Association of a 40-gene expression profile (40-GEPR) with risk of metastatic disease progression of cutaneous squamous cell carcinoma (cSCC) and benefit of adjuvant radiation therapy (ART)

Sarah T Arron, MD PhD1; Javier Cañueto, MD PhD2; Jennifer Siegel, PhD2; Alison Fitzgerald, PhD3; Anesh Prasai, PhD2; Shlomo A Koyfman, MD4; Sue S Yom, MD PhD5

1. Peninsula Dermatology, Burlingame, California, USA; 2. Department of Dermatology, Universitario de Salamanca, Salamanca, Spain; 3. Castle Biosciences, Friendswood, TX, USA; 4. Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Background

Criteria for recommendation of adjuvant radiation therapy (ART) for cutaneous squamous cell carcinoma (cSCC) is based on a wide range of high-risk clinicopathologic features that have not been consistently demonstrated to predict benefit from ART. This has led to a broad scope of patients receiving treatment, with only a subset appearing to benefit.2,5

The 40-gene expression profile (40-GEPR) test is a prognostic tool which classifies patients with a primary cSCC who have one or more clinicopathologic risk factors into low (Class 1), moderate (Class 2A), and high (Class 2B) risk of regional, nodal, or distant metastasis.6

Published validation studies indicate that the 40-GEPR test provides additive prognostic value to current risk assessment methods,6 and may positively influence treatment decisions for high-risk cSCC patients.5,10

Methods

Initial eligible patients consisted of a merge of two validation cohorts for the 40-GEPR test for which patients were confirmed eligible for testing and had a successful 40-GEPR test result (>99%). After patient exclusion specific to this study were applied, all 920 qualifying patients were matched on clinical risk factors, stratified by ART status. Random sampling (±10,000) of ART status pairs and bootstrapping were used to avoid dropping any qualified patients and allow results to be generalizable to the cSCC high-risk population. Each sampled and resampled cohort was analyzed using survival methods and stratified by GEP result and ART status.

Results

Table 1. Class 2B result is the only factor in the study that identifies patients that will benefit from ART, in contrast to clinicopathologic risk factors or risk assessment systems

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<table>
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<th>40-GEPR</th>
<th>Class 1, 2A, 2B</th>
<th>0.05</th>
<th>0.05</th>
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<td>Tumor diameter</td>
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<td>PI (</td>
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Figure 1. Matched cohort analysis shows benefit of ART for patients with a Class 2B cSCC for 5-year MFS

Figure 2. Class 2B patients receiving ART show significant reduction in cumulative probability of metastasis

Figure 3. Within cohort differences in predicted metastasis progression. Eighty-eight percent (88%) of Class 2B patients receive a benefit from ART

Conclusions

The 40-GEPR identified patients who benefitted most from ART with improved metastasis-free survival and delay of nodal or distant metastasis.

The 40-GEPR test was also able to identify those patients who were less likely to show significant benefit from ART in controlling metastatic disease progression.

The 40-GEPR test can identify patients who would most likely benefit from ART as a reduction in metastatic disease progression.

Clinical Issue and Objective

Use of ART in cSCC has been shown to benefit some patients; but use of clinicopathologic factors to identify patients who are likely to benefit from those who may not be a major clinical challenge.

The objective of this study was to determine whether the biology 40-GEPR test could identify high-risk cSCC patients who achieve benefit from ART in controlling metastatic disease progression from those who may not.

References

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Disclosures

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Table 1. Class 2B result is the only factor in the study that identifies patients that will benefit from ART, in contrast to clinicopathologic risk factors or risk assessment systems

40-GEPR: Expressed as gene set expression ratio

Class 2B: Tumor thickness ≥ 4 mm

NCCN: National Comprehensive Cancer Network

ART: Adjuvant radiation therapy

PI: Poorly differentiated

Class 1: Tumor thickness < 4 mm

Class 2A: Tumor thickness ≥ 2 cm, < 4 cm

Class 2B: Tumor thickness ≥ 4 cm

Risk factor: NCCN location (L, M, H); Immunocompromised (Yes, No); Differentiation status (Well or moderate, Poor); Invasion into fat (yes, no); Tumor diameter (<2 cm, ≥ 2 cm); PI (cutoff <0.9, ≥ 0.9); Tumor thickness (≤ 4 mm, > 4 mm); Surgeon type (Mohs, W & E, other)

Within cohort differences in predicted metastasis progression. Percentage of within-cohort delay in disease progression (ART benefit) is indicated. cCPR = Cumulative Predictive Accuracy, p = 0.01, not significant for Class 1 and Class 2A

No significant impact of ART in cohort as a whole or within Class 1

No significant impact of ART in cohort as a whole or within Class 2A

ART treated Class 2B patients show significant reduction in metastasis

Cumulative distribution plots (Kolmogorov-Smirnov 2-sample test), show the underlying function of disease progression. Class 1 and Class 2A, ART- and non-ART-treated patient cohorts accumulated metastatic events according to a sigmoidal function in contrast, non-ART-treated Class 2B patient cohorts showed exponential accumulation of events

Class 1

Class 2B

Within Cohort Difference: ART-Treated - no ART

Within Cohort Difference: ART-Treated - no ART

Figure 2. Class 2B patients receiving ART show significant reduction in cumulative probability of metastasis

Figure 3. Within cohort differences in predicted metastasis progression. Eighty-eight percent (88%) of Class 2B patients receive a benefit from ART