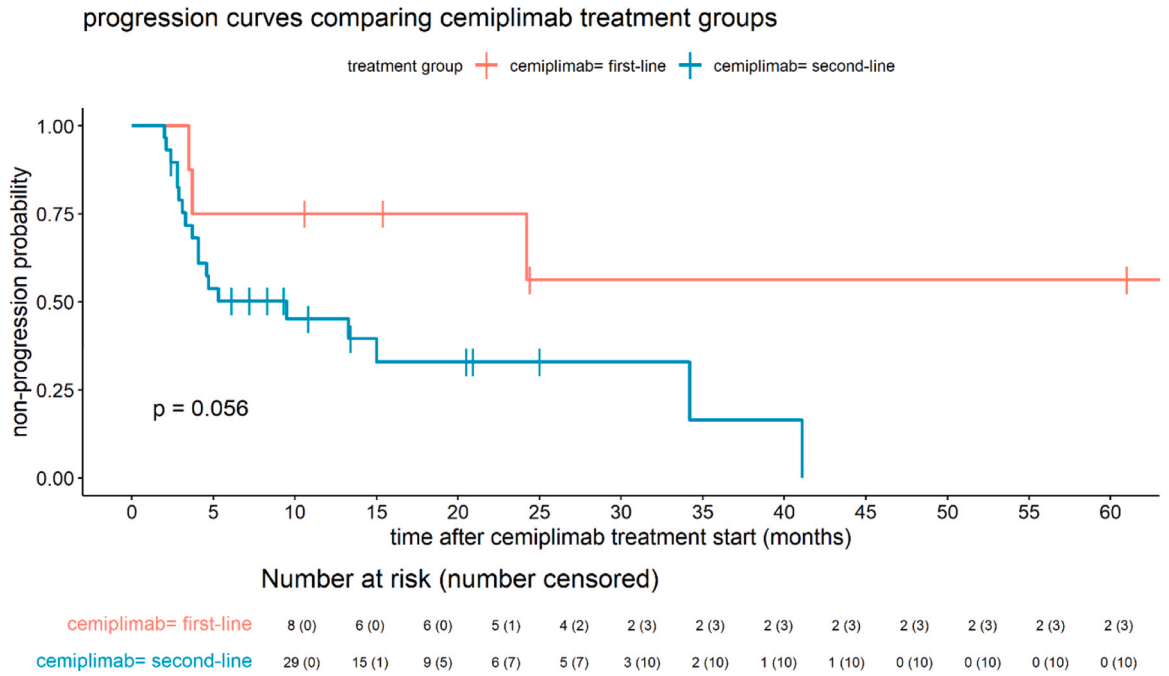


**Fig. 2.** Kaplan-Meier estimates (n = 37) for progression-free survival following cemiplimab treatment initiation. Blue curve represents patients with cemiplimab first-line treatment, red curve with cemiplimab second-line treatment (p = 0.056).

**Table 3**
Overall response rates (ORR). PD1i: PD1-inhibition; HHI: hedgehog inhibition; BR: best response; CR: complete response; PR: partial response; MR: mixed response; SD: stable disease; PD: progressive disease; NA: not available; ORR: overall response rate; R: responder; NR: non-responder.

| treatment lines | | | | 1st line | | 2nd line | 3rd line |
|---|---|---|---|---|---|---|---|
| | | | all | PD1i | HHI | PD1i | HHI |
| BR | CR | n(%) | 5 (13.5) | 2 (25.0) | 3 (10.3) | 2 (6.9) | 0 (0.0) |
| | PR | n(%) | 15 (40.5) | 3 (37.5) | 24 (41.4) | 7 (24.1) | 2 (20.0) |
| | MR | n(%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (3.4) | 0 (0.0) |
| | SD | n(%) | 10 (27.0) | 2 (25.0) | 8 (27.6) | 5 (17.2) | 3 (30.0) |
| | PD | n(%) | 7 (18.9) | 1 (12.5) | 6 (20.7) | 12 (41.4) | 5 (50.0) |
| | NA | n(%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (6.9) | 0 (0.0) |
| ORR | R | n(%) | 20 (55.1) | 5 (62.5) | 15 (51.7) | 9 (31.0) | 2 (20.0) |
| | NR | n(%) | 17 (45.9) | 3 (37.5) | 14 (48.3) | 18 (61.1) | 8 (80.0) |
| | NA | n(%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (6.9) | 0 (0.0) |

**Table 4**
Treatment-related adverse events (AE) documented under PD1i treatment.

| First-line PD1i treatment | | |
|---|---|---|
| AE | CTCAE grade | frequency |
| pruritus | 1 | 2 |
| arthralgia | 1 | 1 |
| hyperthyroidism | 1 | 1 |
| colitis | 1 | 1 |
| bullous dermatitis | 2 | 1 |
| pneumonitis | 2 | 1 |
| **Second-line PD1i treatment** | | |
| AE | CTCAE grade | frequency |
| pain | 1/2 | 2/1 |
| skin and subcutaneous tissue disorders | 1 | 3 |
| fatigue | 1 | 1 |
| general disorders | 1 | 1 |
| hoarseness | 1 | 1 |
| hyperthyroidism | 1 | 1 |
| hypokalemia | 1 | 1 |
| oral dysesthesia | 1 | 1 |
| respiratory, thoracic and mediastinal disorders | 1 | 1 |
| autoimmun-thyreoiditis | 2 | 1 |
| muscle weakness | 2 | 1 |
| hypotension | 3 | 1 |
| neoplasms benign, malignant and unspecified | 3 | 1 |
| radiculitis | 3 | 1 |

Conceptualization. **Martin Kaatz:** Writing – review & editing.

## Ethics statement

The patients in this manuscript have given written informed consent for participation in the ADOREG and to publication of their case details.

## Ethical approval

The ADOREG was approved by the Medical Ethics Committee of the University Duisburg-Essen (14–5921-BO).

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## Declaration of Competing Interest

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115590.

## Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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