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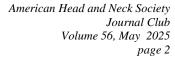## Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma

Christian U Blank, Minke W Lucas, Richard A Scolyer, Bart A van de Wiel, Alexander M Menzies, Marta Lopez-Yurda, Lotte L Hoeijmakers, Robyn P M Saw, Judith M Lijnsvelt, Nigel G Maher, Saskia M Pulleman, Maria Gonzalez, Alejandro Torres Acosta, Winan J van Houdt, Serigne N Lo, Anke M J Kuijpers, Andrew Spillane, W Martin C Klop, Thomas E Pennington, Charlotte L Zuur, Kerwin F Shannon, Beatrijs A Seinstra, Robert V Rawson, John B A G Haanen, Sydney Ch'ng, Kishan A T Naipal, Jonathan Stretch, Johannes V van Thienen, Michael A Rtshiladze, Sofie Wilgenhof, Rony Kapoor, Aafke Meerveld-Eggink, Lindsay G Grijpink-Ongering, Alexander C J van Akkooi, Irene L M Reijers, David E Gyorki, Dirk J Grünhagen, Frank M Speetjens, Sonja B Vliek, Joanna Placzke, Lavinia Spain, Robert C Stassen, Mona Amini-Adle, Céleste Lebbé, Mark B Faries, Caroline Robert, Paolo A Ascierto, Rozemarijn van Rijn, Franchette W P J van den Berkmortel, Djura Piersma, Andre van der Westhuizen, Gerard Vreugdenhil, Maureen J B Aarts, Marion A M Stevense-den Boer, Victoria Atkinson, Muhammad Khattak, Miles C Andrews, Alfons J M van den Eertwegh, Marye J Boers-Sonderen, Geke A P Hospers, Matteo S Carlino, Jan-Willem B de Groot, Ellen Kapiteijn, Karijn P M Suijkerbuijk, Piotr Rutkowski, Shahneen Sandhu, Astrid A M van der Veldt, Georgina V Long

Abstract

BACKGROUND: In phase 1–2 trials in patients with resectable, macroscopic stage III melanoma, neoadjuvant immunotherapy was more efficacious than adjuvant immunotherapy.

METHODS: In this phase 3 trial, we randomly assigned patients with resectable, macroscopic stage III melanoma to two cycles of neoadjuvant ipilimumab plus nivolumab followed by surgery or surgery followed by 12 cycles of adjuvant nivolumab. Only patients in the neoadjuvant group with a partial response or nonresponse received adjuvant treatment. The primary end point was event-free survival.

RESULTS: A total of 423 patients underwent randomization. At a median follow-up of 9.9 months, the estimated 12-month event-free survival was 83.7% (99.9% confidence interval [CI], 73.8 to 94.8) in the neoadjuvant group and 57.2% (99.9% CI, 45.1 to 72.7) in the adjuvant group. The difference in restricted mean survival time was 8.00 months (99.9% CI, 4.94 to 11.05; $P<0.001$; hazard ratio for progression, recurrence, or death, 0.32; 99.9% CI, 0.15 to 0.66). In the neoadjuvant group, 59.0% of patients had a major pathological response, 8.0% had a partial response, 26.4% had a nonresponse (>50% residual viable tumor), and 2.4% had progression; in 4.2%, surgery had not yet been performed or was omitted. The estimated 12-month recurrence-free survival was 95.1% in patients in the neoadjuvant group who had a major pathological response, 76.1% among those with a partial response, and 57.0% among those with a nonresponse. Adverse events of grade 3 or higher that were related to systemic treatment occurred in 29.7% of patients in the neoadjuvant group and in 14.7% in the adjuvant group.

CONCLUSIONS: Among patients with resectable, macroscopic stage III melanoma, neoadjuvant ipilimumab plus nivolumab followed by surgery and response-driven adjuvant therapy resulted in longer event-free survival than surgery followed by adjuvant nivolumab. (Funded by Bristol Myers Squibb and others; NADINA ClinicalTrials.gov number, NCT04949113.)
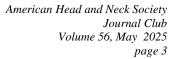
Summary statements
- This Phase III trial provides level 1 evidence supporting a neoadjuvant approach using nivolumab and ipilimumab before surgery compared to adjuvant nivolumab given after surgery.
- This study also supports an approach adapting adjuvant therapy after neoadjuvant therapy based on pathologic response rates and melanoma BRAF mutation status.
- The primary endpoint of this study was event free survival (EFS). Overall and melanoma specific survival data remain to be studied and reported.

Strengths
- The NADINA trial provides supportive evidence for an approach that changes the standard of care for stage III melanoma.
- Among patients who did not receive a major response to neodadjuvant treatment, those with activating BRAF mutations received adjuvant dabrafenib/trametinib, while patients with BRAF wildtype tumors received adjuvant nivolumab. This could have confounded the overall difference in EFS observed in the two study treatment arms, however the investigators demonstrate that the improvement in EFS was observed in both the BRAF mutant and BRAF wildtype subgroups.

Weaknesses
- The primary endpoint is EFS, and follow up in the study is relatively short. Long term follow up is necessary to determine if improvements in EFS translates into improved long term melanoma specific and long term survival.
- Selection of ipilimumab + nivolumab for neoadjuvant treatment was associated with higher grade III or higher adverse events. A treatment arm in this study comparing neoadjuvant single agent PD-1 inhibition would have helped to determine if such an approach reduced AEs with similar/acceptable improvements in EFS.

The Prognostic Value and Clinical Utility of the 40-Gene Expression Profile (40-GEP) Test in Cutaneous Squamous Cell Carcinoma: Systematic Review and Meta-Analysis

Razan Masarwy, Shahaf Shilo, Narin Nard Carmel Neiderman, Liyona Kampel, Gilad Horowitz, Nidal Muhanna, Jobran Mansour

Abstract

Background: The current tumor staging systems for cutaneous squamous cell carcinoma (cSCC) are considered inadequate and insufficient for evaluating the risk of metastasis and for identifying patients at high risk of cSCC. This meta-analysis aimed to assess the prognostic significance of a 40-gene expression profile (40-GEP) both independently and integrated with clinicopathologic risk factors and established staging systems (American Joint Committee on Cancer, eighth edition (AJCC8) and Brigham and Women's Hospital (BWH)).

Methods: Electronic databases, including PubMed (MEDLINE), Embase, the Cochrane Library, and Google Scholar, were systematically searched to identify cohort studies and randomized controlled trials on evaluations of the prediction value of 40-GEP in cSCC patients up to January 2023. The metastatic risk analysis of a given 40-GEP class combined with tumor stage and/or other clinicopathologic risk factors was based upon log hazard ratios (HRs) and their standard error (SE). Heterogeneity and subgroup analyses were performed, and data quality was assessed.

Results: A total of 1019 patients from three cohort studies were included in this meta-analysis. The overall three-year metastatic-free survival rates were 92.4%, 78.9%, and 45.4% for class 1 (low risk), class 2A (Intermediate risk), and class 2B (high risk) 40-GEP, respectively, indicating a significant variation in survival rates between the risk classification groups. The pooled positive predictive value was significantly higher in class 2B when compared to AJCC8 or BWH. The subgroup analyses demonstrated significant superiority of integrating 40-GEP with clinicopathologic risk factors or AJCC8/BWH, especially for class 2B patients.

Conclusions: The integration of 40-GEP with staging systems can improve the identification of cSCC patients at high risk of metastasis, potentially leading to improved care and outcomes, especially in the high-risk class 2B group.

Summary statements

- Meta-analysis of 1,019 cSCC patients across three independent cohorts.
- 3-year Metastasis-free survival was 92.4% for class 1, 78.9% for class 2A, and 45.4% for class 2B.
- Combined 40-GEP class 2B with AJCC8 or BWH yielded a more than three-fold improvement in the prediction of metastasis when compared with AJCC8 (HR of 9.98 vs. 2.61) or
- BWH alone (HR of 8.62 vs. 2.18).
- Class 2B was associated with increased HR for metastasis compared to clinicopathologic risk factors, such as perineural invasion, HR 11.61 vs 3.28, respectively.
- Integration of 40-GEP with clinical staging improved prognostic accuracy, supporting its use in refining risk-adapted management strategies for high-risk cSCC patients.

Strengths
- Large Sample Size: The meta-analysis included over 1,000 patients from three independent cohorts, enhancing the statistical power and robustness of the findings.
- Validation Across Diverse Populations: The consistent performance of the 40-GEP across heterogeneous patient populations and varying clinical settings (different studies and patient populations) supports its external validity and real-world applicability.
- Clinical Integration Potential: The study showed that combining 40-GEP with traditional clinicopathologic factors improved metastasis prediction, supporting a practical model for real-world risk stratification rather than relying on molecular testing alone.

Weaknesses
- Retrospective Design: All three cohorts included in the meta-analysis were retrospective, which introduces potential biases related to patient selection, missing data, or variability in clinical staging and management across institutions.
- Heterogeneity in Staging and Risk Factor Documentation: Inconsistencies in recording clinicopathologic risk factors across studies may have influenced the comparative performance of the 40-GEP test.
- Limited Follow-Up Duration: The median follow-up of 2-3 years is relatively short, potentially underestimating late metastatic events and limiting the evaluation of long-term prognostic accuracy.

Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): a randomised, phase 2b study
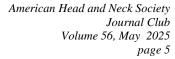
Jeffrey S Weber, Matteo S Carlino, Adnan Khattak, Tarek Meniawy, George Ansstas, Matthew H Taylor, Kevin B Kim, Meredith McKean, Georgina V Long, Ryan J Sullivan, Mark Faries, Thuy T Tran, C Lance Cowey, Andrew Pecora, Montaser Shaheen, Jennifer Segar, Theresa Medina, Victoria Atkinson, Geoffrey T Gibney, Jason J Luke, Sajeve Thomas, Elizabeth I Buchbinder, Jane A Healy, Mo Huang, Manju Morrissey, Igor Feldman, Vasudha Sehgal, Celine Robert-Tissot, Peijie Hou, Lili Zhu, Michelle Brown, Praveen Aanur, Robert S Meehan, Tal Zaks

Abstract

Background: Checkpoint inhibitors are standard adjuvant treatment for stage IIB-IV resected melanoma, but many patients recur. Our study aimed to evaluate whether mRNA-4157 (V940), a novel mRNA-based individualised neoantigen therapy, combined with pembrolizumab, improved recurrence-free survival and distant metastasis-free survival versus pembrolizumab monotherapy in resected high-risk melanoma.

Methods: We did an open-label, randomised, phase 2b, adjuvant study of mRNA-4157 plus pembrolizumab versus pembrolizumab monotherapy in patients, enrolled from sites in the USA and Australia, with completely resected high-risk cutaneous melanoma. Patients with completely resected melanoma (stage IIIB-IV) were assigned 2:1 to receive open-label mRNA-4157 plus pembrolizumab or pembrolizumab monotherapy. mRNA-4157 was administered intramuscularly (maximum nine doses) and pembrolizumab intravenously (maximum 18 doses) in 3-week cycles. The primary endpoint was

recurrence-free survival in the intention-to-treat population. This ongoing trial is registered at ClinicalTrials.gov, NCT03897881.

Findings: From July 18, 2019, to Sept 30, 2021, 157 patients were assigned to mRNA-4157 plus pembrolizumab combination therapy (n=107) or pembrolizumab monotherapy (n=50); median follow-up was 23 months and 24 months, respectively. Recurrence-free survival was longer with combination versus monotherapy (hazard ratio [HR] for recurrence or death, 0·561 [95% CI 0·309-1·017]; two-sided p=0·053), with lower recurrence or death event rate (24 [22%] of 107 vs 20 [40%] of 50); 18-month recurrence-free survival was 79% (95% CI 69·0-85·6) versus 62% (46·9-74·3). Most treatment-related adverse events were grade 1-2. Grade ≥3 treatment-related adverse events occurred in 25% of patients in the combination group and 18% of patients in the monotherapy group, with no mRNA-4157-related grade 4-5 events. Immune-mediated adverse event frequency was similar for the combination (37 [36%]) and monotherapy (18 [36%]) groups.

Interpretation: Adjuvant mRNA-4157 plus pembrolizumab prolonged recurrence-free survival versus pembrolizumab monotherapy in patients with resected high-risk melanoma and showed a manageable safety profile. These results provide evidence that an mRNA-based individualised neoantigen therapy might be beneficial in the adjuvant setting.

Summary statements
- This precision oncology strategy is based on genomic sequencing of the tumor and identification of cancer-specific neoantigens which are then being overexpressed by the host using mRNA-4157 injected to the patient to invoke immune response.
- The mRNA-based individualized neoantigen therapy combined with anti PD-1 antibodies improved recurrence-free survival and distant metastasis-free survival in patients with resected high-risk cutaneous melanoma.
- This combination therapy has been shown to be superior to anti PD-1 antibodies alone in an adjuvant treatment setting.

Strengths
- Randomized phase 2b clinical trial.
- Long follow-up.
- Precision Oncology: Tumor-specific individualized therapy.

Weaknesses
- Unequal allocation (2:1 randomization)
- Relatively small cohort
- Higher toxicity in the combination arm

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Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

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Abstract

Background: Whether pembrolizumab given both before surgery (neoadjuvant therapy) and after surgery (adjuvant therapy), as compared with pembrolizumab given as adjuvant therapy alone, would increase event-free survival among patients with resectable stage III or IV melanoma is unknown.

Methods: In a phase 2 trial, we randomly assigned patients with clinically detectable, measurable stage IIIB to IVC melanoma that was amenable to surgical resection to three doses of neoadjuvant pembrolizumab, surgery, and 15 doses of adjuvant pembrolizumab (neoadjuvant-adjuvant group) or to surgery followed by pembrolizumab (200 mg intravenously every 3 weeks for a total of 18 doses) for approximately 1 year or until disease recurred or unacceptable toxic effects developed (adjuvant-only group). The primary end point was event-free survival in the intention-to-treat population. Events were defined as disease progression or toxic effects that precluded surgery; the inability to resect all gross disease; disease progression, surgical complications, or toxic effects of treatment that precluded the initiation of adjuvant therapy within 84 days after surgery; recurrence of melanoma after surgery; or death from any cause. Safety was also evaluated.

Results: At a median follow-up of 14.7 months, the neoadjuvant-adjuvant group (154 patients) had significantly longer event-free survival than the adjuvant-only group (159 patients) (P = 0.004 by the log-rank test). In a landmark analysis, event-free survival at 2 years was 72% (95% confidence interval [CI], 64 to 80) in the neoadjuvant-adjuvant group and 49% (95% CI, 41 to 59) in the adjuvant-only group. The percentage of patients with treatment-related adverse events of grades 3 or higher during therapy was 12% in the neoadjuvant-adjuvant group and 14% in the adjuvant-only group.

Conclusions: Among patients with resectable stage III or IV melanoma, event-free survival was significantly longer among those who received pembrolizumab both before and after surgery than among those who received adjuvant pembrolizumab alone. No new toxic effects were identified. (Funded by the National Cancer Institute and Merck Sharp and Dohme; S1801 ClinicalTrials.gov number, NCT03698019.).

Key points:
- This study is an open label, phase 2 trial with randomization into neoadjuvant-adjuvant (NA) vs adjuvant-only (A) pembrolizumab in patients with stage IIIB to IVC surgically resectable melanoma. These represent high risk, primarily cutaneous cases including those with nodal metastases in multiple regional basins and oligometastatic disease deemed to be resectable.
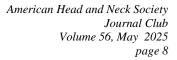
- Primary end point is event free survival, with events defined as toxicity or progression precluding surgery (NA group), disease progression and inability to resect all gross disease, surgical complications, toxic effects preventing initiation of adjuvant therapy within 84 days of surgery, recurrence of melanoma after surgery and all cause death. Overall survival was recorded but not able to be analyzed due to low numbers. This was an intention to treat analysis.

- Median follow up was 14.7 months. Event-free survival at 2 years was reported at 72% (95% confidence interval [CI], 64 to 80) in the NA group and 49% (95% CI, 41 to 59) in the A group. 88% of the NA group and 95% of the A group successfully underwent surgery. In the NA group, 12 patients failed to undergo surgery due to disease progression. The other cases had toxic side effects from the drug (1) or withdrew consent (2). Patients in the NA groups underwent imaging to evaluate response; 6% had a complete response and 41% a partial response. 21% of patients had a complete pathologic response reported on postoperative pathology.

- Among the NA group that received at least one neoadjuvant dose of pembrolizumab, 7% had grade 3 or 4 adverse events related to the drug. Of those who went on to surgery, 7% had a grade 3 or 4 adverse event related to the surgery. In the A group, 4% of patients had a grade 3 or 4 event related to surgery. The incidence of grade 3 or 4 adverse events in the two groups during adjuvant was similar at 12% (NA) and 14% (A).

- Both groups received the same number of pembrolizumab doses in total (18), but at the time of data cutoff, 9 pts in the NA group and 41 pts in the A group had disease recurrence after treatment or during the year of adjuvant pembrolizumab.

Strengths
This is a randomized study with a centralized assignment process. The NA and A groups appear to be similar in terms of demographics and tumor characteristics. Many institutions were included which implies that results were obtained with a number of different surgeons and settings. There were low numbers of consent withdraw. Assessment for recurrence was done often and thoroughly up to 5 years post treatment. Event free survival was reported at a 2 year estimate.   This study evaluated both the safety of giving neoadjuvant pembrolizumab and the potential risk of disease progression during the administration timeframe. It demonstrated a high rate of successful progression to definitive surgery in the NA group as well as an acceptable toxicity profile. Rates of wound complications and infection were also included as possible surgical complications and were low in both groups. A subgroup analysis was done which compared cases by risk factors and disease characteristics. It shows an event free survival benefit across multiple groups, with improved survival in some of the more traditionally high risk groups such as advanced age or tumor ulceration.

Weaknesses
In this study overall survival was not able to be analyzed, which is arguably an important endpoint in the setting of prolonged systemic therapy. Potentially with longer follow up time this endpoint could be delineated. Surgical details such as lymph node yield and margin status were not included, which are material when reporting the end point of recurrence post surgery.   Surgeon experience was also not commented on, though the extent of surgery was reportedly prespecified for all patients. Primary site subgroups within the cutaneous cases were not reported, which could inform applicability to sites with complex lymphatics such as the head and neck. Non-cutaneous subsite numbers (acral and mucosal

melanoma) were too low to allow for comparisons. Finally, confidence intervals in the subgroups analysis were wide in several comparisons owing to low numbers, making conclusions in these groups less precise and comparisons limited. The BRAF mutation subgroup specifically had a high number of unknowns.

Artificial intelligence-based triaging of cutaneous melanocytic lesions

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Abstract

Background: Pathologists are facing an increasing workload due to a growing volume of cases and the need for more comprehensive diagnoses. Aiming to facilitate workload reduction and faster turnaround times, we developed an artificial intelligence (AI) model for triaging cutaneous melanocytic lesions based on whole slide images.

Methods: The AI model was developed and validated using a retrospective cohort from the University Medical Center Utrecht, the Netherlands. The dataset consisted of 52,202 whole slide images from 27,167 unique specimens, acquired from 20,707 patients. Specimens with only benign common nevi, also known as moles, were assigned to the low complexity category (86.6%). In contrast, specimens with any other melanocytic lesion subtype, including non-common nevi, melanocytomas, and melanomas, were assigned to the high complexity category (13.4%). The dataset was split on patient level into a development set (80%) and test sets (20%) for independent evaluation. Predictive performance was primarily measured using the area under the receiver operating characteristic curve (AUROC) and the area under the precision–recall curve (AUPRC). A simulation experiment was performed to study the effect of implementing AI-based triaging in the clinic.

Results: The AI model reached an AUROC of 0.966 (95% CI, 0.960–0.972) and an AUPRC of 0.857 (95% CI, 0.836–0.877) on the in-distribution test set, and an AUROC of 0.899 (95% CI, 0.860–0.934) and an AUPRC of 0.498 (95% CI, 0.360–0.639) on the out-of-distribution test set. In the simulation experiment, using random case assignment as baseline, AI-based triaging prevented an average of 43.9 (95% CI, 36–55) initial examinations of high complexity cases by general pathologists for every 500 cases.

Conclusion: The AI model achieved a strong predictive performance in differentiating between cutaneous melanocytic lesions of high and low complexity. The improvement in workflow efficiency due to AI-based triaging could be substantial.

Summary statements
- This is the largest study to date of patients with cutaneous melanocytic lesion biopsies examined at a single center with expertise in dermatopathology. Aim of this study was the AI-based triaging of 52,202 whole slide images from 27,167 unique H&E-stained specimens (fully digitalized) of 20,707 patients in the Netherlands.
- This team validated their AI model in triaging low complexity (moles) vs high complexity (melanocytomas and melanomas) with excellent results in terms of AUROC of 0.966 (95% CI, 0.960–0.972) and an AUPRC of 0.857 (95% CI, 0.836–0.877) for in distribution (melanocytic lesions).

- The simulation experiment demonstrated that 43.9 (95% CI, 36–55) per 500 cases of initial examinations of high complexity cases were allocated directly to dedicated dermatopathologists obviating initial assessment by general pathologists.

Strengths
- This is the largest study harnessing an AI model for triaging melanocytic lesions and potentially creating a new diagnostic pathway decreasing workload and waiting times for pathologists.
- This model has exceptionally high diagnostic precision in discriminating low and high complexity melonocytics lesions rendering appealing for utilization in large volume centers.

Weaknesses
- This single institution model was not trained to diagnose/stratify non melanocytic (SCC, BCC, MCC) lesions, hence reported AUROC and AUPRC were significantly lower for out of distribution lesions. Also, there was high false positive reports in previously excised melanomas due to the scar presence.
- There is risk of eventual loss of diagnostic expertise for general pathologists if AI models will be routinely introduced.
- There is no cost-benefit analysis released hitherto.

Predictors of distant metastatic recurrence in head and neck cutaneous squamous cell carcinoma with lymph node metastases treated with curative intent: A multicenter study

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Abstract
Background: We aimed to identify predictors of distant metastatic recurrence (DMR) in patients with head and neck cutaneous squamous cell carcinoma (HNcSCC) with nodal metastases treated with curative intent.
Methods: Predictors of DMR were identified using Cox regression in a multicenter study of 1151 patients.
Results: The 5-year risk of DMR was 9.6%. On multivariate analysis, immunosuppression (HR 2.93; 95% CI: 1.70-5.05; p < 0.001), nodal size >6 cm [versus ≤3 cm (HR 2.77; 95% CI: 1.09-7.03; p = 0.032)], ≥5 nodal metastases [versus 1-2 (HR 2.79; 95% CI: 1.63-4.78; p < 0.001)], and bilateral disease (HR 3.11; 95% CI: 1.40-6.90; p = 0.005) predicted DMR. A DMR risk score was developed that stratified risk from 6.6% (no risk factors) to 100% (≥3 risk factors) (p < 0.001).
Conclusions: The risk of DMR in nodal metastatic HNcSCC increases with immunosuppression, nodal size >6 cm, ≥5 nodal metastases, and bilateral disease. A simple DMR risk score estimated prior to treatment may be clinically useful.
Keywords: cutaneous squamous cell carcinoma; distant metastases; head and neck cancer; lymph node metastasis; prognosis.

Summary statements

- This study aims to identify the factors that predict distant metastatic recurrence (DMR) in patients with head and neck cutaneous squamous cell carcinoma (HNcSCC) who had lymph node metastasis and were treated with curative intent.
- 1151 patients were identified who had surgery with or without adjuvant therapy, with the 5-year DMR rate being 9.6%
- Independent predictors of DMR were immunosuppression, nodal size > 6cm, ≥ 5 nodal metastases and bilateral nodal disease.

Strengths

- This is a large multicenter cohort from a country (Australia) with a high rate of HNcSCC over a long period of time (1980 – 2017).
- This is an under researched topic and factors that predict DMR were identified (see above), furthermore a DMR risk score was created with the risk ranging from 6.6% (no risk factors) to 100% (≥3 risk factors).

Weaknesses

- Retrospective and heterogenous data with four decades of data, a time frame in which treatment evolved and improved; for instance, many patients did not have routine surveillance for detection of distant metastases.
- Furthermore, the study relies solely on clinical and macroscopic features such as nodal size and perineural invasion, rather than tumor biology and molecular markers such as PD-1, which have become more recent risk predictors and are going to be the ones that determine the expanded use of immunosuppressive therapy.
- Finally, the DMR risk score has not yet been externally validated.