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Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC)

Alexander M Menzies, Rodabe N Amaria, Elisa A Rozeman, Alexander C Huang, Michael T Tetzlaff, Bart A van de Wiel, Serigne Lo, Ahmad A Tarhini, Elizabeth M Burton, Thomas E Pennington, Robyn P M Saw, Xiaowei Xu, Giorgos C Karakousis, Paolo A Ascierto, Andrew J Spillane, Alexander C J van Akkooi, Michael A Davies, Tara C Mitchell, Hussein A Tawbi, Richard A Scolyer, Jennifer A Wargo, Christian U Blank, Georgina V Long

*From the **Nature Medicine.** February 2021.*

Abstract

The association among pathological response, recurrence-free survival (RFS) and overall survival (OS) with neoadjuvant therapy in melanoma remains unclear. In this study, we pooled data from six clinical trials of anti-PD-1-based immunotherapy or BRAF/MEK targeted therapy. In total, 192 patients were included; 141 received immunotherapy (104, combination of ipilimumab and nivolumab; 37, anti-PD-1 monotherapy), and 51 received targeted therapy. A pathological complete response (pCR) occurred in 40% of patients: 47% with targeted therapy and 33% with immunotherapy (43% combination and 20% monotherapy). pCR correlated with improved RFS (pCR 2-year 89% versus no pCR 50%, $P < 0.001$) and OS (pCR 2-year OS 95% versus no pCR 83%, $P = 0.027$). In patients with pCR, near pCR or partial pathological response with immunotherapy, very few relapses were seen (2-year RFS 96%), and, at this writing, no patient has died from melanoma, whereas, even with pCR from targeted therapy, the 2-year RFS

was only 79%, and OS was only 91%. Pathological response should be an early surrogate endpoint for clinical trials and a new benchmark for development and approval in melanoma.

Summary statements
The article presents prospective data on 192 patients with clinical stage III melanoma, with nodal involvement, collected from 6 clinical trials on neoadjuvant anti-PD-1-based immunotherapy or BRAF/MEK targeted therapy. Recurrence-free and overall survival rates were significantly better in patients who had complete or partial pathological response to neoadjuvant immunotherapy compared to no response.
Pathological response to neoadjuvant therapy (especially immunotherapy) is predictive of excellent survival outcomes and should be considered as a new approach in patients with loco-regionally advanced melanoma.

Strengths:
- Summary of 6 prospective clinical trials looking at a patient population in which the benefit of neoadjuvant treatment is undetermined. This pooled analysis sheds light on the potential role of neoadjuvant therapy in melanoma.
- Evaluation of pathological response in these surgical patients provides an opportunity to correlate response with survival outcomes as well as understand the biology and search for predictive biomarkers.

Weaknesses:
- Patients with in-transit metastases were excluded from the studies. This population might potentially benefit form neoadjuvant therapy.
- There is heterogeneity among the trials in terms of different neoadjuvant and adjuvant treatment regimens.

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Outcomes of Cutaneous Squamous Cell Carcinoma in the Head and Neck Region with Regional Lymph Node Metastasis: A Systematic Review and Meta-analysis

Axel Sahovaler, Rohin J Krishnan, David H Yeh, Qi Zhou, David Palma, Kevin Fung, John Yoo, Anthony Nichols, S Danielle MacNeil

*From the **Meta-Analysis JAMA Otolaryngology Head Neck Surg.** April 2019.*

Importance: There is a need to summarize the available evidence and provide quantitative data of the most important prognostic factors for patients with metastatic cutaneous squamous cell carcinoma of the head and neck region with regional lymph node metastasis (McSCCHN).

Objective: To undertake a PRISMA-compliant systematic review and meta-analysis of all published studies on the risk factors for overall survival (OS), locoregional control (LRC), locoregional recurrence (LRR), and disease-specific survival (DSS) for patients with McSCCHN.

Data sources: PubMed, CINAHL, and Embase were searched from 1946 to August 2018 for English-language articles.

Study selection: Inclusion criteria were randomized clinical trials or observational studies reporting on at least 10 patients with McSCCHN; studies analyzing 1 defined risk factor; reporting OS, LRC, LRR, or DSS; and clinical follow-up of 1 year of more. For the final analysis we included risk factors that were analyzed for the same outcome in at least 3 studies. Of the 2923 articles screened, 21 articles met the inclusion criteria.

Data extraction and synthesis: PRISMA guidelines were used for abstracting the data. Two reviewers independently abstracted the data. Risk of bias was estimated with the Newcastle-Ottawa Scale. Meta-analysis was performed using the random-effects model. All analysis took place between January and October 2018.

Main outcomes and measures: The primary end point was OS. Secondary end points included LRC, LRR, and DSS.

Results: A total of 20 observational studies and 1 randomized clinical trial were identified, representing 3534 patients (some reviewed articles reported no demographic characteristics), and were included in the analysis. Significant risk factors associated with OS were immunosuppression (hazard ratio [HR] of death, 2.66; 95% CI, 2.26-3.13), extracapsular spread (HR, 1.90; 95% CI, 1.12-3.23), adjuvant radiotherapy (HR, 0.45; 95% CI, 0.27-0.78), lymph node ratio (HR, 1.91; 95% CI, 1.09-3.35), and advanced age (HR, 1.03; 95% CI, 1.00-1.07). Immunosuppression (HR, 3.82; 95% CI, 2.47-5.92) and adjuvant radiotherapy (HR, 0.52; 95% CI, 0.33-0.84) were also significant risk factors for DSS.

Conclusions and relevance: Immunosuppressed patients and those with extracapsular extension have poor prognosis. Adjuvant radiotherapy is associated with an improvement in OS. These risk factors will assist with better risk stratification and may also help to inform future clinical trials.

Conflict of interest statement

Conflict of Interest Disclosures: None reported.

Summary statements

- This is a well-designed systematic review and meta-analysis including 3534 patients from 21 articles that met the inclusion criteria by linking the risk factors with the outcome of cutaneous squamous cell carcinoma of the head and neck metastatic to the cervical lymph nodes.
- Immunosuppression, adjuvant radiotherapy and extranodal extension were significantly associated with the overall survival.
- Immunosuppression and adjuvant radiotherapy were significantly associated with disease specific survival.
- Recommendations for future research include:
    - Effect of anti-epidermal growth factor agents and immunotherapies on this patient population.

- Analysis and study of different nodal stages as a risk factor.
- More in-depth studies on the perineural invasion and its effect on the outcome as this study failed to establish association between them despite being evident in the NCCN guidelines.
- Future reliable research should be structured with:
  - Specification of the nature of immunosuppression.
  - Consistent risk factor reporting.
  - Well-defined survival outcome.
  - Adjusted cox proportional outcomes analyses.

Strengths:

- This systematic review and meta-analysis included 21 reports (3534 patients) with their study design being limited only to RCT and observational studies, including at least 10 patients, at least one defined risk factor and an outcome of interest.
- The literature was searched for publications between 1946 and 2018.
- In their literature search, the authors included gray literature and conference abstracts.
- The Newcastle-Ottawa scale was used to assess the quality of the studies. A score of at least 6 was indicated for inclusion. Articles with score less than 6 were subjected to combined reviewer evaluation.
- The authors strictly followed the PRISMA guidelines.
- Studies with overlapping cohort were excluded. Instead, studies with larger patient population were included.

Weaknesses:

- Despite including 21 reports, this systematic review included 20 observational studies and only one RCT.
- The inherent risk of bias in the retrospective non-randomized studies is high. For this the effect of adjuvant radiotherapy may be biased by selecting patients with less comorbidities and better prognosis.
- Age heterogeneity among the included studies was 81% and this affected the clinical significance of a statistically significant association between age and overall survival.
- Confounding factors adjustment was lacking in many of the included articles.
- There was significant heterogeneity in the risk factor reporting and outcome measurement analysis among the included studies.
- The heterogeneity of the included studies also reached the inhomogeneous definition of the nature of immunosuppression.

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Association of Immunosuppression with Outcomes of Patients with Cutaneous Squamous Cell Carcinoma of the Head and Neck

Samantha Tam, Christopher M K L Yao, Moran Amit, Mona Gajera, Xiaoning Luo, Rachel Treistman, Anshu Khanna, Mohamed Aashiq, Priyadharsini Nagarajan, Diana Bell, Adel El-Naggar, Michael Migden, Michael Wong, Bonnie Glisson, Renata Ferrarotto, Bita Esmaeli, David Rosenthal, Guojun Li, Randal S Weber, Jeffrey N Myers, Neil D Gross

*From the **JAMA Otolaryngology Head Neck Surg.** February 2020.*

Importance: Patients with immunosuppression have a higher incidence of cutaneous squamous cell carcinoma (cSCC) and often present with more aggressive, multifocal disease.

Objectives: To determine the risks for mortality in patients with cSCC and immunosuppression compared with no immunosuppression and to compare the difference in mortality risk based on the cause of immunocompromise.

Design, setting, and participants: This retrospective cohort study of patients with cSCC of the head and neck recruited participants from a tertiary cancer care center. Patients who underwent no treatment, wide local excision, or biopsy of the lesions were eligible for inclusion from January 1, 1995, to September 30, 2015. Data were analyzed from March 21, 2018, to April 4, 2019.

Exposures: Immunocompromise, defined as having solid organ transplant, stem cell transplant, hematopoietic malignant disease, autoimmune disease requiring treatment with immunosuppressive therapy, type 1 or 2 diabetes treated with insulin, HIV or AIDS, or other hematoproliferative disorder.

Main outcomes and measures: Patients were divided into 2 groups according to their immune status (immunosuppression vs no immunosuppression). The primary outcome measure was disease-specific survival. A Cox proportional hazards regression model was used to determine the association of immune status with disease outcome.

Results: A total of 796 patients (680 men [85.4%]; median age, 69 [range, 27-98] years), including 147 with and 649 without immunosuppression (IS and non-IS groups, respectively), constituted the final cohort. In the IS group, 77 (52.4%) had diabetes, 39 (26.5%) had lymphoma or leukemia, 25 (17.0%) had an organ or stem cell transplant, and 3 (2.0%) had HIV. Five-year disease-specific survival was 68.2% in the IS group compared with 84.1% in the non-IS group (difference, 15.9%; 95% CI, 3.5%-27.4%). Immunosuppression was independently associated with worse disease-specific survival (hazard ratio, 2.32; 95% CI, 1.53-3.50).

Conclusions and relevance: This study's findings suggest that immunosuppression is independently associated with a worse outcome in cSCC, with a 2.32 times increased risk of disease-specific death after adjusting for age, history of skin cancer, recurrent or persistent disease status, disease stage, and treatment.

Conflict of interest statement:

Conflict of Interest Disclosures: Dr Migden reported receiving personal fees from Regeneron Pharmaceuticals, Inc, outside the submitted work. Dr Wong reported receiving personal fees from Regeneron Pharmaceuticals, Inc, EMD-Serono, Pfizer, Inc, and Merck & Co outside the submitted work. Dr Ferrarotto reported receiving advisory board and consulting fees from Ayala Pharmaceuticals, consulting fees from Medscape and Cellestia Biotech AG, and serving on the advisory board of Sanofi-Regeneron. Dr Rosenthal reported receiving personal fees from Merck & Co outside the submitted work. Dr Gross reported receiving research support from Regeneron Pharmaceuticals, Inc, outside the submitted work and serving on the advisory board of Sanofi-Regeneron. No other disclosures were reported.

Summary statements

- This is a retrospective cohort study conducted at a tertiary care center including 796 patients with cutaneous squamous cell carcinoma of the head and neck (cSCCHN). Patients were divided into two groups according to their immune status (immunosuppressed "IS" versus non-immunosuppressed "non-IS").
- The study aimed at evaluating the survival after treatment of SCCHN between both groups. IS group included 147 patients versus non-immunosuppressed group including 649 patients.
- IS group had significantly lower overall survival (OS) at 3, 5 and 10 years and lower disease-specific survival (DSS) at 3, 5 and 10 years compared to non-IS group. IS was independently associated with outcome in this cohort with a 2.32-fold increased risk of disease specific death, after adjusting for other co-variants.
- Subgroup analysis showed that HIV/AIDS subgroup had worst prognosis in IS group. However, no meaningful difference was found between cause of IS and the OS or DSS.
- Directions for future research:
    - Research establishing safety and efficacy of targeted therapy and immune-modulating therapies in IS group and focus on the risk of graft rejection with their use.
    - The use of epidermal growth factor receptor inhibitors in high-risk populations.
    - The value of incorporating IS into staging system of cSCCHN.
    - The establishment of standardized reporting system for the immunosuppression status in cSCCHN.

Strengths:

- Large cohort including 796 patients included in the study. The IS cohort was satisfactory for subgroup analysis including 147 patients. This also allowed for inclusion of multiple causes of IS in this group.
- The study was conducted over a long period (1995 – 2015) with excellent follow up duration (10 years).

Weaknesses:

- Heterogeneity of the patients' age (range: 27 – 98).
- Non-IS group (649) is significantly larger than IS group (147).
- Heterogeneity in the IS groups.
- Retrospective nature of the study with inherent drawbacks in documentation and data retrieval.
- The authors included the development of a second primary with the patterns of failure.

Soft Tissue Metastases in Head and Neck Cutaneous Squamous Cell Carcinoma

Craig P Mooney, Kan Gao, Jonathan R Clark, Ruta Gupta, Kerwin Shannon, Carsten E Palme, Ardalan Ebrahimi, Sydney Ch'ng, Tsu-Hui Hubert Low

*From the **Laryngoscope.** April 2021.*

Objective: Soft tissue metastases (STM) in head and neck cutaneous squamous cell carcinoma (HNcSCC) are non-nodal based metastases to the parotid and cervical soft tissues of the head and neck. This is a unique subgroup of regional metastases amongst patients with cSCC and have been shown to be associated with poor prognosis. Detailed studies of this subgroup are lacking in the literature. A retrospective cohort analysis was performed to characterize the prognostic significance of STM in HNcSCC based on individual clinicopathological features.

Methods: Patients with HNcSCC with STM were identified from the Sydney Head and Neck Cancer Institute database. Clinicopathological characteristics were extracted from the histopathological reports. Recurrence and follow-up data were analyzed to determine disease-free and overall survival using the Kaplan-Meier method and Cox proportional hazards models.

Results: After excluding all patients with lymph node metastasis with no STM, there were 200 patients identified (161 parotid, 32 cervical, and seven with concurrent parotid and cervical STM) with a 5-year overall survival of 36%. In univariable analysis, age of patients, size of the deposits, location of the deposits, and patients that were not offered adjuvant radiotherapy have worse overall survival. However, on multivariable analysis, age, and the number of STM deposits were independent factors that predict for worse survival.

Conclusion: The presence of STM in patients with HNcSCC is associated with poor prognosis. Increasing number of STM deposits, as well as involved margin of the regional excision, negatively impacted on the overall prognosis.

Level of evidence: Level III - retrospective cohort study. Laryngoscope, 131: E1209-E1213, 2021.

Keywords: Cutaneous squamous cell carcinoma; head and neck cancer; metastasis; soft tissue metastasis; survival.

Summary Statements

- 200 patients with head and neck cutaneous squamous cell carcinoma (HNcSCC) with soft tissue metastasis (STM) were identified. Note that STM was defined as non-nodal based metastases to the parotid and cervical soft tissues.
- To further elaborate, included were tumor deposits within the soft tissue, not in continuity with the primary lesion or within the scar and no evidence of associated lymphoid tissue on final pathological analysis.
- On multivariate analysis for disease free survival (DFS), age (p=0.002) and the number of STM deposits (p=0.004) were the factors that predicted for worse survival.

- On overall survival (OS), age (p<0.002), number of STM (p=0.003) and involved margins (p=0.048) were the factors that predicted for worse survival.

Strengths:

- Data is from a geographic center known for its high prevalence of cutaneous squamous cell carcinoma (Sydney Head and Neck Cancer Institute – SHNCI).
- Significant number of patients (n = 200) collected over a long period of time (1989 – 2017), that demonstrates poor survival in patients with STM, with the 5-year DFS being 32% and the OS 36%
- Further survival analysis was performed based on size (with a cutoff <30mm or > 30mm) and multiplicity, the former to establish some consistency with the AJCC nodal staging system. As expected, multiple deposits >30mm were associated with worse DFS and OS (p < 0.001).

Weaknesses:

- Definition of STM is still evolving and to echo the author's words it is uncertain whether they "represent truly extra-nodal deposits of tumor or nodal deposits with complete effacement of the lymphoid architecture".
- Finally, while a very minor weakness, data such as this would be further strengthened if it was multi-institutional.

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Cemiplimab In Locally Advanced Cutaneous Squamous Cell Carcinoma: Results from An Open-Label, Phase 2, Single-Arm Trial

Michael R Migden, Nikhil I Khushalani, Anne Lynn S Chang, Karl D Lewis, Chrysalyne D Schmults, Leonel Hernandez-Aya, Friedegund Meier, Dirk Schadendorf, Alexander Guminski, Axel Hauschild, Deborah J Wong, Gregory A Daniels, Carola Berking, Vladimir Jankovic, Elizabeth Stankevich, Jocelyn Booth, Siyu Li, David M Weinreich, George D Yancopoulos, Israel Lowy, Matthew G Fury, Danny Rischin

*From the **Clinical Trial Lancet Oncology.** February 2020.*

Background: Cemiplimab has shown substantial antitumour activity in patients with metastatic cutaneous squamous cell carcinoma. Patients with locally advanced cutaneous squamous cell carcinoma have poor prognosis with conventional systemic therapy. We present a primary analysis of the safety and antitumour activity of cemiplimab in patients with locally advanced cutaneous squamous cell carcinoma.

Methods: This pivotal open-label, phase 2, single-arm trial was done across 25 outpatient clinics, primarily at academic medical centres, in Australia, Germany, and the USA. Eligible patients (aged ≥18 years with histologically confirmed locally advanced cutaneous squamous cell carcinoma and an Eastern Cooperative Oncology Group performance status of 0-1) received cemiplimab 3 mg/kg intravenously over 30 min every 2 weeks for up to 96 weeks. Tumor

measurements were done every 8 weeks. The primary endpoint was objective response, defined as the proportion of patients with complete or partial response, according to independent central review as per Response Evaluation Criteria in Solid Tumors version 1.1 for radiological scans and WHO criteria for medical photography. Data cutoff was Oct 10, 2018, when the fully enrolled cohort reached the prespecified timepoint for the primary analysis. Analyses were done as per the intention-to-treat principle. The safety analysis comprised all patients who received at least one dose of cemiplimab. This study is registered with ClinicalTrials.gov, number NCT02760498.

Findings: Between June 14, 2016, and April 25, 2018, 78 patients were enrolled and treated with cemiplimab. The median duration of study follow-up was 9·3 months (IQR 5·1-15·7) at the time of data cutoff. An objective response was observed in 34 (44%; 95% CI 32-55) of 78 patients. The best overall response was ten (13%) patients with a complete response and 24 (31%) with a partial response. Grade 3-4 treatment-emergent adverse events occurred in 34 (44%) of 78 patients; the most common were hypertension in six (8%) patients and pneumonia in four (5%). Serious treatment-emergent adverse events occurred in 23 (29%) of 78 patients. One treatment-related death was reported that occurred after onset of aspiration pneumonia.

Interpretation: Cemiplimab showed antitumour activity and an acceptable safety profile in patients with locally advanced cutaneous squamous cell carcinoma for whom there was no widely accepted standard of care.

Funding: Regeneron Pharmaceuticals and Sanofi.

Summary Statements:
Migden's Phase 2 clinical trial involving 78 patients with locally advanced cutaneous squamous cell carcinoma (SCC) treated with cemiplimab (3 mg/kg intravenously) showed a complete clinical response in ten (13%) patients and partial response in 24 (31%); overall objective clinical responses were observed in 34 (44%). Responses were durable for the duration of the trial and up to 24 months, and not subject to other therapies (surgery or radiation). Toxicities included hypertension and pneumonia.

Strengths:

- This trial provides strong evidence for using a novel treatment approach for select cutaneous SCCs.

Weaknesses:

- Patients with autoimmune or lymphoproliferative disorders, or history of solid organ transplantation were not eligible. Testing therapies in populations susceptible to aggressive cutaneous SCCs is needed.
- No pathologic data to assess pathologic response
- Short duration of follow up-a median 9 month follow up only.

[1]Migden, M. R., Khushalani, N. I., Chang, A. L. S., Lewis, K. D., Schmults, C. D., Hernandez-Aya, L., ... Rischin, D. (2020). Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results

from an open-label, phase 2, single-arm trial. *The Lancet Oncology*, *21*(2), 294–305. doi:10.1016/s1470-2045(19)30728-4

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